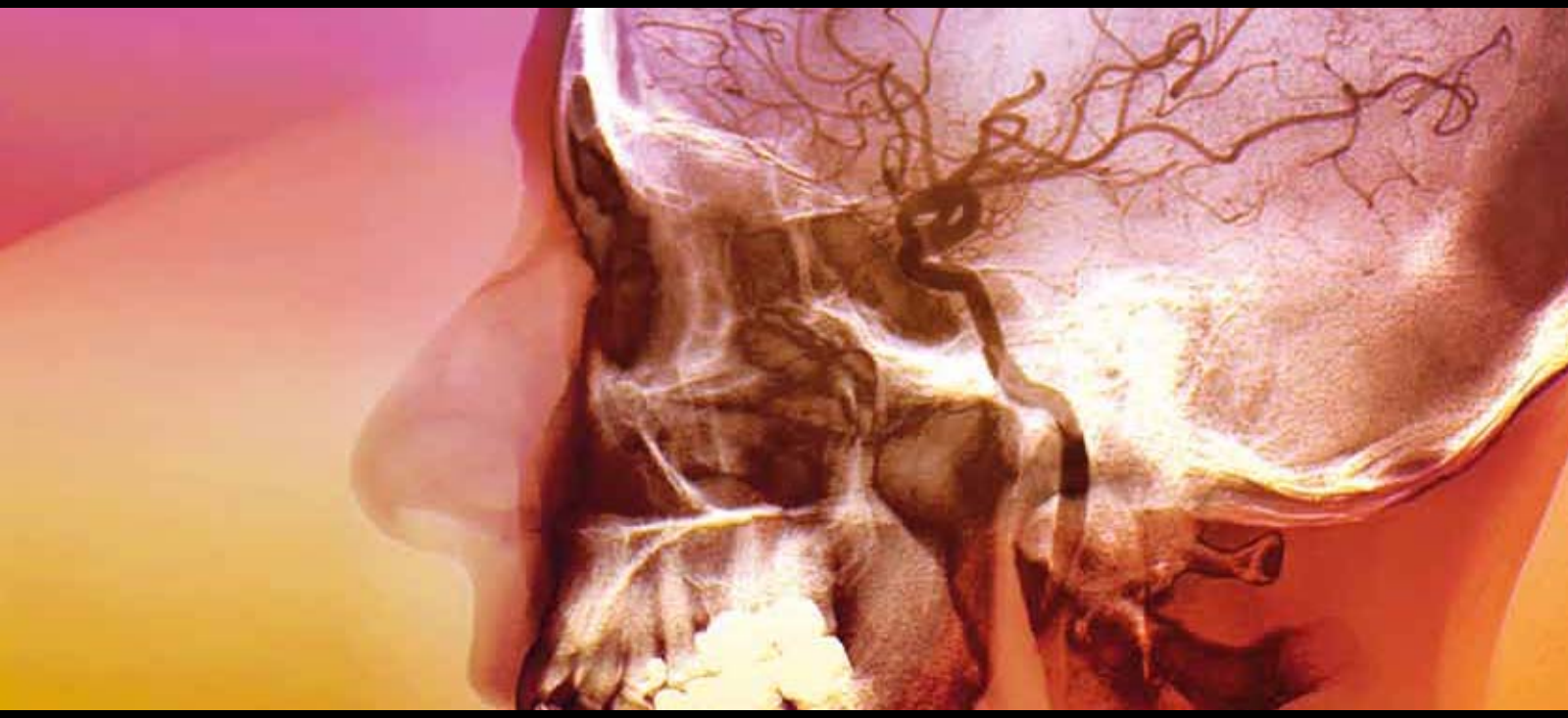
Stroke Research and Treatment

Stroke in the Young

Guest Editors: Halvor Naess, Turgut Tatlisumak, and Janika Kõrv



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Editorial Board

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Editorial

Stroke in the Young

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Study of stroke among young adults and children has been a relatively neglected area until recently. Stroke in young adults is often considered to be rare, but this misconception is colored by the high incidence of stroke in old people. Approximately 5% of all strokes occur in people younger than 45 years of age, another 5% occur in those 45 to 50 years of age, and 1/4 occur in working aged individuals. Although stroke mortality is lower among the young, their risk to die from their stroke is almost 100 times compared to their non-stroke age counterparts, whereas the same ratio is only 4-fold in the elderly. Similarly, stroke morbidities are lower in the young, but these patients live with their neurological deficits much longer and many have to give up their work and social life. Stroke care in young people is especially demanding because it often affects work, education, and close family to a large extent and because of expected long survival.

The study of stroke among young people is important for several reasons. The etiology of stroke is much more diverse in the young compared to old patients. This has therapeutical consequences and may affect outcome both in the short and the long term. Risk factors for stroke differ between young and old patients and may indicate separate approaches as to secondary preventive treatment. Stroke in young adults provides an opportunity to study stroke in general because of less comorbidity than in old patients. This may disclose mechanisms also relevant to older patients.

Stroke in children is rare and is associated with unique challenges. Diagnosis is often delayed because symptoms may be subtle and unspecific. Furthermore, etiology and risk factors in children with stroke differ from young adults with stroke.

Once almost neglected, now stroke in children and young adults is under intense research. Started with single-center small studies and shifted to several multicenter collaborations, scientists establish firmly many facades of stroke in children and in the young, including epidemiologic, etiologic, genetic, and prognostic features. Describing risk factor profiles has led to improved treatments. Evidence-based treatments have started to emerge, for example, in Sickle cell disease. New etiologic classifications and one international guideline for childhood stroke have appeared. Few textbooks have been published or are under preparation, and an international meeting dedicated to young stroke is planned.

This special issue is one of the numerous efforts in disseminating state-of-the-art information on the field covering a broad range of important topics as to stroke in children and young adults. It includes two case reports, two research articles, three clinical articles and 15 reviews. Seven articles deal with stroke in children, and 15 articles with stroke in young adults. Several review articles in this special issue stress the importance of extensive investigations in children with stroke including MRI to disclose the underlying etiology and risk factors. Rare causes including diabetic ketoacidosis-associated stroke, cardiac diseases, vascular abnormalities such as Moyamoya disease, but also more general causes such as dissection must be considered. A clinical study concludes that correct prophylaxis reduces the rate of recurrence in children with stroke. Other review articles disclose that more than half of the surviving children have long-term neurological sequels. A research article reports impaired cognitive development and impaired performance as to writing, reading, and arithmetic in children with stroke. A review article reports that the annual incidence of stroke in adults under 45 years ranges between 8.7 and 21 per 100,000. Several review articles show that etiology of cerebral infarction in young adults is varied. Most cerebral infarcts in the elderly are

caused by conventional etiologies, for example, large-artery atherosclerotic disease, cerebral embolism (mainly atrial fibrillation), and small-vessel disease, and only 10% are caused by rare etiologies or cause remains undetermined. Conversely, one-fourth of cerebral infarcts in children and young adults are caused by unconventional etiologies and roughly one-third remains undetermined even after a complete workup. Where atrial fibrillation is a common cause of cerebral infarction in old patients, structural heart diseases including patent foramen ovale are frequent in young adults. However, a review article points out that atherosclerosis, which is a common cause of cerebral infarction in old patients, may be threatening even to the young adults. Genetic causes of stroke are more common in young adults than in old adults with stroke. Several review articles report on genetic thrombophilic disorders, genetic connective tissue diseases such as Ehlers-Danlos syndrome, and Fabry disease which is an X-linked lysosomal storage disorder. Stroke in developing countries is associated with etiologies which are uncommon in industrialized countries. Thus, a review article highlights the importance of cardioembolic stroke due to endocarditis in India. Stroke in pregnancy and the puerperium represents unique challenges. Two review articles address this rare but important topic. Previous studies have disclosed a link between migraine and cerebral infarction. However, this association is poorly understood. A review article presents several important issues which must be considered in this regard including patent foramen ovale, migraine specific drugs, and genetic components.

Psychological adjustment is an important concern after stroke in young adults. A review article addresses this issue with particular consideration on service provision and return to work. A clinical article report that there was no difference as to ischemic stroke severity on admission and one week after stroke onset between patients younger than 50 years and patients older than 50 years. Because of long expected survival, information on long-term outcome after stroke in young adults is important. A review article provides a summary of long-term outcome both as to mortality, recurrent vascular events, and function.

We hope that the present special issue provides important information on stroke in children and young adults and to be of help both as to treatment of our patients and in stimulating further research.

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Review Article

Ischemic Stroke in Infants and Children: Practical Management in Emergency

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Stroke is a rare disease in children, with an estimated incidence 13/100000 and a significant impact on morbidity and mortality. Clinical presentation and risk factors, present in almost half of pediatric patients, are not the same as in adults. The diagnosis of stroke in children is often delayed because signs and symptoms can be subtle and nonspecific. History and clinical examination should exclude underlying diseases or predisposing factors. Neuroimaging is crucial in defining diagnosis. Other tests might be necessary, according to the clinical picture. We present here the most recent practical directions on how to diagnose and manage arterial stroke in children, according to different international guidelines on the subject.

1. Introduction

The World Health Organization (WHO) defines stroke as "a clinical syndrome of rapidly developing focal or global disturbance of brain function lasting >24 hours or leading to death with no obvious nonvascular cause" [1]. This definition should be integrated by a reference to neuroimaging, at present considered essential to define the neurovascular origin of symptoms. A modern definition could be "a clinical syndrome characterized by (1) a neurological deficit related to the perfusion territory of a cerebral artery and (2) neuroradiological evidence of an ischemic lesion" [2, 3].

Transient ischemic attacks (TIAs) are defined as "a sudden, focal neurologic deficit that lasts for less than 24 hours, of presumed vascular origin, confined to an area of the brain or eye perfused by a specific artery" [4]. In childhood, on the contrary, even in the presence of transient symptoms, imaging often shows a cerebral infarction [5].

Strokes are classically divided in primarily ischemic or hemorrhagic. While adult strokes are prevalently ischemic (80%) and due to atherosclerosis, in childhood up to 45% of strokes are hemorrhagic and are associated with a wide spectrum of risk factors [6].

The estimated incidence of ischemic stroke in children older than 28 days of life is variable [7–9] but, according to a large prospective, population study, it averages 13/100.000 for all strokes, 7.9/100.000 for ischemic strokes, and 5.1 for hemorrhagic strokes [8]. Approximately 20% of children die after an ischemic stroke while more than 50% of those surviving present neurological sequelae, most commonly hemiparesis [7, 9]. The cumulative stroke recurrence rate has been reported to be 15% at 1 year, and 19% at 5 years [10], and up to 41% at 5 years [11].

A risk factor is present in almost half of the children at the time of stroke [12] (Table 1). Common risk factors in childhood are congenital heart disease, sickle cell disease, infections, and various prothrombotic conditions [13–15]. The most common cause of stroke in children is probably heart disease, detected in 19% of children with arterial thrombosis (Canadian Pediatric Ischemic Stroke Registry) [16]. Recent studies underline the importance of infection: it seems that at least a third of cases of childhood stroke occur in such a context. A fifth of the children with ischemic infarction of unknown origin has a history of prior chickenpox [16–18].

In about 80% of children with arterial stroke, arterial imaging is abnormal [12].

The purpose of this paper is to provide practical up-to-date directions on how to diagnose and manage arterial stroke in children (1 month–18 years), in an emergency department. Neonatal stroke is not included because of its peculiar characteristics.

Table 1: Risk factors for pediatric stroke.

Congenital heart disease
Ventricular/atrial septal defect
Patent ductus arteriosus
Aortic/mitral stenosis
Coarctation
Cardiac rhabdomyoma
Complex congenital heart defects
Acquired heart disease
Rheumatic heart disease
Prosthetic heart valve
Endocarditis
Cardiomyopathy
Myocarditis
Atrial myxoma
Arrhythmia
Systemic vascular disease
Systemic hypertension
Volume depletion or systemic hypotension
Hypernatremia
Superior vena cava syndrome
Diabetes
Vasculitis
Meningitis
Systemic infection
Systemic lupus erythematosus
Polyarteritis nodosa
Granulomatous angiitis
Takayasu's arteritis
Rheumatoid arthritis
Dermatomyositis
Inflammatory bowel disease
Drug abuse (cocaine, amphetamines)
Hemolytic-uremic syndrome
Vasculopathies
Ehlers-Danlos syndrome
Homocystinuria
Moyamoya syndrome
Fabry's disease
Malignant atrophic papulosis
Pseudoxanthoma elasticurn
NADH-CoQ reductase deficiency
Vasospastic disorders
Migraine
Ergot poisoning
Vasospasm with subarachnoid hemorrhage
Hematologic disorders and coagulopathies
Hemoglobinopathies (sickle cell anemia, sickle cell-hemoglobin C, sickle-thalassemia)
Immune thrombocytopenic purpura
Thrombotic thrombocytopenic purpura
Thrombocytosis
Polycythemia
Disseminated intravascular coagulation
Leukemia or other neoplasms
Congenital coagulation defects
Oral contraceptive use
Antithrombin III deficiency
Protein S deficiency
Protein C deficiency
Congenital serum C2 deficiency
Liver dysfunction with coagulation defect
Vitamin K deficiency
Lupus anticoagulant
Anticardiolipin antibodies
Structural anomalies of the cerebrovascular system
Arterial fibromuscular dysplasia
Agenesis or hypoplasia of the internal carotid or vertebral arteries
Arteriovenous malformation
Hereditary hemorrhagic telangiectasia
Sturge-Weber syndrome
Intracranial aneurysm
Trauma
Child abuse
Fat or air embolism
Foreign body embolism
Carotid ligation
Vertebral occlusion following abrupt cervical rotation
Posttraumatic arterial dissection
Blunt cervical arterial trauma
Arteriography
Posttraumatic carotid cavernous fistula
Coagulation defect with minor trauma
Penetrating intracranial trauma

In preparing this work we followed the most recent guidelines on arterial stroke in childhood (Pediatric Stroke Working Group, 2004; American College of Chest Physicians, 2004; Italian Society of Pediatrics, 2007; American Stroke Association, 2008).

Additionally, a literature review was made, analyzing relevant articles on the subject, up to August, 2010 by searching Pubmed, EMBASE, Cochrane Library and in bibliographies of relevant articles. Search terms were "stroke," "emergency," "child," "childhood," "management."

2. Diagnosis

2.1. Clinical Presentation. The clinical presentation of stroke differs depending on age, involved artery, and cause [19, 20].

Table 2: Clinical presentation of stroke depending on the involved artery.

Vascular territory	Symptoms
Internal carotid artery	Hemiparesis, aphasia, and hemianopsia
Anterior cerebral artery	Hemiparesis, especially leg
Middle cerebral artery	Arm hemiparesis, hemianopsia, and aphasia
Posterior cerebral artery	Hemianopsia, ataxia, hemiparesis, and dizziness
Basilar artery	Breath, sensory or balance disturbances, ataxia, nystagmus, opisthotonus, tremor, and vomiting
Cerebellar artery	Sensory disturbances, headache, fever, vomit, and cerebellar signs

While in infancy symptoms are usually aspecific, in older children, the most frequent presenting symptoms are focal neurologic deficits such as hemiplegia or a gross, focal motor deficit [21].

Symptoms according to the involved artery are listed in Table 2. The vascular territory of the middle cerebral artery is the most frequently affected.

2.2. Differential Diagnosis. Diagnosis of stroke in children is often delayed because signs and symptoms can be subtle and nonspecific, such as mild single limb weakness, incoordination, and sensory disturbances, initially attributed to causes other than stroke [22].

In a child presenting with an acute neurologic deficit, before a diagnosis of ischemic stroke is made, other cerebrovascular diseases (hemorrhagic stroke, cerebral venous sinus thrombosis) need to be considered.

Frequent causes of acute hemiplegia are Todd's palsy, where focal seizures usually precede monoparesis or hemiplegia, and hemiplegic migraine, in which hemiplegia is preceded by visual or sensitive disorders and followed by headache. It is also necessary to exclude meningoencephalitis, generally associated with fever, headache and altered consciousness.

Acute neurologic deficits may be caused by tumors, central nervous system disorders including acute disseminated leukoencephalitis, cerebellitis, reversible posterior leukoencephalopathy, alternating hemiplegia, metabolic disorders, epilepsy, and psychogenic diseases [23].

2.3. Early Investigations (on Presentation). The first step to detect a stroke is including this option in the differential diagnosis of an acutely ill child. Early diagnosis allows prompt starting of appropriate therapy.

2.3.1. History. Clinical history should include ethnic origin, the presence of sickle cell disease or congenital heart disease, head or neck trauma (associated with intracranial hemorrhage and dissection), recent infection (especially chickenpox), vasculitis and blood disorders [19], as well as cerebrovascular diseases, coagulopathies, or immunologic disorders among first-degree relatives.

How and how rapidly symptoms develop is of major importance. Up to a third of children who have had a stroke have a history of recent events consistent with TIAs [24].

2.3.2. Physical Examination. A complete physical and neurologic examination, including monitoring of vital parameters, will identify neurologic damages and allow presumptive diagnosis of the brain vessel involved. Signs of systemic diseases that increase the risk of stroke should be looked for.

2.3.3. Imaging Studies. Non-contrast computed tomography (CT) can be performed promptly and quickly in emergency. It can adequately exclude hemorrhagic stroke or parenchymal abnormalities that produces a mass effect, and it may reveal a low-density lesion in arterial ischemic stroke and cerebral venous sinus thrombosis. However, CT is usually normal within the first 12 hours after the onset of symptoms [6]. It should be requested whenever magnetic resonance (MR) is not available [19].

MR, in fact, is the "gold standard" imaging modality for the investigation of arterial ischemic stroke in infants and children [25] due to its greater sensitivity and specificity. MR is useful to differentiate stroke from "stroke mimics" but it is rarely available in emergency [26]. The diagnostic efficiency of MR can be further improved by perfusion techniques, that quantify relative cerebral blood flow, volume, and transit time by the use of bolus administration of gadolinium-based contrast material [5, 27, 28].

MR with diffusion weighting is very useful in accurately identifying regions of early ischemia and infarction [26]. MR angiography is a noninvasive procedure that detects large vascular abnormalities [29], and it is as effective as cerebral angiography in identifying large ischemic lesions [30]. MR angiography is a reasonable alternative to conventional arteriography in most patients [31, 32]. If the pattern of brain injury could be consistent with venous infarction, emergency vascular imaging should include MR venography. In fact, 10% of hemorrhagic strokes in children are secondary to cerebral venous sinus thrombosis [6].

Vascular imaging of the extracranial circulation, such as cervical MRA or Doppler ultrasound, should also be performed, particularly if the history is suggestive of a cervical arterial dissection.

2.3.4. Other Investigations. Complete blood cell count, iron studies, prothrombin time, partial thromboplastin time, sedimentation rate, and antinuclear antibodies could be useful [19].

2.4. Second-Line Investigations (after 48 Hours as Indicated). Once stroke has been diagnosed, several studies may be helpful for the ongoing evaluation and management of the patient.

Electrocardiogram and transthoracic or transesophageal echocardiogram are always necessary in all children with known or suspected congenital heart disease who have had a stroke [20, 33].

Echocardiography may be helpful to diagnose patent foramen ovale; this abnormality can be up to four times

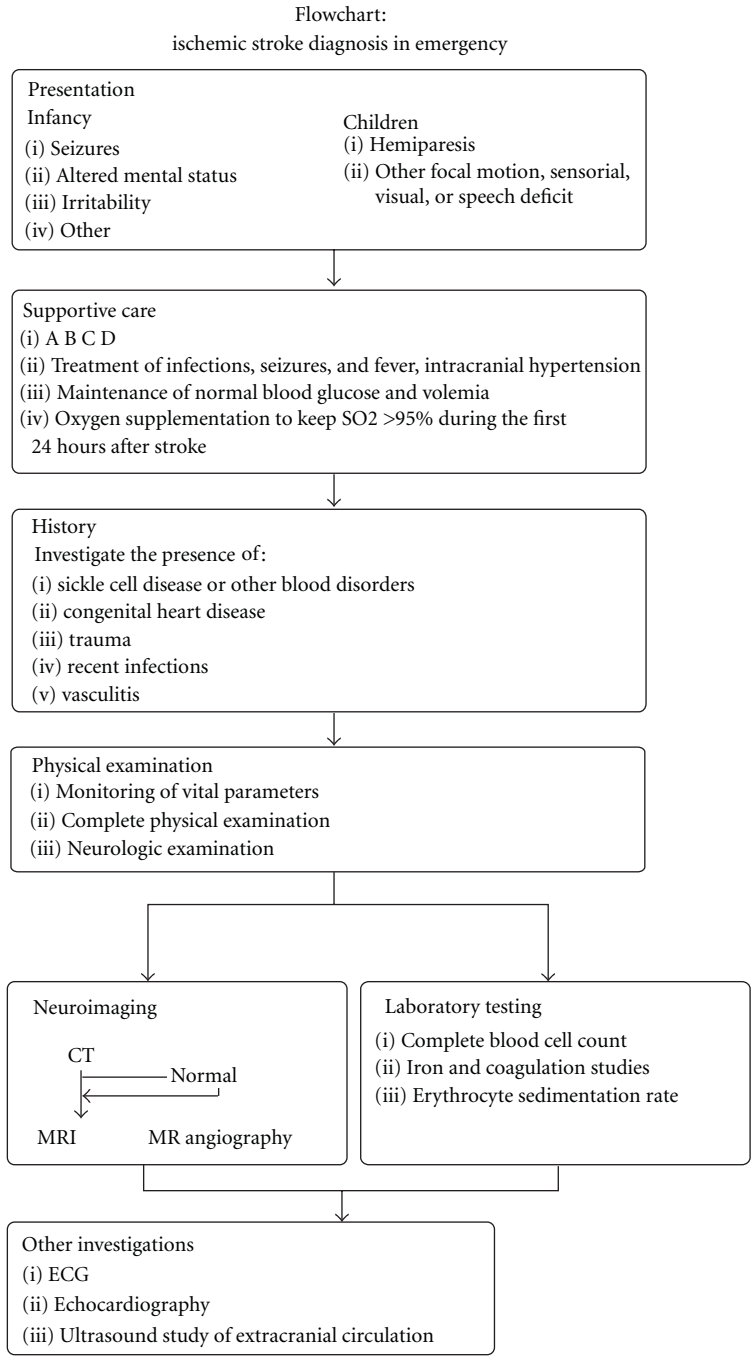

Figure 1: Flowchart: diagnosis of ischemic stroke in emergency.

greater in children with stroke with undetermined etiology than in the general population [34].

The diagnosis of some conditions, including extracranial arterial dissection, particularly involving the posterior circulation, and small-vessel vasculitis, is difficult using MR angiography alone. In these circumstances, catheter cerebral angiography is sometimes required. However, catheter cerebral angiography is an invasive procedure, not commonly performed in children, and it has similar diagnostic yield as MR combined with MR venography and MR arteriography [6].

Conventional angiography can be necessary in order to identify moyamoya syndrome [19].

Hemoglobin electrophoresis and urine drug screening, particularly for sympathomimetics may be indicated. A full evaluation for thrombophilia is reasonable in all children with stroke. It should include evaluation of protein C and protein S deficiency, antithrombin III, heparin cofactor II,

plasminogen, von Willebrand's antigen, factor VIII, factor XII, factor V Leiden, activated protein C resistance, prothrombin 20210 gene, serum homocysteine, methylene-tetra-hydro-folate-reductase, lipoprotein (a), and antiphospholipid antibodies [35–37]. When indicated on the basis of clinical suspicion, more extensive diagnostic testing, such as cerebrospinal fluid analysis, lipid profile, Varicella-Zoster and human immunodeficiency virus, and screening for metabolic disorders might be performed. However, in the majority of cases, the results of these studies will not have an impact on emergency care [19]. We suggest a flow chart for diagnosis of ischemic stroke in emergency (see Figure 1).

3. Management in Emergency

Guidelines based on strong evidence for the acute care of childhood stroke do not exist, with the exception of sickle cell disease. Therefore, treatment recommendations for ischemic stroke in children are extrapolated from adult guidelines.

Children with early acute ischemic cerebral stroke need to be admitted to a clinical unit where continuous monitoring is possible. Only in selected cases treatment in intensive care units is needed [38, 39].

3.1. Supportive Care. The general approach in emergency includes simple measures such as maintenance of respiratory and cardiovascular functions, aggressive treatment of infection, seizures and fever, maintenance of normoglycemia and normovolemia [20, 40], and oxygen supplementation to keep $SaO_2 > 95\%$ during the first 24 hours after stroke [41]. Medical or surgical treatment of intracranial hypertension, when present, is important, because children have higher risk of tonsillar herniation due to cerebral edema. Hyperventilation is a short term solution that should be used for imminent herniation until a definitive therapy, such as decompressive neurosurgery, can be offered [40, 42, 43].

3.2. Anticoagulant Therapy and Antiplatelet Agents. The choice between anticoagulant and antiplatelet agents is controversial and there are few data to guide this decision in children [44].

As anticoagulation therapy, both unfractionated heparin and low molecular weight heparin (LMWH) have been used in children with AIS. Current guidelines recommend anticoagulation in children with proven arterial dissection or cardioembolic stroke or during the diagnostic evaluation period, until a cardiac source or an arterial dissection has been excluded [42]. Heparin should be used in children thought to have a high risk of recurrence and a low risk of secondary hemorrhage [5, 45].

According to the international literature, LMWH at the dose of 1 mg/kg every 12 hours represents a safe initial therapy for ischemic stroke in infants and children. Hemorrhagic stroke needs to be excluded before starting treatment [46–49]. Low molecular weight heparin offers several advantages over standard unfractionated heparin and oral anticoagulants: lower risk of heparin-induced thrombocytopenia, fewer drug interactions, fewer adverse effects on bone when given long term, and lower cost. Furthermore, LMWH is administered subcutaneously, and it demonstrates predictable age-dependent pharmacokinetics and less need for monitoring, thus reducing the need for multiple venipunctures [46]. Enoxaparin (1 mg/kg subcutaneously for children more than 2 months of age, or 1.5 mg/kg for infant less than 2 months of age) is the most frequently used LMWH in children [47]. In children with cardiac embolism or vascular dissection, LMWH is administered for 3 to 6 months [50].

Concerning antiplatelets, even in absence of randomized clinical trials for the use of aspirin in the acute treatment of AIS in children, most experts agree that this drug use is reasonable for secondary stroke prevention. Standard dosage of 1 to 5 mg/kg/day for a minimum of 3 to 5 years from the acute event is recommended as secondary prevention [50]. The increased risk of Reye's syndrome should be considered. Clopidogrel has been used at dosages of about 1 mg/kg per day in children unable to take aspirin [42, 51].

Thrombolysis with tissue plasminogen activator (tPA) is not currently used and the Royal College of Physicians, AHA Stroke Council, and ACCP guidelines do not recommend it. In fact, the diagnosis of stroke in children is usually made after the time interval required for intravenous or intraarterial tPA thrombolysis (3 hours and 6 hours after stroke onset, resp.) [3, 52–54].

The International Paediatric Stroke Study group recommends that thrombolysis should not be used unless it is part of randomised control trial [55, 56].

4. Hemorrhagic Stroke

Hemorrhagic stroke is as common as arterial ischemic stroke with an estimated incidence of 1.5–2.9 per 100.000 children per year [41]. It includes spontaneous intraparenchymal hemorrhage and nontraumatic subarachnoid hemorrhage.

Structural lesions are the most common causes of intraparenchymal hemorrhages in a population-based cohort [57]. Brain tumors (27%) and arteriovenous malformations (17%) are the most frequent. Medical etiologies are less common. Coagulopathies (13%) include various causes of thrombocytopenia, hemophilia and von Willebrand's disease, sickle cell anemia (6%), hypertension (10%), and infections (6%). Intraparenchymal hemorrhages of idiopathic origin are also frequent (23%).

Non-traumatic subarachnoid hemorrhages are most often caused by intracranial aneurysms. Ruptured aneurysms account for 10% of intracranial hemorrhages in children. The incidence of subarachnoid hemorrhage is increased in various congenital and hereditary conditions such as cerebral artero-venous malformations, cardiac disorders (coarctation of the aorta, bacterial endocarditis, and atrial myxoma), autosomal dominant polycystic kidney disease, connective tissue abnormalities (Marfan's syndrome, fibromuscular dysplasia, and Ehlers-Danlos type IV), hematological disorders (sickle cell disease, G6PD deficiency, and thalassemia), phakomatoses (neurofibromatosis type 1, especially following radiation therapy and tuberous sclerosis) [58].

Headache or vomiting due to raised intracranial pressure, seizures and focal neurologic deficits are the presenting symptoms in children [41]. During evaluation of pediatric

Table 3: Risk factors for stroke in sickle cell disease.

(i) high blood flow velocity on transcranial Doppler
(ii) low hemoglobin value
(iii) high HbS level
(iv) high white cell and platelet counts
(v) hypertension
(vi) silent brain infarction
(vii) history of chest crisis, transient ischemic attacks, meningitis, seizures, surgery, priapism, acute anemia, and transfusion within 2 weeks before the stroke

stroke it is mandatory to exclude an acute intraparenchymal bleeding. To this end non-contrast TC should be performed.

Treatment of hemorrhagic stroke requires a multidisciplinary team management with neurological and neurosurgical care.

Management options in hemorrhagic stroke fall into two categories: general efforts to stabilize the patient and measures to reduce the risk of rebleeding [5].

Surgical management is controversial, and there is no evidence that surgical evacuation of a supratentorial intraparenchymal hematoma is beneficial at any age [59, 60]. However, evacuation of a rapidly expanding hematoma causing cerebral herniation may be of benefit [6]. Surgical or endovascular obliteration of aneurysms and artero-venous malformations is effective for many individuals, but stereotactic radiotherapy is being used increasingly in children with artero-venous malformations that are small or difficult to approach surgically. Several large retrospective studies have shown that stereotactic radiotherapy is safe and effective for the treatment of children with an artero-venous malformation [61, 62].

Treatment of coagulation defects and hematologic disorders should reduce the risk of subsequent hemorrhage. Emergency splenectomy is indicated for intraparenchymal bleeding associated with idiopathic thrombocytopenic purpura. Other important complications of non-traumatic subarachnoid hemorrhage that require treatment are hydrocephalus, vasospasm, and hyponatremia [5].

5. Stroke in Sickle Cell Disease

The most common hematologic risk factor for stroke is sickle cell disease (SCD). Eight percent of patients younger than 19 years will develop a stroke. In this group the highest rate of first ischemic stroke is in children between 2 and 5 years of age while hemorrhagic stroke affects adults aged 20 to 30 years. Both familial and environmental factors seem to be involved in the occurrence of stroke [19]. In the absence of therapy recurrence of stroke is as high as 40% [63].

Small infarctions have been found on MR in 20 to 35% of children with SCD in the absence of symptoms [64, 65]. These so-called "silent infarcts," predominantly located in frontal and parietal cortical, subcortical, and border-zone areas are associated with deterioration in cognitive function and with an increased risk of clinically symptomatic stroke [66, 67].

Stroke may also be due to large vessel vasculopathy that generally involves the middle cerebral artery territory. Some individuals develop progressive vasculopathy of the intracranial internal carotid artery and of its distal collateral vessels, a picture called moyamoya syndrome. Small infarctions typically involve the basal ganglia and the deep white matter within the anterior circulation.

Risk factors for stroke in SCD are summarized in Table 3.

5.1. Prevention. The presence of high cerebral blood flow velocity as measured by transcranial Doppler (TD) identifies patients at high risk of primary prevention.

In healthy children, the velocity in the middle cerebral artery is around 90 cm/s while in SCD children it is 130–140 cm/s. Stroke risk is high when velocity is >200 cm/s.

A randomized trial (Stroke Prevention Trial in Sickle Cell Anemia: STOP) compared periodic blood transfusion with standard care in 130 children with SCD who were selected for high stroke risk on the basis of TD results. The trial was halted because of the high number of strokes in the standard-care arm compared with the transfusion-treated group (11 versus 1), in whom the risk of stroke was reduced from 10% to <1% per year [68].

The current National Heart, Lung, and Blood Institute of the National Institutes of Health (NHLBI) recommendation is to evaluate children between 2 and 16 years with SCD using TD at 6 month intervals. If velocity is >200 cm/s, confirmed after a control performed few weeks later, chronic transfusion therapy should be started [63] and should not be discontinued even if TD normalizes (as demonstrated by the randomized controlled trial STOP II [5]).

5.2. Therapy. The treatment of acute ischemic infarction resulting from SCD includes intravenous hydration and exchange transfusion to keep HbS <30% and Hb between 10–12.5 g/dL [69]. Exchange transfusion avoids the theoretical risk of increasing blood viscosity that could accompany a rapid increase of the hematocrit [5].

6. Conclusions

Stroke is relatively rare in children, except, as mentioned, in sickle cell disease. It represents, however, one of the ten "top causes" of childhood death. Its relatively rarity causes a lack of awareness that cerebrovascular disease occurs in children. Furthermore, risk factors and clinical presentation are distinctive compared to adults. For these reasons diagnosis is often delayed. It has been estimated that 48–72 hours frequently elapse between the onset of symptoms and diagnosis [70].

When evaluating a child with stroke, several tests, including imaging studies, are helpful to confirm the diagnosis, to differentiate hemorrhagic from ischemic stroke, and to guide the emergency management.

No uniform approach exists for the treatment of childhood stroke. Until data based on randomized pediatric clinical trials will be available, treatment recommendations for the acute care of children with stroke will continue to be extrapolated from adult guidelines.

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Clinical Study

Treatment Challenges in Pediatric Stroke Patients

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Aim. In this study we presented our experience of 18 years on the etiology, risk factors, prophylactic and acute treatment, the effect of treatment to recurrence rate of patients with stroke. *Methods*. The population included 108 patients who had been treated for stroke at Pediatric Neurology Department of Ankara University with the diagnosis of arterial ischemic stroke and sinovenous thrombosis between January 1992 and August 2010. Forty-one girls (38%) and 67 boys (62%) with mean symptom age 3.1 ± 4.04 years, (0–18 years old) were followed up with a mean period of 4.9 ± 3.78 years (0–17 years). *Results*. 30 patients had no risk factors, 34 patients had only one risk factor and 44 patients had multiple risk factors. Recurrence was seen in three patients. There was no any statistical correlation between the recurrence of stroke and the existence of risk factors ($P = .961$). Seventeen patients received prophylactic treatment; 2 of them without any risk factors, 3 had one risk factor, 12 patients, who constituted the majority of our patients, had multiple risk factors ($P = .024$). *Conclusion*. With this study we showed that the right prophylaxis for right patients reduces the rate of recurrence.

1. Introduction

In recent years, the incidence for paediatric stroke has reached up to 8 per 100,000 children per year and is attributed to the increase in the sensitivity and the specificity of noninvasive imaging methods (i.e., CT, MRI, MRA, and cranial ultrasound studies) and the increased survival rate due to more effective treatments for diseases like prematurity, congenital heart disease, and leukemia that predispose to stroke [1–4]. Stroke in children and adolescents has different presentation compared to that in adults. The 80–85% of adult stroke cases is reported to be ischemic while it is around 55% in children. The rest is hemorrhagic strokes for both age groups [5]. Ischemic strokes are thought to be underdiagnosed in infancy and childhood. It is very important to increase our knowledge about stroke in children, especially regarding etiology, outcome, and also possible treatments to reduce morbidity, mortality, and recurrence [6–13].

One fourth of "stroke in the young" is seen in children. The incidence of childhood AIS (acute ischemic stroke) is at least 2.6 per 100,000 children per year [14]. Neonates make up 25% of paediatric AIS patients and are therefore at considerably increased risk. In newborns with seizures, 12 to 14% are diagnosed with underlying cerebral infarction. There is a slight male predominance (60%) in childhood AIS [15, 16].

In paediatric cases, the diagnosis may be delayed or even missed. In neonates, AIS often presents only with lethargy or seizures. In children, the diagnosis of cerebral infarction is frequently delayed. Compared with adults, acute hemiparesis in children is more likely to be attributed to migraine headache, seizure, or focal encephalitis than stroke [17].

Subtle symptoms are less likely to be reported by the child or to be attributed to stroke. In the Canadian Registry, children with AIS presented most frequently with hemiparesis (51%), speech disorder (17%), and seizures (48%). However, the neurological presentations of AIS are age related. In infants with in utero AIS, the diagnosis usually becomes apparent only when pathological early hand dominance develops between 6 and 12 months of age and leads to a CT scan [13, 18]. Neonates with acute stroke present with seizures or lethargy in the first few days after birth, and hemiparesis is present in less than 25% at diagnosis, although it may develop later [7, 14, 19]. Older infants with AIS

typically present with an acute focal neurological deficit, usually hemiparesis. In school-age children, speech deficit or other subtle signs including sensory or visual deficits can be recognized. More than 50% of children experience diffuse symptoms accompanying AIS, including headache, lethargy, or confusion. These symptoms are more common in younger children [14, 20]. It is important to differentiate a postictal hemiparesis from the typically brief Todd's paresis, as seizures can be due to AIS [20].

The duration of a neurological deficit in children with AIS is frequently brief. The classical criteria for stroke in adults include focal neurological deficit persisting for at least 24 hours. Using these criteria, many AIS events in children would be missed. In infants focal signs are rare and in children a very rapid return of neurological function (less than 1 hour) can be associated with an infarct on the CT or MRI scan. In the absence of finding arterial stenosis on vascular imaging, the differentiation of transient ischemic attack (TIA) from migraine or seizure can be difficult. Recognition of TIAs in children is important, however, because appropriate antithrombotic therapy can prevent subsequent AIS [21].

Approximately one half of acute ischemic stroke cases occur in children with no known risk factors [22]. The most frequent causes for AIS in childhood are arteriopathies (fibromuscular dysplasia, moya-moya syndrome), vasospastic disorders (migraine), hemoglobinopathies, leukemia, acquired prothrombotic states, congenital heart disease, and acquired heart diseases [21]. Although risk factors in children with AIS are strikingly different from those in adults, in whom atherosclerosis is the overwhelming etiology, many of the risk factors being discovered in children with stroke also play an important contributory role in adults with stroke [15, 23].

The childhood stroke is underdiagnosed due to its challenging nature. It is in most cases not included in the differential diagnosis of acutely ill children. Acute hemiparesis in children is more likely to be attributed to other causes. It is of critical value to have accurate diagnosis and to identify patient-specific risk factors. As a result, an appropriate treatment can be initiated fast, systemic complications may be minimized and a secondary stroke may be prevented [23].

Although the role of laboratory screening in childhood stroke is not clear, complete blood cell count, iron studies, PT, PTT sedimentation rate, and antinuclear antibody are often sent. Hb electrophoresis and urine drug screens, particularly for sympathomimetics, may be indicated [24]. A full evaluation for thrombophilia is reasonable in all children and should include protein C and protein S, antithrombin III, heparin cofactor II, plasminogen, von Willebrand antigen, factor VIII, factor XII, factor V Leiden, activated protein C resistance, prothrombin 20210 gene, serum homocysteine, methylene-tetra-hydro-folatereductase, lipoprotein (a), and antiphospholipid antibodies. Apart from the gene studies, the blood samples should be taken at least 4–6 months after the insult [25–27].

The optimal method for diagnosis of stroke is MRI with diffusion- and perfusion-weighted imaging. Being a noninvasive procedure MR angiography (MRA) detects large vascular abnormalities. It is proven to be as effective as cerebral angiography in detecting large lesions. MR spectroscopy and diffusion-weighted imaging with MRA increase the sensitivity of MRI detecting ischemia and infarction [24–26, 28–30].

As there is no randomized controlled treatment trials in children with AIS, many of the treatment approaches increasingly used in children have been adapted from studies in adults. However, there are age-related differences in the hemostatic, vascular, and neurological systems compared with adults. This must be taken into account while applying antithrombotic and neuroprotective therapies to children with AIS. Children with stroke are primarily treated for the underlying risk factors and prevention of recurrent cerebral ischemic events [21].

Due to having a negligible risk of recurrence, neonates with AIS do not require routine antithrombotic treatment. However, recurrent TIAs and strokes occur in 7 to 20% in older infants and children with AIS. For these patients, long-term therapy with ASA is needed to prevent the risk. In children with cardiogenic AIS, dissection, high-grade stenosis of a cerebral artery, severe prothrombotic conditions, or failure of ASA therapy in preventing recurrence, LMWH or coumadin is frequently continued for several months. The risk of recurrent cerebral thrombotic events must be balanced against the risks of treatment, particularly bleeding risk [21, 31].

Thrombolytic agents should only be used in the setting of a clinical trial until safety and feasibility data are available as they carry an unknown but potentially very significant risk of hemorrhage in children with AIS [32, 33].

Clinical presentation, underlying cause, size of infarct, and stroke subtype appear to be influential factors on the outcome. Infarct volume greater than 10% of intracranial volume is associated with worse outcome. Although mortality among children is lower than in adults, stroke in children is associated with long-term sequelae. According to the studies, 55% of children develop sensory or motor problems, seizure, developmental delay, or cognitive disorders; 15% die and 35% are neurologically normal [4, 5, 34].

The general rate of stroke recurrence is between 26% and 30%, particularly during the first 6 months poststroke [28]. It is higher among children with identified risk factors. Because of unidentified risk factors for recurrence or lack of adequate treatment, idiopathic stroke may have a higher recurrence than previously believed [1, 35].

There is limited evidence regarding the efficacy of secondary prevention strategies in childhood stroke; however, ASA (acetyl salicylic ascit) is widely used. ASA is indicated for secondary prevention of AIS in children except in patients with SCD and those with high risk of recurrence and severe hypercoagulable state. Although the ideal prophylactic dose is undefined, doses between 1–5 mg/kg body weight per/day have been effective so far. Platelet antiaggregants are sometimes also used in patients with MMD (Moya Moya Disease). When the patient is a poor candidate for surgery or has a relatively mild disease clopidogrel may be an alternative treatment when long-term therapy with ASA is contraindicated or not tolerated. Clopidogrel should not

be used in combination with ASA in patients with multiple risk factors for intracranial hemorrhage and intracranial vasculopathies [36].

Long-term anticoagulation with heparin or warfarin may be indicated in patients with congenital or acquired heart disease, arterial dissection, selected hypercoagulable states, or recurrence of AIS despite ASA treatment. Some probable risk factors are modifiable [37]. Hyperhomocysteinemia may respond to supplements of folate, vitamin B6, and vitamin B12. Patients with lipid abnormalities can be managed with weight control, dietary modifications, and/or drug therapy. Patients with known inflammatory disorders or lupus should receive disease-specific treatment [28, 38].

In this study, we presented our experience in the etiology, risk factors, prophylactic and acute treatment, and the effect of treatment on recurrence rate in patients who had been treated for stroke at Pediatric Neurology Department of Ankara University for 18 years.

2. Methods

The study was designed on retrospective data. The population included 108 patients who had been treated for stroke at Pediatric Neurology Department of Ankara University with the diagnosis of arterial ischemic stroke between January 1992 and August 2010, and who were younger than 18 years at the time of the stroke. Forty-one girls (38%) and 67 boys (62 %) with mean symptom age of 3.1 ± 4.04 years (0–18 years old) were followed up in our institution for a mean period of 4.9 ± 3.78 years (0–17 years).

The definition of stroke included the presence of an acute thrombotic cerebrovascular event that manifested as hemiplegia, aphasia, visual or balance disturbance, or seizures. In all patients, the clinical diagnosis of ischemic stroke was confirmed with CT, MRI, and magnetic resonance angiography. Only pediatric stroke cases objectively confirmed by suitable imaging methods were included. Written informed consent was obtained from the parents of all patients.

Inclusion criteria were

(1) age 0 days through 18 years,

(2) sudden-onset focal neurological deficit, convulsion and loss of consciousness,

(3) neuroimaging (CT, MRI) demonstrating recent ischemia/infarct of arterial or venous distribution,

(4) cerebral/cervical arterial stenosis demonstrated on MR angiography using a 1.5- or 3-T magnet, CT angiography, or conventional angiography.

All patients underwent echocardiography and hematologic investigation (PT, PTT, fibrinogen, protein C, protein S, antithrombin III, lipoprotein(a), factor VIIIC, factor IX, homocysteine, and prothrombotic gene mutations (FV G1691A, PT G20210A, MTHFR C677T)).

The study was approved by the Ankara University Local Ethics Committee, and informed consent for all blood samples was obtained from parents of patients before the procedures. Blood samples were taken by peripheral venipuncture into plastic tubes without any additives and into plastic tubes containing 1/10 by volume of 3.8% trisodium citrate. After centrifugation, it is stored at −70°C. For genetic analysis, venous blood was obtained in EDTA-treated sample tubes. The FV G1691A, PT G20210A, and MTHFR C677T genotypes were determined by polymerase chain reaction and analysis of restriction fragments as previously reported [39].

F VIII and F IX were studied with one-stage clotting assay, and vWf was studied with immunoturbidimetric assay. Factor VIII and factor IX levels were accepted as high if the value was higher than the cutoff value of 150 IU/dl. Protein C and S were measured with commercially available enzyme-linked immunosorbent assay kits.

Lipoprotein A was studied by "particle enhanced" immunonephelometric assay; the reference range was 0–30 ng/mL. For homocysteine, after 12 hours fasting, blood specimens with EDTA were drawn and measured using AxSYM homocystein assay(Abbot, Wiesbaden, Germany).

Table 1: Initial symptoms.

Initial Symptom	*n*/total	Percent (%)
hemiparesis or hemiplegoia	70/108	64.8
seizures	37/108	34.2
cranial nerve involvement	2/108	1.8
Postoperative period	1/108	0.9
Headache	5/108	4.6
Fever	3/108	2.7
Intracranial hypertension	3/108	2.7
Dystonia	2/108	1.8
Altered state of consciousness	2/108	1.8

3. Statistical Analysis

Statistical analysis of the study was performed using Statistical Package for Social Sciences (SPSS/PC 13.00). The data are presented as the mean ± standard deviation (SD). All categorical data were analyzed with a Chisquare test or Fisher's exact test. A P value of equal to, or less than.05, was considered to indicate statistical significance.

4. Results

Hemiparesis or hemiplegia occurred in 54 (50%), hemiparesis and seizure in 12 (13%), hemiparesis and cranial nerve involvement in 2 (1.9%), and seizures in 23 (21.3%) patients. Five patients presented with headache. Initial symptoms are shown in Table 1.

The overall distribution of prothrombotic risk factors and underlying clinical diagnosis are shown in Table 2.

Eleven patients received acute treatment: 7/93 acute arterial ischemic stroke, 2/8 sinovenous thrombosis, and 2/7 hemorrhagic stroke received acute treatment. Table 3 shows the drugs that were used in acute treatment.

Table 2: Prothrombotic risk factors and underlying clinical diagnosis.

	Cholesterol°	Triglyceride°	High-CRP	Fibrinogen°	Homocysteine°	Lipoprotein A°	Factor VIIIμ	Factor IXμ	Protein Sα	Protein Cα	Antithrombin IIIα	APCR	Factor V Leidenβ	MTHFRβ	Prothrombinβ	Total
Idiopathic	2	3	1	—	4	5	11	5	7	5	1	7	6	9	2	59
Encephalitis	—	—	—	1	1	1	5	—	—	1	—	—	1	—	1	9
Malignancy	—	—	—	—	2	1	3	—	1	—	—	—	1	1	—	4
Trauma	—	—	—	—	—	—	—	—	—	1	—	1	1	—	—	2
Congenital heart disease	—	—	—	—	3	1	4	3	1	5	1	1	—	2	—	9
Hypernatremic dehydration	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1	3
Moya Moya disease	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	3
Perinatal hypoxia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Antiphospholipid antibody	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Undergone varicella	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	2
Isolated glucocorticoid	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Congenital adrenal hyperplasia	—	—	—	—	1	1	1	1	1	1	—	—	1	1	—	3
Arterio-venous malformation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Cyclosporin toxicity	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Purulent meningitis	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2
Phenylketonuria	—	—	—	—	—	1	1	—	—	1	—	—	—	—	—	1
Rheumatic heart disease	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Thalassemia major and BMT*	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	1
Behçet's disease	—	—	—	2	1	1	1	—	—	—	—	1	—	—	—	2
Late-onset hemorrhagic disease of newborn	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Megaloblastic anemia	—	—	—	1	1	—	1	—	—	—	—	—	1	1	—	1
Total								—								108

*= bone marrow transplantation, °=hyper, μ=increased, α=deficiency, β=mutation.

Table 3: The medication in acute treatment.

Medication	Acute ischemic stroke *n*(%)	Sinovenous thrombosis *n* (%)	Hemorrhagic stroke *n* (%)
Unfractionated heparin	4 (%4.3)	2 (%25)	—
TPA* + Unfractionated Heparin	2 (%2.2)	—	—
Warfarin	1 (%1.1)	—	—
K-Vitamin	—	—	2 (%28.6)

* =Tissue plasminogen activator.

Table 4: Medication in prophylaxis.

Medication	Acute ischemic stroke *n*(%)	Sinovenous-thrombosis *n*(%)	Hemorrhagic stroke *n*(%)
Aspirin	7 (%7.5)	2 (%25)	—
LMWH*	6 (%6.5)	1 (12.5)	—
Warfarin	1 (%1.1)	—	—

* = low molecular weight heparin.

A total of 7 patients died during the followup: 2 patients died from congenital heart disease (one was receiving aspirin and the other one was receiving LMWH as prophylactic treatment); one patient with antiphospholipid antibody syndrome died at the fourth ischemic stroke attack despite of anticoagulant therapy; the other 4 patients, who were not receiving prophylactic treatment, died from lymphoma, leukemia, encephalitis, and congenital heart disease.

17 patients received prophylaxis: 9 patients aspirin, 7 patients LMWH, and 1 patient coumadin. Table 4 shows the patients on prophylaxis treatment and outcome. Prophylaxis is given to patients especially with congenital heart disease and to children who is carrying prothrombotic risk factors. Table 5 gives the summary of risk factors. Ninetytwo (85%) patients did not received prophylactic treatment. Except from the antiplatelet therapy, 4 patients had folate supplementation for hyperhomocysteinemia.

During the follow-up period (mean, 4.9 ± 3.78 years; range, 0–17 years), recurrence was seen in 4 patients (4.3%). Apart from one patient who died at the fourth ischemic stroke attack (under anticoagulant therapy), one patient with moya moya disease, who had been recruited at the time of the second recurrence, received no prophylactic treatment during the followup and had no other recurrence. Recurrence was observed in another patient with elevated lipoprotein A. However, the patient did not attend the followup. The fourth patient who had recurrence had Thalassemia major and had bone marrow transplantation from his father and his MTHFR mutation was heterozygote. He had no recurrence after prophylaxis.

Table 5 shows prothrombotic risk factors of patients who received prophylaxis; 7 patients had elevated homocysteine, 5 had factor VIII elevation, 4 had MTHFR homozygote mutation, 2 had factor V leiden mutation, 3 had protein C deficiency, and 2 had protein S deficiency.

Table 6 shows the patients on prophylaxis and the outcome of these patients. Prophylaxis is given to patients especially with congenital heart disease and to children who had ongoing underlying prothrombotic tendency like antiphospholipid antibody syndrome and renal transplantation and to the patient who is carrying 6 prothrombotic risk factors. Ninetyone out of 108 (84.3 %) patient did not received prophylactic treatment. Except from the antiplatelet therapy, 4 patients had folate supplementation for hyperhomocysteinemia.

As a result, recurrence was seen in one patient in the group of 17 patients with prophylaxis and no patient had recurrence in the group of 91 patients without prophylaxis. Intracranial bleeding occured in one patient in the prophylaxis group due to aspirin (2 mg/kg/day).

As we can see in Table 7, 30 patients had no risk factors, 34 patients had only one risk factor, and 44 patients had multiple risk factors. Recurrence was seen in three patients; one without any risk factor, one with only one risk factor, and the other patient with multiple risk factors. There was not any statistical correlation between the recurrence of stroke and the existence risk factors ($P = .961$). Seventeen patients received prophylactic treatment: 2 without any risk factors (patients with rheumatic heart disease and antiphospholipid antibody syndrome), 3 had one risk factor, 12 patients had multiple risk factors. The majority of patients who received prophylactic treatment had multiple risk factors (There is statistical correlation. $P = .024$).

5. Discussion

Given the absence of data from randomized controlled trials, it is important to acknowledge the rather flimsy evidence, which is mainly dependent on consensus. This evidence base can be improved by prospective randomized controlled trials in paediatric stroke. There are various obstacles to this lofty aim, one being the low occurrence of childhood stroke and the need for a large population base in order to provide a sufficient sample size for case-control studies or for trials of interventions predicted to have a small benefit. Another challenge is the wide heterogeneity of childhood stroke aetiologies compared with most adult strokes, in which one overriding mechanism, atherosclerosis, predominates. The patients aetiologies, followed in our clinic, were similar to the literature except sickle cell disease [40, 41].

Table 5: The risk factors and prothrombotic risk factors of patients who received prophylaxis.

Risk Factors	Cholesterol	Triglyceride	High-CRP	Fibrinogen	Homocysteine	Lipoprotein A	Factor VIII	Factor IX	Protein S	Protein C	Antithrombin III	APCR	Factor V Leiden	MTHFR	Prothrombin 20210	Total
Protein S deficiency	—	1	—	—	—	—	1	—	3	—	—	—	1	—	—	3
Congenital heart disease	—	—	—	—	3	1	3	2	—	3	1	—	—	1	—	5
Moyamoya disease	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	1
Undergone varicella	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Cyclosporin toxicity	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	1
Rheumatic heart disease	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Thalassemia major-BMT°	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	1
other*	—	—	—	1	2	1	2	1	—	—	—	1	2	3	—	4
Total								—								17

*One of the patients had heterozygous factor V Leiden mutation, one had MTHFR homozygote mutation, one had antiphospholipid antibody syndrome, and the other patient had megaloblastic anemia with MTHFR heterozygote mutation. °bone marrow transplantation.

Table 6: Patients who received prophylaxis and outcome.

Basic disease	Anticoagulant therapy	Prothrombotic risk factors	Outcome
Congenital adrenal hyperplasia	Aspirin	FV Leiden gene mutation in heterozygous form, MTHFR gene 677 TT homozygous mutation, elevated FVIII, FIX homocystein, and lipoprotein(a)	Intracranial bleeding was diagnosed and the aspirin prophylaxis was ceased and no recurrence was observed during the follow-up period
Antiphospholipid antibody syndrome	Coumadin, LMWH	FV Leiden gene mutation, elevated FIX	Died at the fourth ischemic stroke attack
Congenital heart disease	Aspirin	Elevated FVIII, FIX homocystein, and lipoprotein(a)	No recurrence
B12 deficiency-related megaloblastic anemia	Aspirin	FV Leiden gene mutation MTHFR gene 677 TT mutation, elevated F VIII, and homocystein	No recurrence
Congenital heart disease	Aspirin	MTHFR gene 677 TT mutation, elevated F VIII, and homocystein	No recurrence
Protein S deficiency-related sinus venous thrombosis	LWMH	Protein S deficiency, elevated triglyceride	No recurrence
Congenital heart disease	Aspirin		No recurrence
Moyamoya	Aspirin	MTHFR gene 677 TT homozygous mutation, elevated homocystein	No recurrence
Protein S deficiency related sinus venous thrombosis	LMWH	Protein S deficiency, elevated F VIII	No recurrence
İdiopathic	LMWH	MTHFR gene 677 TT homozygous mutation, activated protein C resistance	No recurrence
Receiving cyclosporine for renal transplantation	LMWH		No recurrence
Bone marrow transplantation for beta thalassemia major	LMWH	MTHFR gene 677 TT homozygous mutation, elevated homocystein	Recurrence*
İdiopathic	Aspirin	MTHFR gene 677 TT mutation	No recurrence
Congenital heart disease	Aspirin	Protein C deficiency	Died from congenital heart disease
Congenital heart disease	LMWH	Elevated homocystein, protein C, and AT III deficiency	Died from congenital heart disease
Rheumatismal heart disease related prosthetic valve	Coumadin		No recurrence
Down syndrome and congenital heart disease	Coumadin	Elevated homocystein, FVIII, FIX	No recurrence

*prophylaxis was given after recurrence.

Table 7: Recurrence and risk factor relation.

Risk factor	No. of recurrences	recurrence	Total
None	29	1	30
One risk factor	33	1	34
multiple risk factors	43	1	44
Total	105	3	108

Aetiologies can predict treatment effect to a large extent; hence, subgroups of more homogenous patients will need to be studied in some cases. An important issue is the difficulty in recognizing vascular pathologies in children with diverse presentations, such as coma, seizures, and hemiparesis. One of the most effective interventions to improve outcomes in adults who had stroke is the reorganization of services into specialist stroke units. However, the small number of patients with stroke in most paediatric centres creates a challenge for building up such specialized units [42].

As acute treatment recommendations in the guidelines are restricted, 11 patients received acute treatment: 7/93 acute ischemic infarct, 2/8 sinovenous thrombosis, and 2/7 hemorrhagic stroke received acute treatment. Only one patient with antiphospholipid antibody syndrome died at the fourth ischemic stroke attack despite of anticoagulant therapy.

The role of antiplatelet therapy is well established in adult arteriovascular disease. The prevalence of these diseases has prompted the search for "a Better aspirin", and new targets for antiplatelet therapy are being actively sought.

Currently, the use of antiplatelet therapy in paediatric disease is significantly limited.

Neonates with AIS do not require routine antithrombotic treatment because they have a negligible risk of recurrence. However, in older infants and children with AIS, long-term therapy with ASA is needed to prevent recurrent TIAs and strokes, which occur in 7 to 20% of patients. In children with cardiogenic AIS, dissection, high-grade stenosis of a cerebral artery, severe prothrombotic conditions, or failure of ASA therapy in preventing recurrence, LMWH, or coumadin is frequently continued for several months. The risk of recurrent cerebral thrombotic events must be balanced against the risks of treatment, particularly bleeding risk. Thrombolytic agents carry an unknown but potentially very significant risk of hemorrhage in children with AIS, and should only be used in the setting of a clinical trial until safety and feasibility data are available. And in our study Intracranial bleeding was occured in one patient in the prophylaxis group due to aspirin.

Related literature (Lynch, Fullerton, Lanthier, and others) points to a varying rate of stroke recurrence which is between 26% and 30%, particularly during the first 6 months after stroke and is higher among children with identified risk factors [21, 22, 43]. While following our patients, we utilize the guidelines and the majority of the patients who received prophylactic treatment had multiple risk factors [37]. We had seen 3 recurrences, one without any risk factor. There has not been any recurrence in the group of patients who received prophylactic medication since we always consider to provide prophylaxis for eligible patients. However, the physicians who are following stroke in pediatric age must pay attention to the stroke patients who had no risk factors for recurrence.

Long-term followup for children is better than for adults. Most of our patients achieved an age-appropriate independency. The use of antithrombotic therapy appears to be increasing in pediatric AIS, as almost all children were independent at followup.

6. Conclusion

Stroke among children is a rare disease. However, significant morbidity and mortality have been identified. Stroke should be included in the differential diagnosis of any child presenting new-onset focal deficits, altered speech, or disequilibrium and be thoroughly investigated. Advanced imaging techniques have improved the diagnosis and understanding of paediatric stroke. Studies to determine the optimal acute treatment of childhood stroke and secondary prevention and risk factor modification are of critical importance and urgently needed. Until prospective randomized data on chronic anticoagulation in pediatric patients are available, pediatric patients should be treated on an individual basis.

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Review Article

Pediatric Stroke: Clinical Findings and Radiological Approach

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This paper focuses on radiological approach in pediatric stroke including both ischemic stroke (Arterial Ischemic Stroke and Cerebral Sinovenous Thrombosis) and hemorrhagic stroke. Etiopathology and main clinical findings are examined as well. Magnetic Resonance Imaging could be considered as the first-choice diagnostic exam, offering a complete diagnostic set of information both in the discrimination between ischemic/hemorrhagic stroke and in the identification of underlying causes. In addition, Magnetic Resonance vascular techniques supply further information about cerebral arterial and venous circulation. Computed Tomography, for its limits and radiation exposure, should be used only when Magnetic Resonance is not available and on unstable patients.

1. Introduction

Pediatric stroke (PS) is a relatively rare disease, having an estimated incidence of 2.5–13/100,000/year [1–4], but remains one of the most common causes of death in childhood, with a mortality rate of 0.6/100,000 dead/year [5, 6]. PS has also seriously high morbidity and long-term outcome and is nowadays gaining more interest because of its heavy consequences and costs, both personal and social. Indeed, about half of the surviving patients develop some neurologic or cognitive impairment, and just more than a quarter, epilepsy.

As in adults, PS can be ischemic or hemorrhagic; although ischemic stroke is more common, prevalence is variable [7, 8]. Ischemic stroke includes Arterial Ischemic Stroke (AIS) and Cerebral Sinovenous Thrombosis (CSVT); Hemorrhagic Stroke (HS) includes intracerebral and subarachnoid haemorrhage [9].

AIS, both in neonatal and childhood forms, has a higher incidence among males [5, 10–14] and black people [5, 7]. AIS is relapsing in 6%–37% of little patients [15–19] and the risk appears highest in the first 6 months after the first episode [19, 20]. Risk factors for relapse include vascular abnormalities as first stroke cause [19, 20], and the presence of thrombotic risk factors [20], either isolated or as part of multiple risk factors [20, 21].

CSVT has an incidence of 2.6/100,000 children/year in the neonatal period and of 0.4 and 0.7/100,000 children/year in childhood [22].

The incidence of hemorrhagic stroke (HS) is estimated between 0.7 to 5.1/100,000 children/year [23, 24] and, similar to childhood AIS, is more common in males and blacks [11, 25]. The mean age at diagnosis is 6–10 years [1].

A prompt and precise diagnosis of PS, associated to an effective management of vascular emergencies, is a crucial point to reach a correct therapy and, consequently, a positive outcome.

This paper will focus on main clinical features and radiological diagnosis of pediatric stroke.

2. Cause and Pathophysiology

2.1. Ischemic Stroke

2.1.1. Arterial Ischemic Stroke

AIS is defined as ischemia, infarction, or encephalomalacia in a vascular arterial distribution territory [5].

Classification of AIS has always been object of debate thus leading to the development of different systems. The need to subclassify patients with AIS arises from several reasons. In fact, prognosis, risk of recurrence, etiological factors, and choices of management differ between the subtypes. AIS can be divided into subgroups according to PSC (Pediatric Stroke Classification) proposed by Wraige et al. [26]. This classification is based on main etiopathological differences between pediatric and adult stroke and derives from the TOAST one, used for adult stroke [27]. PSC includes eight subtypes of AIS: (1) sickle cell disease, (2) cardioembolic, (3) Moya-Moya Syndrome, (4) cervical arterial dissection, (5) steno-occlusive cerebral arteriopathy, (6) other determined etiology, (7) multiple probable/possible etiologies, and (8) undetermined etiology.

Pediatric AIS shares with adult AIS an embolic or in situ thrombosis ground but, unlike adult stroke, degenerative vascular and chronic degenerative diseases (e.g., atherosclerosis) have very little role in its genesis. Most frequently reported risk factors for pediatric AIS are congenital or acquired heart diseases, hematologic and metabolic disorders, and vascular disorders and infections [21, 28]. Nevertheless, approximately one half of pediatric AIS occurs in children with unknown risk factors [29].

Predisposing factors for AIS are summarized in Table 1.

Vasculopathies such as Transient Cerebral Arteriopathy (TCA), arterial dissection, fibromuscular dysplasia, and Moya-Moya Disease (MMD) have been identified in 18%–80% of children with AIS [19]. Congenital heart disease is reported in association with large vessel dissection or MMD [30, 31].

The most common arteriopathy associated with pediatric stroke is TCA. This is a monophasic arterial disease characterized by a unilateral focal or segmental stenosis, which involves the distal part of the internal carotid and the initial segments and branches of the anterior and/or middle cerebral artery, and is followed by complete or partial resolution [32].

The pathophysiology of TCA is uncertain but in 44% is associated with Post-Varicella Arteriopathy (PVA), an acute vasculitis caused by varicella virus infection of the arterial wall. In this cases a varicella zoster infection is identified in the 12 months prior to AIS [33, 34].

Other infectious agents, which are frequently responsible for TCA, are Parvovirus B19, CMV, Mycoplasma pneumoniae, Borrelia burgdorferi, Enterovirus, HIV, and Helicobacter pylori.

Furthermore, some patients with TCA present angiograms compatible with arterial dissections [22, 35].

MMD is a progressive bilateral stenosis of Willis circle arteries, which usually causes vascular insufficiency or repeated ischemic episodes, despite the development of collateral blood flow [36]. It can be primary or secondary to underlying disorders, in which case it is known as Moya-Moya Syndrome.

Primary or idiopathic MMD accounts for 12% of AIS cases [37].

The most common hematologic risk factor of stroke is Sickle Cell Disease (SCD). In this disease hemoglobin, in a deoxygenated environment, acquires higher density making red blood cells susceptible to sickle. SCD has a lot of neurologic complication, among them cerebral infarction is the most common. The stroke pathophysiology in SCD may be a combination of chronic haemolytic anemia and vaso-occlusion [38]. Indeed, chronic hemolysis leads to anemia and subsequently to tissue hypoxia; anemia determines increased stress and red cell adhesion to endothelial cells with consequent injury. Damaged endothelial cells suffer alterations, including intimal hyperplasia and prothrombotic/proadhesive events. On the other hand, vaso-occlusion decreases blood flow, leading to tissue ischemia and infarction.

Alterations in vasoregulation generate a cascade precipitating acute cerebrovascular events [39].

Prothrombotic disorders such as protein C and protein S deficiency, antithrombin III deficiency, factor V Leiden mutation, factor XII deficiency, factor VIII deficiency, prothrombin 20210A mutations, and antiphospholipid antibodies have been found in approximately one third of children with AIS [40, 41].

Congenital metabolism errors such as Fabry disease, homocystinuria, organic acid disorders, ornithine transcarbamylase deficiency, and carbohydrate-deficiency glycoprotein syndrome are also well-established risk factors of children AIS [42].

Another important cause of pediatric stroke is substance abuse, especially in teenage patients. Drugs such as amphetamines, ecstasy, cocaine, and inhalants (such as glue sniffing) have been shown to be a risk for stroke from both cerebral infarct and hemorrhage. The use of marijuana has been reported as a cause of strokes with cerebellar infarction among adolescents [43]. Strokes related to these substances are thought to be caused by toxic vasculitis, transient cerebral vasoconstriction, prothrombotic effects, and exacerbation of previously unrecognized cardiovascular disease [23, 44]. The risk of stroke has been placed as high as 6.5 per 100,000 per year in young adult drug abusers [45].

2.1.2. Cerebral Sinovenous Thrombosis. Thrombosis within the venous system results in outflow obstruction with subsequent venous congestion and persistent increase in capillary hydrostatic pressure, which drives fluid into interstitium producing edema. An increased hydrostatic pressure reduces also arterial inflow with subsequent ischemia [22].

The brain injury spectrum in CSVT varies from venous congestion to parenchymal ischemic injury, which may be cortical, subcortical, or involving deep gray matter.

Most of the parenchymal infarcts are hemorrhagic but CSVT can also lead to subarachnoid/subdural hemorrhage.

In preterm and term neonates there is also an association between CSVT and intraventricular hemorrhage (IVH) [22, 46]. Indeed, several studies demonstrate that CSVT is the most frequently identified cause of symptomatic IVH, and is associated, in term neonates, with basal ganglia or thalamic hemorrhage.

Table 1: Risk factors and causes of Arterial Ischemic Stroke.

Cardiac
(1) Congenital
(a) Dysrhythmias
(b) Congenital heart disease
(c) Cardiomyopathy
(d) Cardiac tumours
(2) Acquired
(a) Cardiomyopathy
(b) Carditis
(c) Arrhythmias
(d) Artificial valves
(e) Endocarditis
(3) Iatrogenic
(a) Cardiac catheterization
(b) Cardiac surgery/cardiopulmonary bypass
(c) Carotid ligation
Hematologic
(1) Hemoglobinopathies
(a) Sickle Cell Disease
(b) Thalassemia
(2) Thrombophilia
(a) Primary
(b) Secondary
(3) Iron deficiency anemia
(4) Thrombocytopenia
Infectious
(1) Meningitis
(a) Viral, bacterial, fungal
(b) Encephalitis
Vasculitis
(1) Primary
(a) Primary angiitis of CNS
(2) Secondary
(a) Post-infectious
(i) Varicella
(ii) Other
(b) Infectious
(i) Encephalitis
(ii) Meningitis
(c) Associated with collagen vascular disease or systemic vasculitides

Table 1: Continued.

Other vasculopathies
(1) Transient/focal cerebral arteriopathy
(2) Down syndrome
(3) Fabry disease
(4) NF1
(5) PHACE syndrome
(6) Sickle Cell Disease
(7) Moya-Moya Disease (primary)
(8) Moya-Moya Syndrome (secondary)
(a) Down syndrome
(b) NF1
(c) SCD
(d) William syndrome
(e) Post-irradiation
(9) Fibromuscular dysplasia
(10) Vasospasm
(a) Migraine
(b) Other
(11) Dissection
Other
(1) Trauma
(a) Dissection
(b) Fat/air embolism
(2) Toxins/Drugs
(a) Cocaine
(b) L-asparaginase
(c) Oral contraceptives
(3) Metabolic
(a) Shock/dehydration
(b) Carbohydrate deficient glycoprotein syndrome
(c) Homocysteinuria

Deep venous thrombosis can be accompanied by haemorrhage into the ventricles, as a result of blockage, and hypertension in the deep venous drainage system [47].

Presumed perinatal ischemic stroke is a subgroup of perinatal stroke and encompasses imaging-confirmed focal infarction, which may be venous or arterial, presenting after the neonatal period [48].

Perinatal Venous Infarction (PVI) is one of these periventricular infarction syndromes and is an underrecognized cause of congenital hemiplegia [29, 35].

Risk factors and causes of CSVT are summarized in Table 2.

2.2. Hemorrhagic Stroke. Most nontraumatic hemorrhagic strokes are intracerebral hemorrhages, which may also

Table 2: Risk factors and causes of CSVT.

(1) General
(a) Dehydration
(b) Infection
(c) Fever
(d) Hypoxic-ischemic injury
(e) Post lumbar puncture
(2) Head and neck infections
(a) Otitis media and mastoiditis
(b) Meningitis
(c) Sinusitis
(d) Upper respiratory tract infection
(3) Other head and neck disorders
(a) Head injury
(b) Post intracranial surgery
(c) Hydrocephalus (±ventriculoperitoneal shunt)
(4) Anemia
(a) Iron deficiency
(b) Sickle cell disease
(c) Thalassemia
(d) Autoimmune hemolytic anemia
(e) Paroxysmal nocturnal hemoglobinuria
(5) Autoimmune disorders
(a) Behçet disease
(b) Systemic lupus erythematosus
(c) Antiphospholipid antibody syndrome
(d) Inflammatory bowel disease (ulcerative colitis, Crohn disease)
(e) Thyrotoxicosis
(f) Cushing syndrome
(g) Idiopathic thrombocytopenic purpura
(6) Malignancy
(a) Leukemia
(b) Lymphoma
(c) Central nervous system tumors
(7) Cardiac disease
(a) Cyanotic congenital heart disease
(b) Post-operative
(c) Postcatheterization
(8) Renal disease
(a) Nephrotic syndrome
(b) Hemolytic-uremic syndrome
(9) Drugs
(a) L-Asparaginase
(b) Oral contraceptives
(c) Corticosteroids
(d) Epoetin-α
(10) Chromosomal disorders
(a) Down syndrome
(11) Metabolic conditions
(a) Diabetic ketoacidosis
(b) Homocystinuria

Table 3: Risk factors and causes of Hemorrhagic Stroke.

Genetic vasculopathy
(1) Arteriovascular malformation
(2) Intracranial aneurysm
(3) Cavernous angioma
(4) Neurocutaneous disorders
(5) Ehlers-Danlos syndrome
(6) Moya-Moya Syndrome
(7) Fibromuscular dysplasia
(8) Fabry disease
Hematologic disorders
(1) Hemoglobinopathy
(2) Platelet disorders
(3) Coagulopathy
(4) Hypofibrinogenemia
Trauma
Hypertension
(1) Congenital adrenal hyperplasia
(2) Stimulant drug use
(3) Coarctation of aorta

originate in or extend into the intraventricular, subdural, or subarachnoid space [43, 44].

Risk factors and causes of HS are summarized in Table 3.

Studies about children with HS show that first cause is vascular malformations, which are responsible of 5%–29% of cerebral hemorrhages, whereas other causes are hematological disorders, such as thrombocytopenia or hemophilia, and neoplasms [43, 44].

The most common vascular malformations are arteriovenous malformations (AVMs), aneurysms, and cavernous malformations [43, 44]. Aneurysms and hypertension, although commonly associated with adult HS, are an infrequent cause in children [45].

Most AVMs are diagnosed in patients between 20 and 40 years, but about 18% to 20% will become symptomatic during childhood [44, 49]. In a series of 37 children with AVMs, 70% presented with HS; the annual risk of HS in children with an AVM is 3.2%, and the risk of recurrent relapsing is 6%–33% in the first year after the initial bleed [50, 51].

The incidence of intracranial aneurysms in children is about 1 per million per year, substantially less than the adult rate [43, 44]. About 1% to 2% of aneurysms will become symptomatic in childhood, mainly with HS.

3. Clinical Presentation

The clinical presentation of AIS is extremely various, depending on age, cause, and involved vascular territory [9, 23]. Usually, embolic stroke tends to present suddenly, whereas thrombosis may have a more gradual onset [9, 23]. Focal neurologic deficits (cranial nerve palsies, hemiparesis, and hemisensory loss) are the most common presentation

of AIS in children. Seizures, headache, language and speech difficulties, and altered mental status are also possible [9, 52]. Stroke in the posterior circulation can present as ataxia, vertigo, and vomiting. In infancy, typical presentation includes seizure, lethargy, and/or apnea often without focal neurologic deficits [9]. Pediatric stroke can also impact behavioural and psychiatric functions.

The clinical presentation of HS depends on the child's age and the size and location of the hemorrhage. Main signs and symptoms include headache, vomiting, seizures, impaired consciousness, and/or focal neurologic deficits [44].

The clinical manifestations of CSVT are nonspecific, may be subtle and may overlap with predisposing conditions such as infection and dehydration. Seizures, altered levels of consciousness and encephalopathy, focal neurologic deficits and diffuse neurologic symptoms (headache, nausea, and vomiting) may result; presentation with pseudotumor cerebri and isolated headache has also been documented [22].

4. Radiological Diagnosis

Key points in the diagnosis of childhood stroke are causal investigation, laboratory tests, and imaging studies.

Radiological exam is often the first step in the evaluation of an acutely ill child.

The two imaging modalities to be used in emergency are Computed Tomography (CT) and/or Magnetic Resonance (MR).

Which is the first-choice imaging modality is still object of debate.

Our experience, derived from acute and followup observation of 41 patients, permits to consider MR imaging (MRI) as first-line emergency examination [4].

In fact MRI, especially with the integration of diffusion-weighted (DWI) and perfusion-weighted (PWI) imaging, is optimal for diagnosing stroke. DWI is the most sensitive tool in the diagnosis of cytotoxic edema, thus offering the unique possibility of diagnosing an acute ischemic stroke also in cases with apparently normal CT and MRI conventional sequences [4] (Figure 1). Moreover, perfusion imaging can offer a prognostic value: in acute stroke, in fact, it allows to determinate the volume of tissue at risk and the vascular distribution of the ischemia; the level of perfusion to the ischemic tissues may also help to determine the relative benefits and risks of a given therapy [53]. It is well known, in fact, that the perfusion/diffusion "mismatch" reflects the difference between the ischemic core and surrounding penumbra: the areas of DWI abnormalities with decreased ADC values are assumed to have suffered irreversible injury, by the time of patient examination; hence, an area of lowered PWI and normal DWI is an index of the penumbra, or tissue that has potentially reversible ischemia. These values had been recently considered as useful screening for systemic or intra-arterial thrombolysis approach in adulthood.

The role and the indications of intra-arterial thrombolysis in pediatric stroke has not been definitively assessed yet because a very few cases have been reported and clinical trials are in course. Anyway, as reported in literature, outcomes of children with stroke who underwent thrombolysis, suggest that this treatment may also be beneficial in pediatric population. Controlled randomized trials are needed in order to determine the appropriate dosage, safety, and efficacy of intra-arterial thrombolysis; feasibility of mechanical thrombolysis should be evaluated as well [54–57].

On the other hand, the use of MR angiography (MRA) allows the detection and location of intracerebral arterial lesions in a noninvasive way, although the characterization of the type of lesion is the main limit of MRA (circumferential clefts, intimal flaps, intraluminal thrombi, or tapering of middle cerebral artery branches) [58].

MR spectroscopy (MRS) and DWI with MRA could also, in selected cases, increase the sensitivity of MRI in the detection of ischemia and infarction [59]. According to English guidelines, cross-sectional brain imaging is mandatory in children presenting with clinical stroke, and brain MRI is recommended for investigation in these patients [25]. Brain MRI should be undertaken as soon as possible after presentation. If brain MRI will not be available within 48 hours, CT is an acceptable initial alternative [25]. Brain imaging should be undertaken urgently in children with clinical stroke who have a depressed level of consciousness at presentation or whose clinical status is deteriorating, in which case CT scanning should be used.

If the identified infarct has unusual features, more specific venous imaging investigations may then be applied by the radiologist as necessary. In the first instance, noninvasive options such as MR venography (MRV) or CT venography (CTV) are preferred over intra-arterial digital subtraction angiography (IADSA) [25].

MRI and MRV are actually the preferred methods for investigation of CSVT because of their sensitivity and specificity and for the excellent anatomical correlation between venous drainage system and location of parenchymal infarcts. DWI and PWI may play a role in detecting venous congestion in cerebral venous thrombosis and in the differentiation of cytotoxic and vasogenic edema, but do not differentiate venous from arterial infarction.

The diagnosis is established by demonstrating a lack of flow in the cerebral veins with or without typical images of brain infarction [22].

MRI and MRV allow to demonstrate both the infarct and the clot within the vessels. On MRI, the thrombus is easily recognizable in the subacute phase, when it appears hyperintense on T1-weighted images. In the acute phase, the thrombus is isointense with brain on T1-weighted images and hypointense on T2-weighted images. This appearance can be mistaken for flowing blood (Figure 2), but MRV will demonstrate an absence of flow in the thrombosed sinus. T2*-weighted images seems to be more sensitive than T1- or T2-weighted or Fluid Attenuated Inversion Recovery (FLAIR) images in demonstrating venous thrombosis and associated hemorrhage [60].

When MRI exam cannot be performed, unenhanced CT may detect deep venous thrombosis as linear densities in the expected locations of the deep and cortical veins. As the thrombus becomes less dense, contrast may demonstrate the "empty delta" sign, a filling defect, in the posterior part of

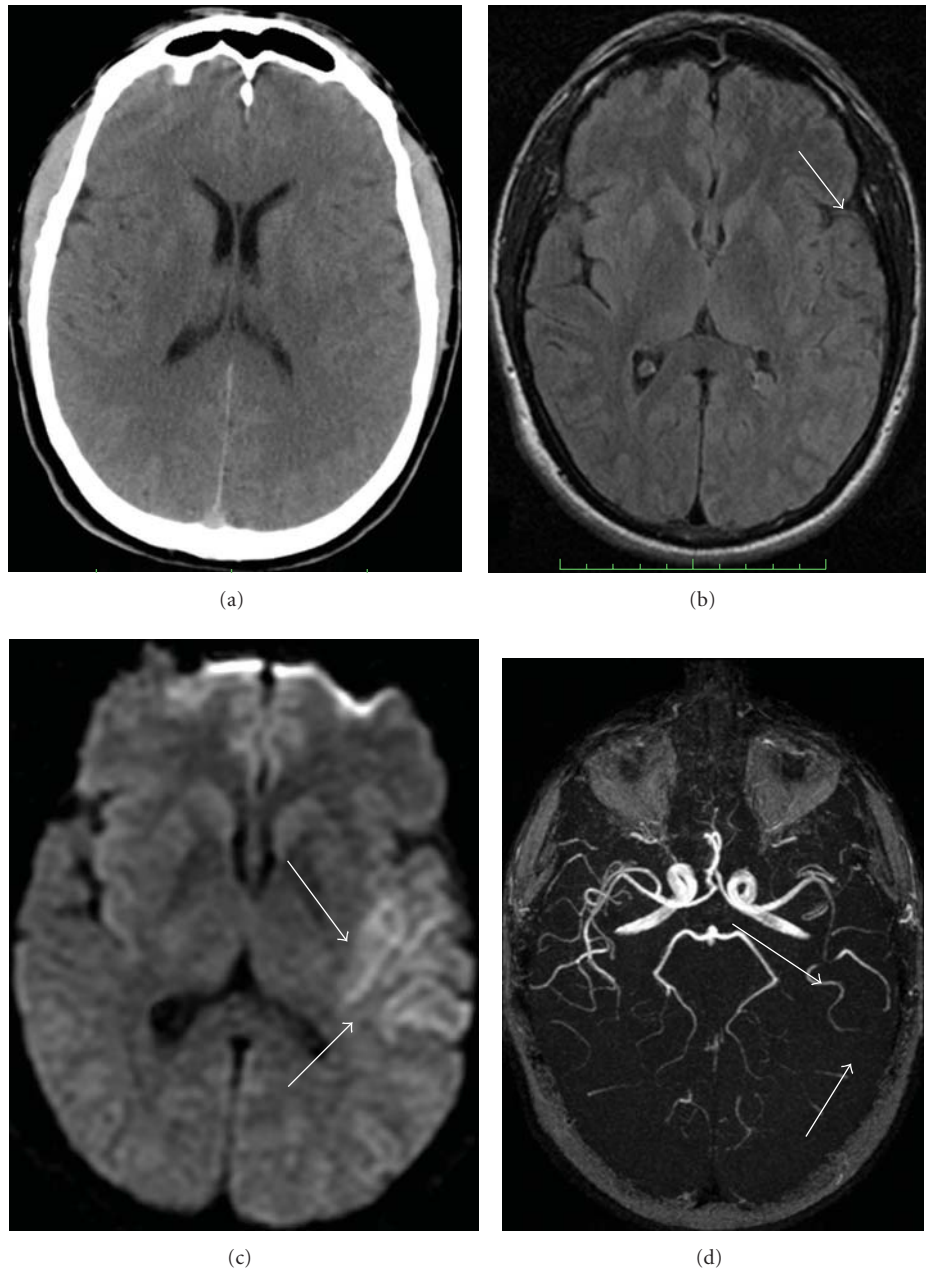


Figure 1: A 14-year-old male with right-sided hemiparesis started 3 hours before MRI. (a) Plain CT scan does not show significant density abnormality. (b) MRI T2-weighted Fluid Attenuated Inversion Recovery image does not show significant signal intensity abnormality of cerebral parenchyma even if hyperintensities of distal branches of middle cerebral artery are visible and suggest vessel occlusion (arrow). (c) MRI Diffusion-weighted image shows bright signal of left insular and temporal cortex indicating cytotoxic edema (arrows). (d) 3D-Time of Flight MR-angiogram shows poor representation of distal branches of left middle cerebral artery (arrows).

the sagittal sinus (Figure 2). However, CT scan with contrast misses the diagnosis of CSVT in up to 40% of patients [22] so CTV can be a reasonable in-depth examination.

In every case, imaging of the cervical and proximal intracranial arterial vasculature should be performed in all children with AIS and imaging of the cervical vasculature to exclude arterial dissection should be undertaken within 48 hours of presentation with AIS [25]. Transthoracic cardiac echocardiography should be undertaken within 48 hours after presentation in all children with AIS [25].

The limit usually attributed to MRI, related to the length of the examination, can be easily overcome by the use of dedicated "fast protocols".

Another limit classically attributed to MRI, is its presumed reduced sensitivity to acute bleeding, but different studies [4, 61] report that MR is always able to identify the acute bleeding and to distinguish spontaneous intracranial hematoma from the hemorrhagic transformation of ischemic stroke. Moreover, even when intracranial bleeding is diagnosed with CT, identification of the cause of

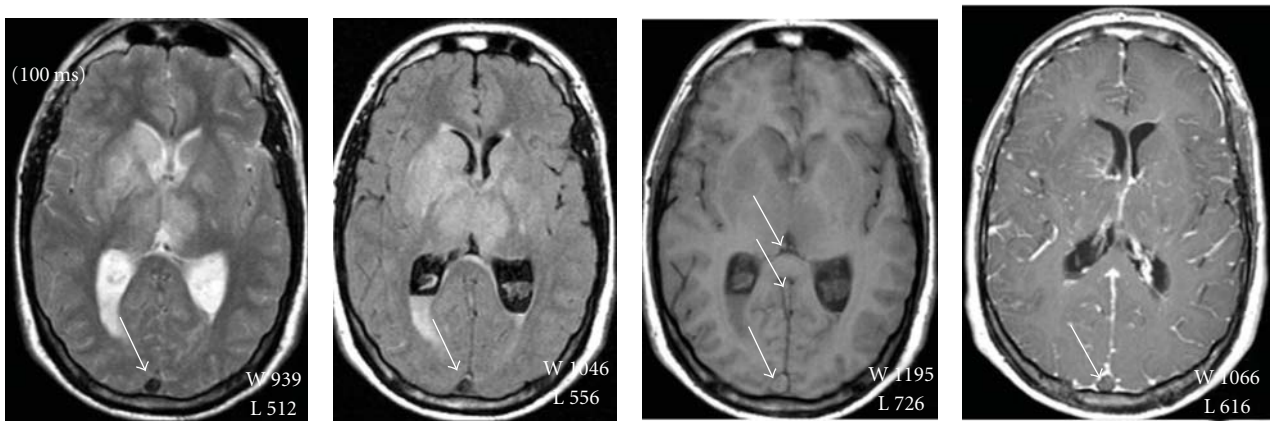


Figure 2: A 16-year-old female with progressively worsening headache, generalized seizures on the 4th day and coma on the 5th day. MRI exam was performed on the 5th day. MRI T2-weighted Turbo Spin Echo (a) and T2-weighted Fluid Attenuated Inversion Recovery images (b) show altered signal intensity involving bilaterally medial thalamus, lentiform nucleus, and caudate nucleus. Intraventricular bleeding is present and hemorrhagic infarct involving right frontoparietal junction (not shown) was also detected. Superior sagittal sinus and internal cerebral veins seem to have regular "flow void" signal (arrows), due to the dark signal of subacute thrombus. MRI T1-weighted images before (c) and after (d) administration of contrast agent better show occlusion of superior sagittal sinus, vein of Galen and internal cerebral veins (arrows). Visible advanced signs of venous stasis and the so-called "delta sign" (arrow) (d).

hemorrhage is often difficult without MR. In fact, MR is rapidly able to recognize the cause of the hemorrhage, and identify the presence of vascular malformations eligible to surgical or interventional treatment (Figures 3 and 4) [4].

The "real" limitation of MRI is probably the need for cooperative patients or for sedation. In most cases, anaesthesiological support, for both sedation and clinical monitoring, is required; CT, otherwise, is much faster and can be more easily performed even on unstable patients.

Considering that many pediatric patients are comatose or already under general sedation before being transferred to diagnostic imaging, MRI can be proposed as the first-choice examination even in the acute phase of a stroke [4]. Moreover, in selected cases where differential diagnosis includes nonischemic pathology, use of paramagnetic contrast agent can be used safely. CT should be performed only on uncooperative/unstable patients and when MRI is not available; after overcoming of the critical phase it is anyway recommended that MRI is performed in the immediate followup [4].

Moreover, even if CT is very sensitive and specific in the detection of hemorrhagic lesions, in the acute phase of cerebral infarction, parenchymal abnormalities may be subtle on CT, and early/small lesion(s) in the posterior fossa can be missed [9].

CT angiography (CTA) is a noninvasive method for evaluation of intra, and extracranial circulation. CTA performed in early stages of cerebral ischemia may provide crucial information regarding cerebral circulation [62]. Disadvantages of CTA include radiation exposure, use of intravenous contrast, and the difficulty in timing the contrast bolus in small children [9].

As mentioned before also MRI and MRA supply precise information regarding intra, and extracranial vascular lesions, especially in craniocervical arterial dissections. The presence on intramural hematoma can be assessed with cross-sectional T1-, T2-, and PD-weighted images while a global visualization of vessel structure can be obtained with MRA. Time-of-flight (TOF) MRA can demonstrate a T1 hyperintense intramural clot, whereas phase-contrast (PC) MRA and contrast-enhanced (CE) MRA demonstrate only the vessel lumen [63–65]. Diagnosis of cervical artery dissection with cross-sectional images depends on the characteristics of the intramural hematoma, surrounding structures and MR sequences. An optimal exam should include T1- and T2-weighted with and without fat suppression and PD-weighted sequences. Subacute hematoma appears on fat suppressed T1-weighted images as a crescent-shaped hyperintense area around an eccentric flow void corresponding to the vessel lumen. Acute dissection can be missed on fat suppressed T1-weighted images because isointense hematoma may be obscured when surrounded by isointense tissues [64, 65].

The gold standard for the definitive assessment of cerebral vasculature is IADSA which should be considered in children when pathology of small distal artery is suspected and with an unexplained infarct or hemorrhage not elucidated by MRI or MRA evaluation [66].

IADSA is used to diagnose MMD, showing bilateral stenosis of the internal carotid artery and the development of a collateral network (rete mirabile) with the appearance of the typical pattern known as "puff of smoke" (Figure 5), or in suspected dissection [9, 36]. MRI and MRA, and in some cases IADSA, should be repeated in cases of identified arteriopathies 3 to 6 months after the initial investigation, and again at 6 to 12 months in most patients, and at the appearance of any new clinical manifestations to evaluate for additional subclinical infarcts and progression or regression of previously identified vasculopathy [9, 67].

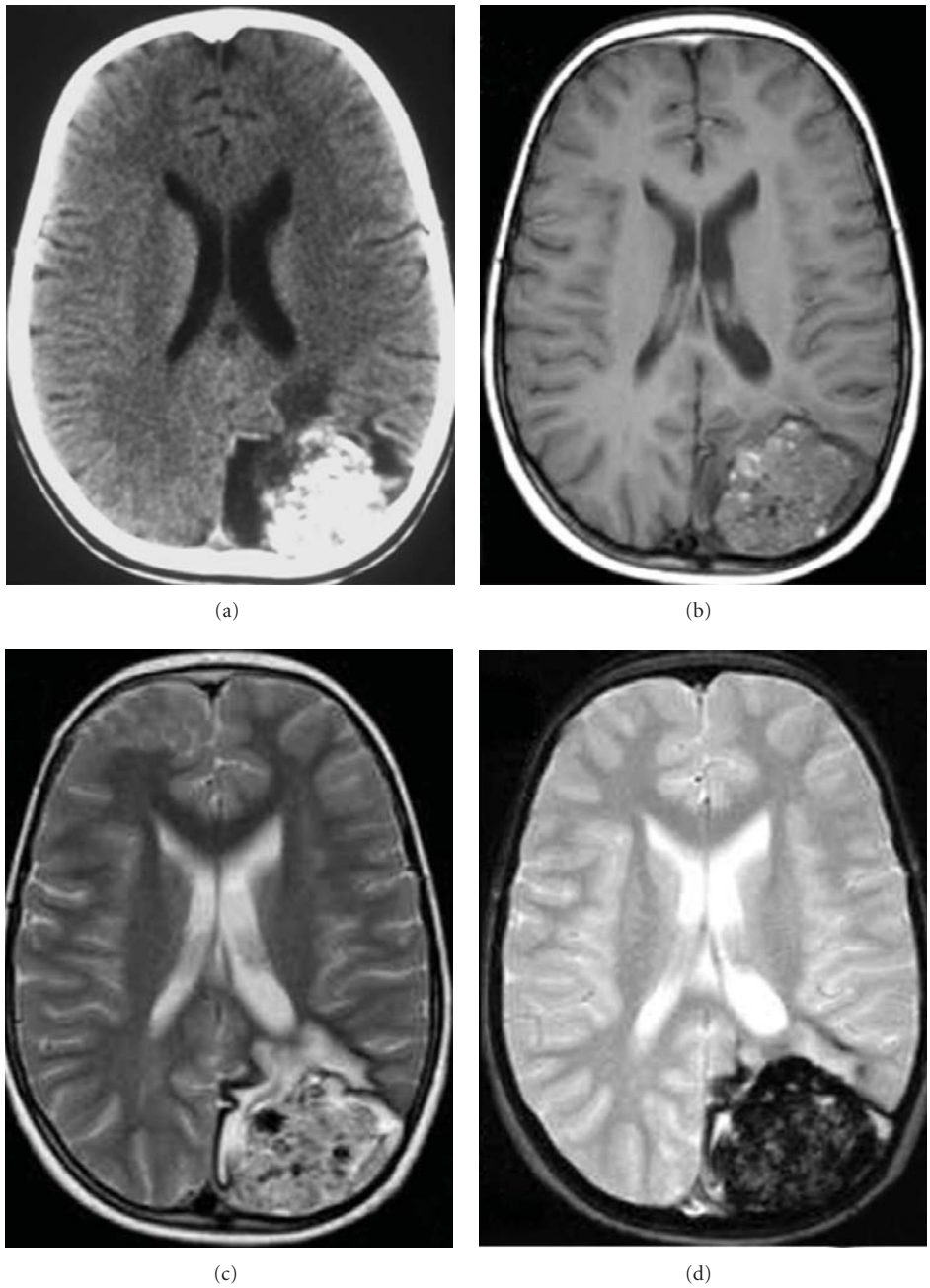
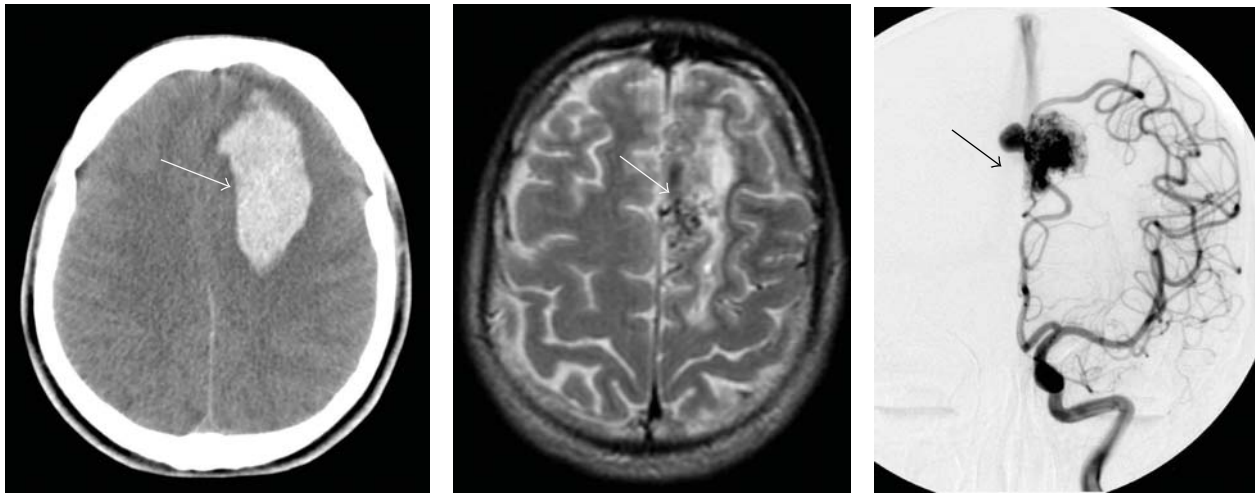


Figure 3: A 5-year-old male with sudden onset of visual defect followed by generalized seizures without previous hepileptic history. (a) Plain CT scan showing grossly calcified extracerebral occipital mass with loss of brain tissue. (b) MRI T1-weighted image shows typical "salt and pepper" mixed signal in the mass. (c) MRI T2-weighted Turbo Spin Echo image shows the same mass with features indicating hemosiderine rim and different stages of blood clot. (d) MRI T2*-weighted Fast Field Echo image confirms susceptibility sensitive signal consistent with blood degradation products and different stages of bleeding. All MRI features suggested the diagnosis of giant, mostly extracerebral cavernoma, surgically confirmed.

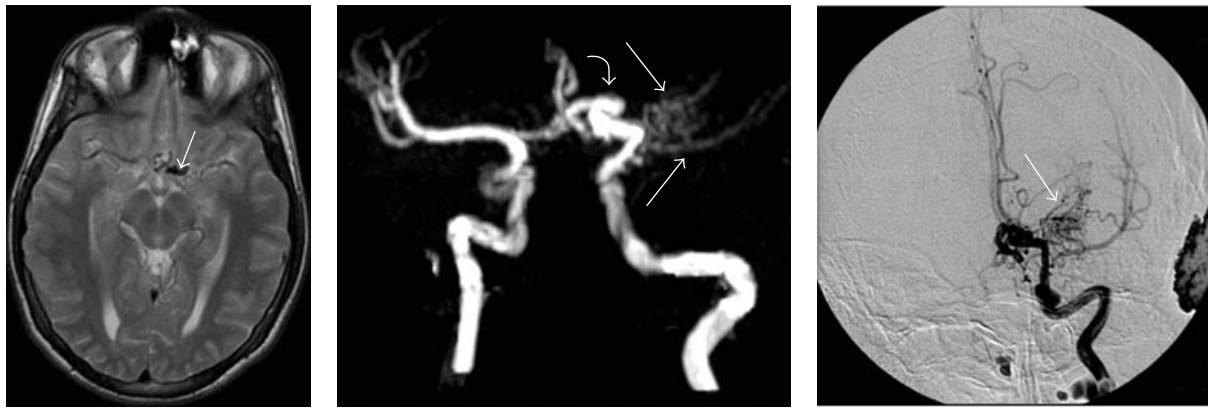
5. Conclusions

Pediatric stroke is a dramatic disease that requires urgent multidisciplinary competence and approach. In both cases of ischemic and hemorrhagic origin, the radiological approach to be obtained in emergency leads to the first screening and the first therapeutic possibility. Our and others experience suggest that in cooperating children as well as in comatose one or in patients already under general anesthesia, MRI should be considered as the first diagnostic step, offering a complete diagnostic set of information. In cases in which MRI is not available or in noncooperative children, it is recommended to perform a CT scan as first diagnostic step, followed as soon as possible by an MRI study.



(a) (b) (c)

Figure 4: A 17-year-old male with headache, neck stiffness, and right hemiparesis. (a) Plain CT scan shows left frontal intraparenchymal hemorrhage (arrow). (b) MRI T2-weighted Turbo Spin Echo performed 4 days after surgical evacuation of hemorrhagic lesion shows the cause of bleeding: an arteriovenous malformation (arrow). (c) Intra-arterial digital subtraction angiography confirms and better evaluates the arteriovenous malformation (arrow).



(a) (b) (c)

Figure 5: A 15-year-old male presenting with transient right hemiparesis. (a) MRI T2-weighted Turbo Spin Echo image shows vascular abnormality in left portion of the circle of Willis (arrow). (b) MR-angiogram shows a progressive reduction of diameter of the supraclinoid internal carotid artery associated with occlusion of the origin of left middle cerebral artery (curved white arrow) and presence of tiny newly formed compensatory network (white arrows). (c) Intra-arterial digital subtraction angiography better shows the occlusion of left middle cerebral artery and the typical presence of tortuous tiny vessels appearing as the so-called "puff of smoke" ("moya-moya") (arrow), formed to compensate for the supply blockage.

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Review Article

Diabetic Ketoacidosis-Associated Stroke in Children and Youth

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Diabetic ketoacidosis (DKA) is a state of severe insulin deficiency, either absolute or relative, resulting in hyperglycemia and ketonemia. Although possibly underappreciated, up to 10% of cases of intracerebral complications associated with an episode of DKA, and/or its treatment, in children and youth are due to hemorrhage or ischemic brain infarction. Systemic inflammation is present in DKA, with resultant vascular endothelial perturbation that may result in coagulopathy and increased hemorrhagic risk. Thrombotic risk during DKA is elevated by abnormalities in coagulation factors, platelet activation, blood volume and flow, and vascular reactivity. DKA-associated cerebral edema may also predispose to ischemic injury and hemorrhage, though cases of stroke without concomitant cerebral edema have been identified. We review the current literature regarding the pathogenesis of stroke during an episode of DKA in children and youth.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a common autoimmune condition that often presents in childhood and may be complicated by episodes of diabetic ketoacidosis (DKA). DKA is a state of severe insulin deficiency, either absolute or relative, resulting in hyperglycemia, ketonemia, acidemia, and systemic inflammation. Compared with adults, episodes of DKA in children carry a higher risk of morbidity and mortality. This is predominantly attributable to intracerebral complications [1–5], which occur in 3–10 pediatric patients per 1000 cases of DKA [6]. The most common intracerebral complication of DKA is cerebral edema (DKA-CE), which results in the death of 21–24% of affected patients, and significant morbidity in a further 10–35% [6–8]. Less common, and perhaps underappreciated, is the risk of acute ischemic or hemorrhagic stroke during the acute DKA episode. It has been estimated based on case series that approximately 10% of intracerebral complications of DKA are due to hemorrhage or ischemic brain infarction [4, 5]. While some cases of brain infarction may arise secondary to DKA-CE-induced herniation with resultant vessel occlusion, it has become clear that not all cases of stroke in DKA are associated with cerebral edema (CE). As the presentation of stroke associated with DKA may mimic that of CE but requires different management strategies, it is imperative for the clinician to be cognizant of this potential complication. This review will examine the etiology and pathogenesis of stroke associated with episodes of DKA in children and youth (age <20). While Type 2 diabetes mellitus is becoming more commonly recognized in the pediatric population and may present with, or be complicated by, DKA [9, 10], cerebral thrombosis-associated stroke has not been reported with Type 2 diabetes mellitus. Thus, the review focuses on children with T1DM.

2. Pathogenesis of Ischemic Stroke

Diabetes mellitus is a known independent risk factor for ischemic stroke, conferring two times the risk of an ischemic event in adults compared to the nondiabetic population

[11, 12]. There are several characteristics of DKA that place children at higher risk of cerebral ischemia. The reported cases on DKA-associated stroke in children and youth are presented in Table 1.

2.1. DKA as a Systemic Inflammatory Illness. DKA is more than simply a deterioration of glucose metabolism; it is also associated with a systemic inflammatory response characterized by vascular endothelial injury and coagulopathy. The inflammatory state accompanying DKA is characterized by elevated levels of inflammatory markers (CRP), cytokines (IL6, IL1β, TNFα), and complement activation [26–30]. It is likely that the oxidative stress induced by hyperglycemia and ketosis [31] contributes to this inflammatory reaction and results in diffuse vascular injury. Evidence of vascular endothelial injury can be seen in pretreatment subclinical CE [1], pulmonary interstitial edema [2, 23, 24, 32], disseminated intravascular coagulation (DIC) [13, 16, 33, 34], and elevated levels of thrombomodulin [35].

Chronically, the vascular endothelium is a primary target of the abnormal glycemic metabolism in T1DM [27]. Children with T1DM may be at risk of a chronic state of inflammation and endothelial activation outside of episode of DKA. Children within 1 year of diagnosis have been reported to have biochemical evidence of inflammation, with increased levels of both serum prothrombin fragments and TNFα compared to children more than 1 year post-diagnosis and to nondiabetic controls [36]. Furthermore, this report detailed evidence of endothelial perturbation, characterized by levels of von Willebrand Factor (vWF) and tissue plasminogen activator (tPA) more than 2 standard deviations higher than control. Another study found that the endothelial cell-specific adhesion molecule, soluble endothelial leukocyte adhesion molecule (sE-Selectin), was elevated in children with T1DM compared to healthy controls, and positively correlated with serum glucose concentration [37]. Analysis of the coagulation system in adults with diabetes has also identified abnormalities in many steps of the coagulation system [38].

2.2. Abnormalities in the Coagulation Cascade. Two case controlled studies [42, 43] found an increased rate (50%) of clinically apparent deep venous thrombosis (DVT) in very young children (less than 3 years) with DKA who required femoral central venous catheter (CVC) insertion when compared with age-matched nondiabetic controls (who also underwent femoral CVC insertion). Comparatively, an incidence rate of 1.5–18.3% has been described for clinically or radiologically apparent femoral CVC-associated DVTs in the PICU population [42, 44]. Although the propensity for hypercoagulability in diabetes mellitus has not been described as a specific isolated risk factor for DVT in children [42], it is clear that the procoagulant mechanisms that place children with an episode of DKA at risk of CVC-related DVT may also act to increase the risk of stroke.

The inflammatory condition seen in DKA, with endothelial perturbation, predisposes to an acquired procoagulant state [26]. While the majority of case studies of children with DKA-associated stroke have not identified consistent, generalized alterations in the coagulation system (Table 1), these studies have mainly examined the coagulation system at a single time point after identification of a neurologic abnormality. More systematic evaluation of coagulation abnormalities during an episode of DKA requires longitudinal consideration, both before and during therapeutic intervention. Indeed, longitudinal studies in children [41] and adults [35] with DKA have identified multiple coagulation abnormalities, including increased platelet aggregation, elevated levels of procoagulants, and decreased activity of anticoagulants. Coagulation factors for which abnormalities have been noted during DKA or its treatment in either children or adults have been summarized (Table 2).

Examination of the coagulation factors of 7 adolescents on presentation with DKA and at several time points after initiation of DKA therapy demonstrated abnormalities in Protein C, Protein S, plasma homocysteine, and von Willebrand Factor (vWF) [41]. Protein C levels are initially elevated but quickly decrease to normal with DKA treatment, while Protein C activity is initially low and slowly normalizes with treatment. Adult patients with T1DM have significantly lower protein C levels than controls [45]. Their protein C levels are inversely related to glucose concentrations but exhibit no relationship with glycosylated hemoglobin A (HbA1c) levels. This latter finding suggests that acute, rather than chronic, variations in blood glucose may determine the response of Protein C, which may itself explain the normal values found in most patients with DKA-associated stroke (Table 1).

Plasma homocysteine is an important factor in atherosclerosis and thrombosis [46] and also decreases protein C activation [47]. Plasma homocysteine levels in adolescents are elevated in DKA and gradually normalize after insulin initiation [41]. The relatively rapid homocysteine rise may result in the very gradual normalization of protein C activity that has been observed. In adolescents, Protein S antigen levels remain normal during DKA while free protein S, the active anticoagulant, is reduced and does not return to baseline with treatment [41]. This is consistent with the finding that low levels of free protein S are the result of increased levels of C4b-binding protein in poorly controlled adult T1DM patients [30].

vWF is synthesized and secreted by endothelial cells, facilitates platelet adhesion, and is a carrier protein for factor VIII. High vWF levels are a marker of endothelial injury and activation. In adolescents, vWF antigen and activity are initially increased in DKA and decrease slowly with DKA therapy [41]. Factor VIII concentration is also elevated in adults with long-standing insulin-dependent diabetes mellitus during an episode of DKA [48, 49]. The fibrinogen concentration remains normal throughout DKA and its management [41]. However, fibrinogen circulating in an environment of high glucose can become hyperglycosylated [50] with resulting fibrin fibers that are resistant to plasmin degradation [51].

In 8 adults receiving a continuous subcutaneous insulin infusion, researchers examined the effects of infusion cessation for 4 hours [40]. All subjects entered early biochemical DKA. Tests of fibrinolytic activity after vascular stimulation

Table 1: Case reports of arterial ischemic stroke, cerebral venous thrombotic stroke, and hemorrhagic stroke associated with an episode of DKA in children and youth.

Patient number	Age (year)	Gender	Pathologic findings	Clinical Presentation	Outcome	Coagulation profile	Reference number
Arterial Ischemic Stroke.							
1	0.25	female	Multiple small vessel thrombi with edema on autopsy	First presentation diabetes, generalized seizure, progressive coma on admission	Death at 24 hours		[13]
2	4	female	Infarction, right posterior cerebral artery distribution	First presentation diabetes, decerebrate posturing, acute herniation	Slowly regained ability to walk and comprehend speech	Low protein C normalized with treatment, elevated Factor VIII-vWF complex, elevated plasma and platelet thromboxane B2	[14]
3	8	male	Infarction of left thalamus, left temporal lobe, B/L occipital lobes	Decerebrate posturing	Slow recovery	Low protein C antigen, normalized	[14]
4	10	unknown	Basilar artery thrombosis on CT	Restless, decreasing LOC over 4.5 hours, respiratory arrest at 7 hours	Persistent vegetative state		[4]
5	14	female	CT edema and infarction of left lentiform nucleus, thalami, B/L peduncles	Headache, deteriorating LOC. Pupils midline, fixed, dilated after 12 hours	Mild left hemiparesis, behavioral disturbances		[15]
6	5	male	Infarction left posterior cerebral artery distribution, geniculate nuclei, left thalamus	First presentation diabetes, generalized seizure	Moderate left hemiplegia	Low protein S, elevated factor VIII and factor V	[5]
7	6	male	Infarction B/L anterior cerebral artery distributions, basal ganglia, left cingulate gyrus	First presentation diabetes, lethargy and posturing of upper extremities	Emotionally labile, intellectual and motor impairment	Low AT III antigen, AT III functionally normal, increased platelet aggregation	[5]
8	7	male	Ischemia in globus pallidus, B/L cingulate gyri. Infarctions left thalamus, right medial occipital lobe. No CT edema	First presentation diabetes, decreased level of consciousness with incontinence, stiffness, pupils poorly reactive	Hemiplegia, normal cognition, abnormal behavior and affect,	Decreased platelet aggregation	[5]
9	8	male	Infarction thalamus, midbrain, basal ganglia, cingulated gyrus. No CT edema	First presentation diabetes, unresponsive, flaccid, pupils dilated	Vegetative state	Low aPTT (21 seconds)	[5]
10	10	male	Infarction right anterior cerebral artery distribution, left putamen, B/L globus pallidus	First presentation diabetes, decreased LOC, left extensor posturing, abnormal papillary response	Severe focal neurologic impairment		[5]
11	6	female	Infarction proximal left middle cerebral artery, left basal ganglia	First presentation diabetes, irritability, lethargy, right hemiparesis, aphasia. Had 2 mitral valve thrombi	Regained speech, residual right hemiparesis	Normal pro-thrombotic studies	[6]

Table 1: Continued.

Patient number	Age (year)	Gender	Pathologic findings	Clinical Presentation	Outcome	Coagulation profile	Reference number
12	18	female	Infarction right common carotid artery territory with distal emboli in right anterior and middle cerebral arteries	First presentation diabetes, left hemiparesis 10 hours after carotid artery puncture	Moderate clinical recovery		[16]
Cerebral Venous Thrombosis.							
13	5	female	Thrombosis of straight sinus and vein of Galen. Infarction of basal ganglia, thalamus	Confusion, decreased LOC, rigidity, fisting. Significant iron deficiency anemia	Mild learning difficulties	Normal clotting screen and thrombophilia screen	[17]
14	11	male	Multiple areas of infarction on MRI without hemorrhage or edema	Headache, nausea and vomiting, acute deterioration with fixed, dilated pupils. Had DVT of right superficial femoral and popliteal veins	Brain death	Decreased protein C function (36%), normal protein S and factor VIII, no anticardiolipins. Heterozygous factor V Leiden	[18]
15	19	female	Superior sagittal sinus thrombosis	First presentation diabetes. Anxiety progressed to psychosis, dysphasia, left abducens palsy, right inferior facial palsy, tetraparCsis with upper motor neuron signs	Partial left abducens paresis with diplopia which resolved	coagulopathy screen negative	[19]
16	8	male	Vein of galen and superior sagittal sinus thrombosis. B/L medial cerebral hemisphere infarctions	First presentation diabetes, loss of consciousness, sluggish pupillary reaction, fever	GCS remained 6 when transferred to another hospital	Low platelets, decreased ATIII (60.4%) increased with treatment, elevated D-dimer, increased with treatment	[20]
17	1.1	female	Left transverse sinus thrombosis, no infarction	First presentation of thiamine-responsive megaloblastic anemia, associated with nonimmune insulin-dependent diabetes. Right-sided focal seizure	Normal neurologic status	Prothrombotic screening negative	[16]
18	10	female	Thrombosis of superior sagittal, straight, right transverse, right sigmoid and proximal posterior left transverse sinuses	Headache, 6th cranial nerve palsy day 3, decreased level of consciousness day 5	Recombinant tPA thrombolysis, complete recovery	Heterozygous mutation of the prothrombin gene (G20210A)	[21]
Hemorrhagic infarction.							
19	11	female	Multiple large, B/L posterior temporal lobe hematomas	Behavioral disturbance, lethargy, progressed to unresponsive, pupils dilated and unreactive	Normal neurologic exam		[22]
20	1	unknown	Subarachnoid hemorrhage on CT	Sudden respiratory arrest	Died at 2 days		[4]

Table 1: Continued.

Patient number	Age (year)	Gender	Pathologic findings	Clinical Presentation	Outcome	Coagulation profile	Reference number
21	11	unknown	Subarachnoid hemorrhage on CT	Progressively worsening neurologic status	Death		[4]
22	6.5	unknown	CT suggestive of subarachnoid hemorrhage	Severe headache and restless. Pupils fixed, dilated at 3 hours, respiratory arrest at 6 hours	Death		[4]
23	9	female	Hemorrhagic infarction right caudate nucleus, anterior limb of internal capsule. Non-hemorrhagic infarction of B/L thalami with edema	Ataxia, deteriorating LOC, abnormal respiratory pattern,. Developed decorticate posturing, right-sided tonic seizure	Communication disorder, asymmetric spastic quadriparesis, behavior disturbances.		[15]
24	9	female	Edema and hemorrhagic infarctions basal ganglia, upper brain stem, medial temporal lobes, frontal lobes, occipital lobes	Decreased LOC, left exotropia, unequal and unreactive pupils, papilledema	Quadriplegia, absent oculocephalic reflexes, central right facial paresis, profound cognitive defects		[15]
25	15	female	No cerebral edema in first 24 hours on CT. Multiple small hematomas, mainly parieto-occipital, on day 12 MRI	First episode diabetes. Significant hypotension, unconscious at presentation. Neurologically normal day 4. Bilateral knee clonus, extensor plantar response and peripheral nerve palsies on day 7		Decreased platelets (85,000), normal coagulation profile	[23]
26	11	female	Normal MRI. On autopsy: pin-point hemorrhages with ring-and-ball morphology in hemispheric white matter, throughout brainstem and spinal cord	First presentation diabetes, Hypotension, rapid deterioration in LOC	Death from renal complications	Normal coagulation studies	[24]
27	14	female	Petechial hemorrhages in B/L subcortical white matter U fibers, genu of corpus callosum, posterior limb of internal capsule, frontal lobe on MRI	First presentation diabetes, significant hypotension. Unresponsive and dyspneic	Short term memory loss, moderate cognitive deficits	Normal coagulation studies	[24]
28	5	female	Hemorrhagic infarct left thalamus	First presentation diabetes. Right central facial palsy, right hemiplegia, right babinski sign on day 7 of treatment	Mild learning difficulties	normal bleeding studies, normal protein C and S at time of hemorrhage	[25]

LOC: level of consciousness; B/L: bilateral; tPA: tissue plasminogen activator.

Table 2: Coagulation abnormalities noted in cases of pediatric DKA with stroke and in studies of DKA-associated coagulopathy in adults and children. Pretreatment abnormalities include those noted prior to resolution of biochemical abnormalities. Posttreatment abnormalities include those noted after resolution of biochemical abnormalities.

Factor	Parameter	Pre-treatment abnormality	Post-treatment abnormality	Pediatric versus adult study	Relevant references
Platelet	count	√	√	pediatric	[5, 14, 20, 23, 33]
	aggregation/ activity	√	√	pediatric, adult	[5, 35, 39]
Thromboxane B_2	production		√	pediatric	[14]
Prothrombin time			√	pediatric	[33]
Partial thromboplastin time	levels		√	pediatric	[33]
Tissue Factor	levels	√		adult	[40]
vWF	antigen level	√	√	pediatric	[14, 41]
	activity	√		pediatric	[41]
Factor VIII-vWF complex	levels		√	pediatric	[14]
Factor V	levels		√	pediatric	[5]
Factor VII	levels		√	pediatric	[5]
Factor VIII	levels		√	pediatric	[5]
Homocysteine	levels	√		pediatric	[41]
Folate	levels	√		pediatric	[41]
Prothrombin fragment 1 + 2	levels	√	√	adult	[35]
Thrombin-antithrombin III complex	levels	√	√	adult	[35]
Antithrombin III	levels and activity	√	√	pediatric, adult	[5, 20, 33, 35]
Protein C	activity	√		pediatric	[41]
	antigen level	√	√	pediatric	[14, 18, 41]
Protein S	Free protein level	√		pediatric	[42]
Thrombomodulin	levels	√	√	adult	[35]
tPA	activity	√		adult	[35, 40]
	antigen level	√	√	adult	[35, 40]
PAI-1	activity	√		adult	[35, 40]
	antigen level	√	√	adult	[35, 40]

vWF: von Willebrand Factor; tPA: tissue plasminogen activator; PAI-1: plasminogen activator inhibitor-1.

demonstrated, 1.4-times lower tPA secretion, 2.87-times higher plasminogen activator inhibitor (PAI) activity, and 1.93-times higher PAI antigen level compared to baseline. Combined, these findings suggest that impaired fibrinolytic activity is an early event in DKA. Furthermore, tissue factor (TF), the primary initiator of coagulation, was significantly increased as soon as the insulin infusion was halted. No other coagulation factor demonstrated altered serum levels, and it is not yet clear that TF promotes procoagulant changes in diabetic patients.

An examination of 34 adult patients with uncomplicated DKA demonstrated evidence of endothelial injury, platelet activation, relative hypofibrinolysis, and activation of the coagulation system, even in the absence of clinical signs of thrombosis [35]. Not surprisingly, multivariate analysis indicated that many of the endothelial, clinical, and hemostatic factors were interrelated. Unlike the trial of insulin infusion cessation [40], Ileri and colleagues found that fibrinolytic activity (tPA and plasmin-α_2-antiplasmin complex levels) was increased both before and during DKA treatment. However, the upregulation was not to a degree expected for the increase in coagulation activity (thrombin-antithrombin III complex and prothrombin fragment 1 + 2 levels) at DKA presentation. Not all alterations in the coagulation system are procoagulant. Antithrombin III activity is generally increased in T1DM. In contrast, at DKA presentation, levels are slightly lower than baseline but are still higher than in a control population [35].

2.3. Platelet Numbers and Function. Increased platelet activity has been inconsistently demonstrated in children with stroke [5], though no systematic studies of platelet activity and aggregation have been performed in children during DKA. Although platelet counts are generally normal in T1DM, platelet function is enhanced both chronically [38] and during an episode of DKA. Adult volunteers experiencing acute hyperglycemia following an oral glucose challenge demonstrate an acute increase in platelet aggregability [39]. It has been postulated that increased platelet activity may be related to decreased nitric oxide availability reported during episodes of DKA [52, 53]. Ileri and colleagues found that platelet activation coexisted with DKA and was completely normalized after recovery [35].

2.4. Blood Volume, Flow, and Vascular Reactivity. It has been demonstrated in other conditions that dehydration alone does not account for hypercoagulability [54]. Therefore, although DKA may result in significant fluid losses, other factors such as coagulation system abnormalities, hyperglycemia, acidemia-induced red blood cell rigidity (increased blood viscosity) [55, 56], and vasoconstriction induced by hyperglycemia may all have an additive role. The vascular response in hyperglycemia has generally been considered vasoconstrictive, and there is some evidence that this may be related to decreased availability of nitric oxide [53]. However, vascular endothelial growth factor expression is increased by circulating ketones (β-hydroxybutyrate), leading to activity of nitric oxide-guanylate cyclase pathway, and therefore vasodilation, in mouse models [57]. Clinically, a transcranial Doppler ultrasound study of 5 children with DKA demonstrated significant vascular dysregulation with vasodilation, decreased cerebral blood flow velocity, and loss of normal cerebral blood flow regulation that only normalized after treatment [58]. Another group found normal to increased cerebral blood flow with impaired cerebral autoregulation during episodes of DKA not associated with overt CE in 6 children [59]. Importantly, none of these studies were able to define the effects that DKA has on local microvascular tone and regulation, and therefore on cerebral oxygen delivery.

3. Pathogenesis of Hemorrhagic Stroke

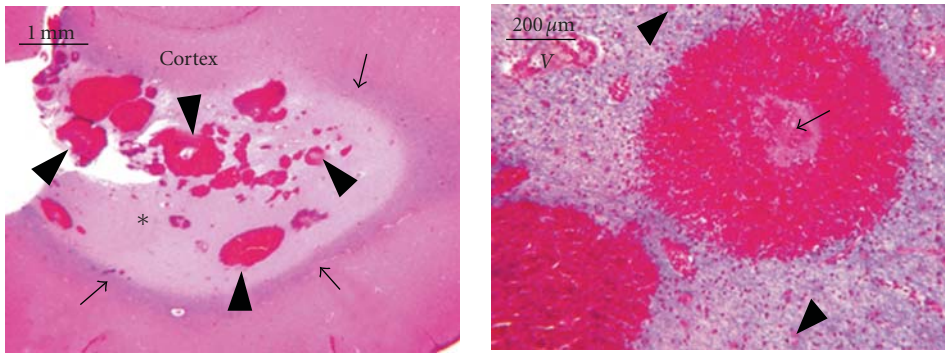
While much of the above discussion has focused on the pathogenesis of thrombosis, it is reasonable to suppose that the pathophysiology of hemorrhagic stroke may involve similar principles to that of hypoperfusion or thrombotic stroke. During an episode of DKA, hemorrhage risk is increased by endovascular perturbation secondary to the proinflammatory state, and to hyperglycemia and acidosis causing oxidative injury [24, 30, 31], as well as ischemic injury to the vessels from cerebrovascular dysregulation [58, 59] or presentation in a shock state [24, 25]. In a case-control study of 41 adult patients with hemorrhagic stroke, 31% of diabetics had hemorrhagic conversion of infarcts compared to 18% of nondiabetic stroke patients [60]. While these were not in the setting of DKA, it does raise the possibility that the aforementioned chronic inflammatory state that exists in diabetes mellitus [27, 36] places these patients at higher risk of hemorrhagic conversion of ischemic brain infarction.

DIC has been reported in children with DKA [33]. The consumption of coagulation factors in DIC may predispose to hemorrhage. Four cases of isolated intracerebral DIC, including one case of a 3-month old (Table 1, patient 1), have been reported [13, 34]. DIC was identified on postmortem examination as wide-spread occlusion of small vessels by thrombus, many of which were surrounded by petechial hemorrhage. Furthermore, vascular malformations such as arteriovenous malformations (AVMs), aneurisms, and cavernous malformations that predispose to stroke may be relevant in this patient group. In children who experience hemorrhagic stroke in the absence of diabetes mellitus, vascular malformations are the most commonly experienced risk factor, occurring in 20–85% in case series [61].

DKA is a proinflammatory condition with vascular endothelial perturbation, and dysregulation of the coagulation system features associated with abnormal levels and activities of several coagulation factors, including platelets, which result in a procoagulant state. Additional factors contributing to the procoagulant state are abnormalities in blood volume, blood viscosity, cerebral autoregulation and blood flow, while vascular injury may be a result of oxidative injury and ischemia related to systemic hypoperfusion, vascular dysregulation, or cerebral edema. Hemorrhagic stroke likely arises secondary to hypoxia and the vascular injury encountered in the oxidative, proinflammatory state of DKA.

4. Pathology: Ischemic versus Hemorrhagic Stroke

We identified cases of stroke associated with DKA in children and youth through an exhaustive search of the literature. We searched PubMed for the following terms: ["stroke" or "brain infarction" or "thrombosis"] and ["DKA" or "diabetic ketoacidosis"]. Titles were hand searched for relevance, and where significance was unclear the abstract was read. All appropriate articles were obtained and their reference lists were scanned for other articles of relevance. This iterative process was continued until no further new reports became apparent. We have presented (Table 1) the reported cases of DKA-associated stroke in the following categories: arterial ischemic stroke [4–6, 14–16], cerebral venous thrombosis [16–21], and hemorrhagic stroke [4, 15, 22–25]. Based on the limited investigative modalities available to those compiling the reports, it is likely that our ability to differentiate between stroke etiologies (e.g., arterial ischemia due to hypoperfusion or thrombus, or hemorrhagic stroke with bleeding that arose de novo versus secondary to bleeding within an ischemic injury) is limited. This was clearly illustrated in the case control series described by Muir and colleagues, in which 4 of 23 children with DKA who had CT scanning after developing clinical signs of cerebral edema demonstrated subarachnoid or intraventricular hemorrhage without radiologic edema [62]. Thus we determined that, where hemorrhage was the only radiologic finding, the patient was included in the "hemorrhagic stroke" group. The 4 patients from the latter study were not included in Table 1, as there was



(a) (b)

Figure 1: White matter hemorrhages associated with DKA. (a) This low-power view of a gyrus (stained with hematoxylin, eosin, and Luxol fast blue) illustrates multiple small and microscopic hemorrhages (arrowheads) associated with "confluent" pallor (asterisks) of the myelin, a thin layer of preserved subcortical myelin (arrows), and normal cortex. (b) A vessel, labeled *V*, is identified for reference. Stained with Luxol fast blue, hematoxylin, and eosin (which stains myelin blue). Central hemorrhage was formed by perivascular necrosis (arrow), a concentric ring of red blood cells, and diffusely rarefied white matter that is speckled with eosinophilic astrocytes (arrowheads). Figure 1 reproduced with permission from *Pediatrics*, volume 126, page 1543, copyright 2007 by the AAP.

no specific individual information given. Where multiple small hemorrhages occurred in the setting of clear thrombus or emboli [13], the patient was included in the "arterial ischemic stroke" group. Cases of venous sinus thrombosis with relevant clinical findings in the acute phase, but with no long-term clinical or radiologic sequelae [16], were included, as they represent acute intracerebral events associated with DKA.

The pathologic tissue findings of a patient having experienced acute cerebral infarction related to an episode of DKA are not expected to be different from those of a nondiabetic child who has had a stroke. Two patients (patients 26 and 27) had hemorrhagic stroke that was characterized histologically by a ring-and-ball morphology (Figure 1) [24]. Widespread small vessel occlusion, diagnosed on autopsy, has also been described [13]. As stroke itself may cause cerebral edema, it becomes difficult to ascertain whether cerebral edema in DKA is the cause or an effect of acute cerebral infarction. Table 1 details the course of four patients (2, 3, 9, 24) who had signs of raised intracranial pressure and may have suffered cerebral hypoperfusion and infarction as a complication of DKA-CE. Patients 2, 3, 6, 8, and 28 had infarction limited to areas supplied by the posterior cerebral artery and anterior choroidal arteries (the areas most susceptible to damage following transtentorial herniation), presumably secondary to raised intracranial pressure. However, some of this group lacked clinical signs or radiological evidence (patients 6, 8, 28) of CE, raising the possibility of a primary thrombotic or hemorrhagic event. Patient 1 had signs of DKA-CE but also clear thrombus formation on autopsy [13].

Two patients were found to have thrombophilic conditions. Patient 14 developed a DVT prior to presentation with central nervous system complications of DKA. MRI demonstrated acute infarctions in multiple areas of the brain, and examination identified heterozygosity for Factor V Leiden [18]. Patient 18, who developed thrombosis of multiple cerebral venous sinuses, was found to have heterozygous mutation of the prothrombin gene (G20210A) [21].

5. Evaluation

The clinical presentation of stroke as a focal neurologic deficit should pose little diagnostic problem. Of greater difficulty is differentiating global neurological impairment in DKA patients from severe acidosis, DKA-CE, or primary stroke. Among the patients presented in Table 1, only 8 (patients 10, 11, 12, 15, 17, 23, 25, 28) had focal neurologic signs. The remainder presented with nonspecific signs consistent with the global dysfunction seen in DKA-CE. As the presentation of CE and primary stroke in DKA can be so similar, it is imperative that the clinician have a high index of suspicion for stroke. Early imaging is warranted once the patient is stabilized in order to optimize management.

The best modality for identification of the ischemia associated with stroke is magnetic resonance imaging (MRI) with perfusion- and/or diffusion-weighted imaging, which have sensitivity nearing 100% [63]. Computed tomography (CT) may be used to rule out CE, hemorrhage or abscess, though the sensitivity for identification of ischemic infarction in the acute phase is only 50% [63]. Additionally, it is agreed that CT may miss cases of cerebral edema, though its sensitivity for identifying elevated intracranial pressure has been reported at 99.1% [64]. Cerebral angiography is the gold standard for assessment of the cerebral vasculature, although MR angiography (MRA) is able to detect large vascular lesions effectively [65], with the benefit of being noninvasive. CT angiography, though it requires injection of contrast, may be used to evaluate the cerebral circulation early in stroke evolution [66]. In cases where neither MRA nor MRI defines suspected pathology in a distal artery, cerebral angiography may be considered.

All patients with suspected intracranial pathology should have a coagulation screen performed. In cases of clear

thrombosis or hemorrhage, more detailed analysis of the hemostatic system is warranted. Identification of the exact histopathology may be done with tissue biopsy [24], though this carries many risks and is not recommended as a matter of course.

6. Management

Fully evidence-based management guidelines for children experiencing acute ischemic or hemorrhagic infarction do not exist and have been extrapolated from adult data. Admission to the critical care unit and close monitoring is appropriate for any patient with suspected or proven central nervous system (CNS) complication of acute DKA. Unless diffuse CE can be absolutely excluded, or another clear cause is present, emergency management for CNS complications of DKA should prioritize the treatment for cerebral edema. Although early reactive treatment for CE appears beneficial [4, 67], it was stated in 1990 that intracerebral complications do not often come with warning signs, and early intervention measures are frequently unsuccessful in preventing complications; so prevention of DKA is the most effective method of preventing complications [4]. In the intervening 20 years, this generally remains true, although there may be some alternative management options for thrombus causing stroke.

Children with stroke should receive aggressive treatment for fever, infection, and seizures [68]. For all forms of stroke, recommendations are for early mobilization and rehabilitation. Current guidelines do not support the use of thrombolytics in pediatric arterial ischemic stroke [69], although thrombotic stroke associated with an episode of DKA is not addressed specifically. Furthermore, multiple case reports document use of thrombolytics treatment associated with good outcome in children with acute ischemic cerebral infarction [70–72], including thrombolysis used successfully up to 36 hours after onset of symptoms [73, 74]. Safe, acute thrombolysis with recombinant tPA was reported for a 10-year-old child with cerebral venous sinus thrombosis that occurred 3 days after onset of DKA, who had complete recovery [21]. However, caution is warranted as the risks of thrombolysis and the optimal tPA doses in children have not been quantified. In light of the lack of evidence or strength of recommendations, it seems prudent that management of arterial ischemic stroke in association with DKA be considered on a case-by-case basis and in consultation with stroke experts.

Beyond the acute phase of ischemic or thrombotic stroke it has generally been agreed that anticoagulation with heparin [75, 76] may be appropriate for pediatric patients who have already experienced arterial ischemic stroke or cerebral venous thrombosis, independent of T1DM and DKA. International guidelines recommend the use of low molecular weight or unfractionated heparin initially, followed by warfarin therapy for 3–6 months [75–77]. There is no clear guidance on the management of children who have experienced hemorrhagic stroke. Adult guidelines suggest that extremely high blood pressures be reduced cautiously and recombinant factor VIIa has shown some promise in decreasing recurrence but is only recommended within clinical trials. However, these guidelines refer to different etiologies for intracranial hemorrhage than are seen in children or in the DKA population. Large hemorrhages compromising neurovascular structures may warrant surgical decompression.

Prophylactic systemic anticoagulation has been suggested for patients in DKA [13, 35, 78]. However, anticoagulation is not addressed in international consensus statements on the management of DKA [1, 79, 80]. In light of the risk of hemorrhagic stroke and the unknown incidence of stroke in pediatric DKA, a broad recommendation for prophylactic anticoagulation cannot be supported at this time.

7. Outcome

Stroke outcome depends on the cerebral regions affect and the extent of the injury. As demonstrated from the case series (Table 1), the majority of children with DKA-associated stroke reported have some form of residual neurologic deficit with death or persistent vegetative state as the outcome in 8 of 28 patients (29%) and full recovery seen in only 4 of 28 cases (14%).

8. Conclusions

Stroke in DKA is uncommon but life-threatening. DKA may be considered an inflammatory condition with vascular endothelial perturbation and dysfunction of the coagulation system. Multiple causes of thrombus have been postulated and studies show several contributing mechanisms. Hemorrhagic infarctions are rare and may be multifactorial but must be considered a risk. Management for CNS complications of DKA should prioritize the treatment for cerebral edema. As the initial presentation of pediatric stroke can be subtle and may be confused with DKA-CE, early imaging for any young person with neurologic deterioration in association with an episode of DKA is imperative following emergency treatment for CE and stabilization.

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Case Report

Paediatric Stroke: Review of the Literature and Possible Treatment Options, including Endovascular Approach

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Stroke is among the top 10 causes of death in childhood. More than half of the surviving children have long-term neurological sequelae. Ischemic stroke (IS) includes arterial ischemic stroke and cerebral venous thrombosis with venous infarction. Haemorrhagic stroke (HS) includes intracerebral haematoma or subarachnoid haemorrhage. Risk factors for stroke are different in children and in adults. 10–30% of IS have no identified risk factors. However, multiple risk factors are recognizable in the majority of stroke in children; thus, a comprehensive diagnostic evaluation is crucial. Vascular abnormalities, such as arteriovenous malformations, aneurysms, vessel dissection, stenosis, and moyamoya disease, are frequently associated with both IS and HS and lead to high recurrence rates. Endovascular and surgical treatment options are sometimes indicated, performed on the basis of expert opinion, and extrapolated from the adult procedures. In the present paper, we review the recent literature and we discuss the treatment in five cases managed at our institutions.

1. Introduction

In young population stroke is often an underestimated cause of neurological disturbances with different possible aetiologies and multiple treatment options. A thorough knowledge of the pathophysiology of the disease, of the natural history and of the possible different therapies including medical or surgical approaches, represents a necessary instrument in order to obtain a prompt and correct diagnosis and a successful recovery. Additionally, diagnosis of paediatric stroke is even more difficult, due to the limited expressive and interpretive skills of symptoms compared to the adult population.

Stroke is among the top 10 causes of death in childhood with an incidence of 2–13 per 100,000 children. More than half of the surviving children who had a stroke have long-term neurological sequelae [1].

Ischemic stroke (IS) refers to both arterial ischemic stroke (AIS) and cerebral venous thrombosis (CVT) resulting in venous infarction. Hemorrhagic stroke (HS) includes intracerebral haemorrhage and nontraumatic subarachnoid haemorrhage. Nearly half of paediatric strokes are hemorrhagic [2].

There are differences in the incidence of stroke during childhood, with incidence rate of 3/100,000 under the age of 1 year (even when neonatal or perinatal stroke, which is known to have a particularly high incidence rate, is excluded) and of 0.7/100,000 at 5–9 years. Another incidence peak is observed in male adolescents probably due to hormonal factors [3].

The risk factors for childhood stroke are markedly different from those in adults, including young adults. Childhood stroke in which no risk factors are identified represent 10–30% of cases [3].

In the next paragraphs we try to give a schematic presentation of the main risk factors for arterial, venous, and haemorrhagic stroke, an overview about the stroke outcome, and of the recurrence rate. In evaluating this complex pathology, it is always important to consider that the same risk factor can determine all the three situations and

that multiple factors can differently combine each others in the same situation.

2. Risk Factors

2.1. Arterial Ischemic Stroke (AIS)

2.1.1. Arteriopathies. In childhood AIS, abnormalities of the cerebral circulation (both intracranial and cervical) have been reported in up to 80% of the cases [3]. The most frequently identified form of arteriopathy is termed transient cerebral arteriopathy (TCA) or focal cerebral arteriopathy of childhood (FCA), defined as vascular stenosis not otherwise classified as dissection, moyamoya, sickle cell arteriopathy (SCA), postvaricella arteriopathy, vasculitis, or other specific diagnoses. TCA or FCA represents a monophasic transient arteriopathy affecting large- or medium-sized vessels that, on follow-up imaging few months after the infarct, generally shows regression or nonprogression. It seems that many cases of FCA have a postinfectious mechanism underlying the arteriopathy, particularly recent upper respiratory tract infections [3].

Craniocervical arterial dissection may be responsible for 7 to 20% of childhood AIS. In children, the anterior circulation is involved more frequently than the posterior circulation. There is a history of trauma in half of the cases although the trauma may be minor; in these cases the cervical arteries are most commonly affected, while intracranial dissection accounts for at least a quarter of the cases. In nontraumatic cases 60% of dissections are intracranial. In dissecting diseases, symptoms can be related either to mass effect, ischemia, or SAH. If all vascular layers of the intradural artery are dissected, a subarachnoid hemorrhagic will occur. Intramural clot formation can cause distal thromboembolic ischemia or occlusion of perforator branches and local ischemia. Chronic dissecting process may eventually lead to formation of a "giant partially thrombosed aneurysm" [4]. Unlike in the adult, an underlying condition predisposing to dissection is seldom found in children. Recurrence rate is about 10% [1, 3, 5].

Moyamoya is a noninflammatory nonatherosclerotic vasculopathy. It is characterized by progressive occlusion or stenosis of the cerebral vasculature particularly involving the vessels feeding the circle of Willis, most commonly of the distal internal carotid arteries, with compensation resulting in the development of an extensive network of hypertrophic arterial collaterals distal to the occlusion. Moyamoya can be idiopathic (disease) or secondary (syndrome) when associated with other causes of vasculopathy, such as sickle cell disease (SCD), Down's syndrome, neurofibromatosis, and previous cranial irradiation. Genetic polymorphisms of HLA class II genes have been associated with idiopathic moyamoya disease [6, 7].

Primary CNS vasculitis or systemic vasculitis (lupus erythematosus, Henoch-Schonlein purpura, Wegener granulomatosis, polyarteritis nodosa, Takayasu arteritis, and Kawasaki disease) have been linked to stroke.

Rare causes of cerebral arteriopathy in children include neurofibromatosis 1 (NF1) arterial dysplasia, postirradiation arteriopathy, fibromuscular dysplasia, and collagen disorders.

2.1.2. Cardiac Diseases. Cardiac disease is one of the most commonly identified risk factors in childhood IS, as it is identified in 15–30% of cases of AIS.

In children with preexisting major congenital cardiac malformations, embolic phenomena are the major cause of stroke. Other factors involved include hypoxia, hypotension, and polycytemia.

An association between IS and cardiac surgery or catheterization is found in about 40% of children with cardiac disease.

Patent foramen ovale (PFO) has been referred to as "the back door to the brain" through which small venous thrombi not filtered by the pulmonary vasculature enter the systemic circulation. In children and young adults with otherwise cryptogenic stroke, an increased prevalence of PFO has been found, even if there are not conclusive data demonstrating causality [8].

Children with AIS may have both cardiac disease and intracranial arteriopathy.

2.1.3. Haematological Disorders. In children with SCD the risk of stroke is about 200 times greater than in other children, and up to one-third of children with SCD have silent strokes (neuroimaging evidence without history of stroke) that frequently lead to cognitive deficits. β-thalassemia can also lead to IS.

Both of these conditions can cause stroke because of anemia and hypercoagulable state. Moreover, development of stenosis of the intracranial internal carotid artery (ICA) and of the proximal middle cerebral artery (MCA) in SCD determines a secondary moyamoya like vasculopathy due to repeated insults on the vessels' walls.

Iron-deficiency anaemia has been found to be present in 20% of previously healthy children with AIS.

A number of genetic thrombophilic traits have been associated with paediatric stroke: prothrombin G20210A, factor V Leiden G1691A, MTHFR C677T, lipoprotein(a), antiphospholipid antibodies/LLAC, protein S deficiency, antithrombin deficiency, protein C deficiency, different haplotypes of genes involved in the nitric oxide pathways and thus in possible endothelial impairment.

2.1.4. Infections. CNS infections, that is, meningitis and encephalitis, are present in 10% of cases of AIS, presumably due to vascular inflammation and thrombosis or due to reduced cerebral perfusion secondary to systemic hypotension, raised intracranial pressure, and low cerebrospinal fluid glucose.

Hypotension and hypercoagulable state as a consequence of bacteraemia or sepsis can lead to IS.

Focal cerebral artery stenosis with a history of varicella infection in the preceding year has been termed postvaricella angiopathy, thought to be due to viral invasion of the artery wall as already mentioned in the previous section on arteriopathies.

The most common risk factor identified in childhood stroke due to CVT is represented by middle-ear and paranasal sinus infections.

2.1.5. Genetics. An increased risk of stroke has been associated with numerous genetic diseases, such as the above-mentioned SCD and genetically inherited thrombophilic traits, Down's syndrome, NF1, Williams syndrome, homocystinuria, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Fabry disease, mitochondrial encephalomyopathy with lactic acidosis and stroke (MELAS) [9].

AIS and CVT share many of the above-mentioned risk factors.

2.2. Cerebral Sinovenous Thrombosis (CVT). CVT in childhood is a rare (incidence 0.4–0.7 per 100000 children per year, most occurring within the neonatal period) but underrecognized disorder, often of multifactorial aetiology, with neurologic sequelae in up to 40% of survivors and mortality approaching 10%. The spectrum of brain injury varies from venous congestion to parenchymal ischemia which may be cortical or subcortical and involve deep grey matter. The majority of the parenchymal infarcts are haemorrhagic. Subarachnoid and subdural haemorrhage are less frequent. In neonates there is a strong association between CVT and intraventricular haemorrhage. Infections appear to be the most common condition associated to CVT. Predisposing systemic comorbidity factors include fever, infection, dehydration, anaemia, and chronic medical conditions such as congenital heart disease, nephritic syndrome, autoimmune diseases, malignancy, and genetic and acquired prothrombotic disorders. Moreover, locoregional factors such as first of all otitis media and mastoiditis, then meningitis, head trauma, and recent intracranial surgery are strongly related to CVT [10].

2.3. Haemorrhagic Stroke (HS)

2.3.1. Structural Lesions. Structural lesions account for at least half of HS in children. Arteriovenous malformations (AVMs) are the most commonly identified structural lesions found in HS (30%), and 80% of the children with an AVM will declare their malformation by HS. Probability of a first haemorrhage is 2–4% per year [11].

The vast majority of arterial cerebral aneurysms in the paediatric age are symptomatic, and they account for 13% of HS, mostly presenting with subarachnoid haemorrhage (SAH). Aneurysms may be idiopathic (30%) or related to arterial dissection (50%), to bacterial or mycotic infections (15%), or to trauma (5–10%) [12]. In traumatic cases, HS often presents 2–4 weeks after the head injury.

HS is also related to SCD (25% of first strokes in children with SCD are haemorrhagic) and moyamoya, due to fragility of the dysplastic collateral vessels.

Cavernous malformations are found to be the cause of bleeding in 15% of HS paediatric cases.

Finally, intratumoral haemorrhage can be a rare feature of intracranial malignancy.

There is a threefold increased incidence of haemorrhage in the posterior circulation in children compared to adults and a fivefold increased incidence in involvement of the internal carotid artery termination [13, 14].

2.3.2. Haematological Disorders. Between 10 and 30% of childhood HS are caused by haematological disorders such as haemophilia, thrombocytopenia, von Willebrand's disease, coagulopathy secondary to hepatic dysfunction, or vitamin K deficiency [3].

About 25% of children have HS of undetermined cause.

3. Outcome

Fatality rates vary from 2 to 20% for IS and from 5 to 54% for HS. Male gender, black ethnicity, and stroke recurrence increase the risk of death. Neurological deficits are reported to be present in at least two-thirds of survivors.

Lesion location and extension is an important predictor of outcome.

Even if it is widely believed that brain plasticity can lead to improved outcome following acquired brain injury at an early age, there is increasing evidence to support the hypothesis that younger age at time of stroke is a predictor of a worse outcome, particularly for cognitive and neuropsychological domains [2, 3, 15, 16]. Mortality rate in paediatric group is reported to be 6 to 30% [17]. Therefore, children should be closely monitored over the time for possible recurrences.

These are aspects that should be taken into consideration also in children with silent infarctions.

4. Recurrence

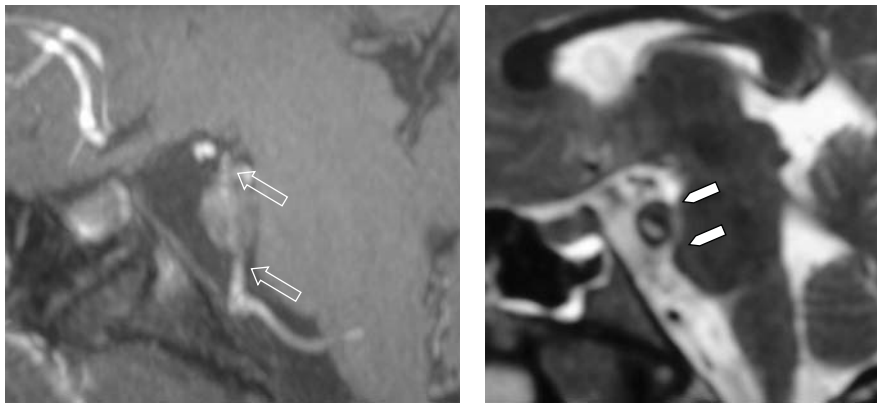
Recurrence risk of AIS is about 1.2% in the perinatal age and 19% in later infancy and childhood, but probably a greater number of children have TIAs or silent reinfarctions. Five-year followup shows no recurrence in children with normal vascular imaging and up to 60% recurrence rate in children with vascular abnormalities [14].

HS recurrence rate is about 10% at 5-year followup. No recurrences are expected in idiopathic HS whereas 13% recurrence rate in children with vascular structural anomalies and in those with medical causes of HS; in the latter cases, recurrence tends to occur within the first week, while in the former it may occur years later [18].

Between 10% and 20% of children who have a CVT will experience a recurrent symptomatic venous event, half of which systemic rather than cerebral [10].

5. Diagnostic Imaging

Cerebral imaging includes computed tomography (CT) particularly when HS is suspected in order to rapidly discriminate between HS and IS and to distinguish between intracerebral haematoma or SAH. Magnetic resonance imaging (MRI) with angio-MR (MRA) helps to precisely identify the site of IS/HS, the involved structures, the presence of oedema, and/or mass effects. Diffusion MR (DWI) and



(a) (b)

Figure 1: MRA (a) and MRI sagittal sections (b), obtained 11 days after the initial symptoms, demonstrate the presence of a BA aneurysm with mass effect on the pons (arrowheads in (b)) and ischemic changes (not shown). At both edges of the aneurysm, stenosis of the BA is recognizable (arrows in (a)).

perfusion MR (PWI) are useful to evaluate the timing of the stroke and the cerebral blood flow in the surrounding areas. Gradient-echo and susceptibility-weighted images MR (GRE/SWI) are able to detect deoxyhaemoglobin in very recent bleeding when other sequences are unable to demonstrate the extent of the haematoma or to detect small amount of haemosiderin in old HS or in cryptic malformations, such as cavernous angiomas. Finally, in selected cases, digital subtraction cerebral angiography (DSA) is recommended to better evaluate the vascular tree. Specifically, dedicated cerebrovascular imaging with DSA is crucial when no cause for stroke is found via noninvasive vascular imaging. Sometimes vascular malformations are not immediately evident after the acute haemorrhage; therefore, when vascular imaging is normal or inconclusive, the studies should be repeated once the clot has been reabsorbed [1, 3, 14, 18].

6. Treatment

Three consensus papers suggest the guidelines for the evaluation and treatment of AIS in childhood [15, 19, 20], and one encompasses guidelines for the treatment or evaluation of paediatric HS [20].

6.1. Medical Treatment. Acute and chronic management of IS includes several options, depending on the aetiology of stroke, timing, extent, and so forth. Antioedema and antiplatelet treatments are often indicated. Anticoagulant therapies are usually employed in cardiac cause, CVT, dissection, and recurrent stroke while on antiplatelet therapy. Exchange transfusion (SCD), cerebral and systemic supportive care, and correction of specific conditions are always required. Paediatrics encompasses a wide range of ages with maturational differences. Optimal dosing is likely to differ as there are age-dependent differences in haemostasis, younger individuals demonstrating diminished specific indices of fibrinolysis and global, increased fibrinolytic capability [17].

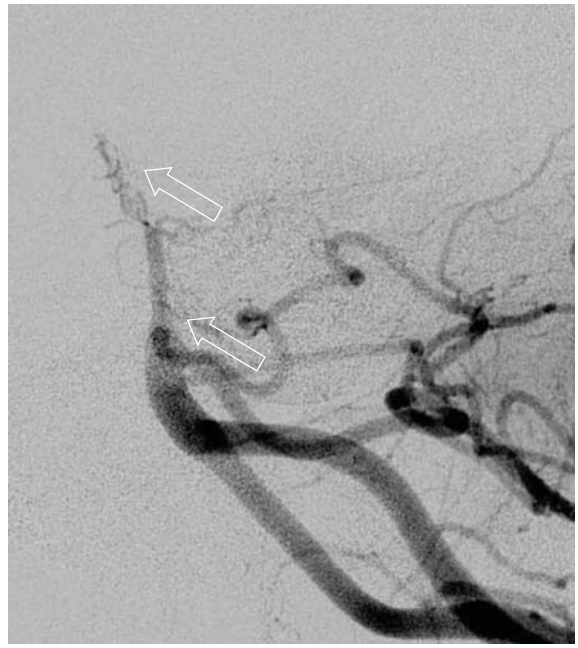
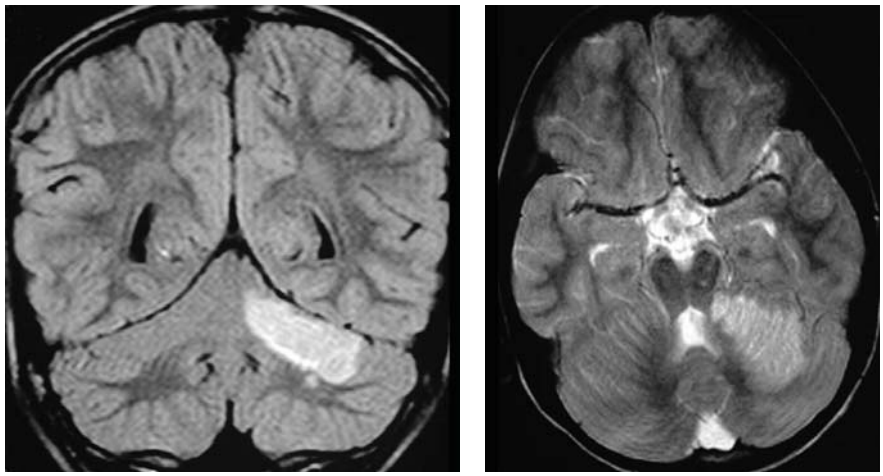


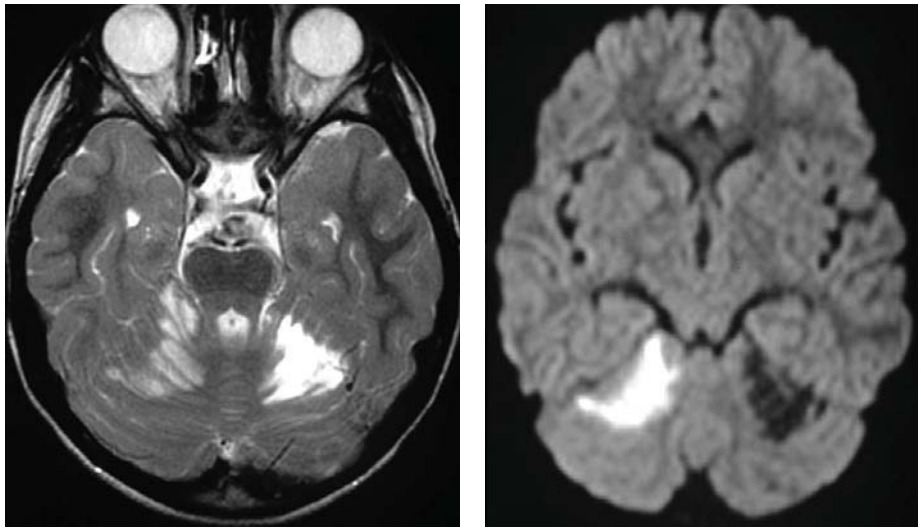
Figure 2: Follow-up angiogram, obtained 11 months after the onset of symptoms, shows complete obliteration of the BA at the level of the dissection, without any evidence of residual filling of the aneurysm.

CVT treatment includes general supportive measures and antithrombotic and nonantithrombotic therapies. Anticoagulant and antiplatelet treatment regimens vary between centers, and some of them prefer unfractioned heparin in the acute state, as the effects of heparin can be reversed if intracranial haemorrhage occurs. In the following 3 to 6 months, chronic anticoagulation is maintained with Low Molecular Weight Heparin (LMWH) or Coumadin [10]. Treatment of neonates with LMWH appears to be safe and should at least be considered. There are very few reports



(a) (b)

Figure 3: MRI coronal FLAIR (a) and axial T2-weighted (b) images show an infarction in the left superior cerebellar hemisphere, in the territory of one hemispheric branch of the left SCA.



(a) (b)

Figure 4: MRI axial T2-weighted (a) and diffusion-weighted (DWI) (b) images demonstrate the old infarction in the left superior cerebellar hemisphere and the new lesion in the right superior cerebellar hemisphere with identical distribution. The restricted diffusivity (high signal intensity in (b)) indicates a recent infarction.

on the use of antiplatelet agents such as acetylsalicylic acid (ASA) or dipyridamole in the acute or chronic settings in paediatric age [10]. If significant ICH is associated with CVT, the use of anticoagulants is controversial. Septic situation requires antibiotics and may need surgical removal and drainage of the infection. Medical treatment of HS is mainly supportive, with correction of treatable haemorrhage risk factors or correction of specific conditions such as, for instance, antimicrobial treatment in infectious aneurysms.

While a neuroprotective role has been ascribed to hypertonic solutions of albumin, memantine HCl, and magnesium sulphate that are recommended for the treatment of adult ischemic stroke patients, no data are available in order to make recommendations regarding use in paediatric AIS [17].

6.2. Surgical Options. Within the management of paediatric stroke, invasive treatments are rarely performed in selected cases, based on expert opinion [11, 12, 16, 21–27].

Surgical revascularization procedures include direct surgical bypass or indirect procedures to encourage development of collateral blood vessels such as the encephaloduroarteriomyosinangiosis in moyamoya. In case of massive cerebellar oedema or haematoma, decompressive craniectomy and haematoma evacuation can be performed to prevent tonsillar herniation. Decompressive surgery is

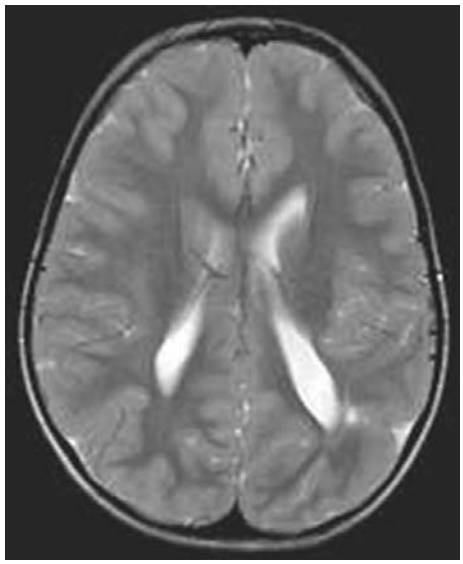


Figure 5: MRI axial T2 weighted shows the cortical-subcortical abnormalities in the left temporo-parietal-occipital region.

required in supratentorial large cerebral lesions with mass effect and transtentorial herniation. In hydrocephalus, after intraventricular haemorrhage or SAH, external ventricular drainage may be required. In vascular malformations such as aneurysms or AVMs, open surgery represents a possible treatment.

6.3. Endovascular Options. The endovascular options in case of IS comprise (1) intra-arterial thrombolysis and/or mechanical revascularization in thromboembolic lesions, (2) revascularization procedures with stenting with or without angioplasty in stenoses or dissections, and (3) intra-arterial administration of vasodilator drugs in vessels spasm. In cases of HS due to bleeding from vascular malformations, endovascular repair with platinum detachable coils or flow diverter for aneurysms, and histoacrylic or polymeric glue injections in AVM are possible alternatives. In selected cases, surgical and endovascular approaches can be combined. An additional option for the treatment of small AVM is represented by radiosurgery [28]. In case of cardiac disease (i.e., PFO), correction of the cardiac defect should be considered.

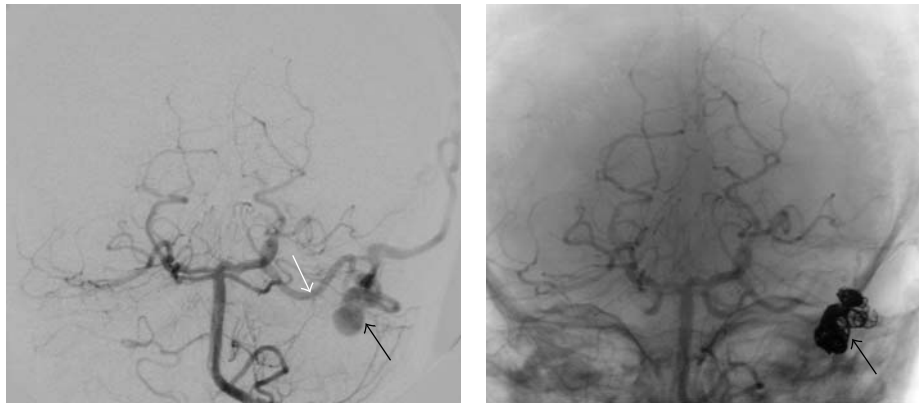
7. Illustrative Cases

7.1. Case 1 (Figures 1 and 2). A 15-year-old female patient was admitted to our hospital for angiographic followup and possible treatment of a partially thrombosed basilar artery (BA) dissecting aneurysm extending from the mid-basilar portion to the origin of the superior cerebellar arteries (SCAs). One week before her first hospitalization the patient had complained of sudden nuchal headaches sometimes associated with nausea, vomiting, and visual changes, which disappeared without any treatment. No history of previous trauma was reported. Physical and neurological examinations were within normal limits. Four-vessel cerebral digital subtraction angiography (DSA) and MRA (Figure 1) demonstrated the presence of the BA aneurysmal dilatation measuring 5 mm in its patent portion with an extension of 2 cm in length. Stenosis of the BA was recognizable proximal and distal to the aneurysm (Figure 1). Both SCAs were injected from the BA. MR imaging also visualized small ischemic areas in the left lower part of the pons and in the left cerebral peduncle (Figure 1). The patient was discharged on antiplatelet therapy (ticlopidine 250 mg/dL) to prevent further thrombotic events. The 2- and 4-month follow-up MR imaging with MRA showed further progression of the BA stenosis. Due to the good clinical condition of the patient, endovascular revascularization was not performed because of the high procedural risks. Finally, the follow-up angiogram (Figure 2) obtained 11 months after the initial symptoms demonstrated complete obliteration of the BA at the level of the dissection (arrows) without any evidence of filling of the aneurysmal pouch and adequate collateral flow to the upper BA, posterior cerebral arteries (PCAs), and SCAs provided by the internal carotid arteries via the posterior communicating arteries. MR imaging performed at the same time demonstrated shrinkage of the aneurysm without new ischemic lesions. The 19-month follow-up MR imaging ruled out the presence of new ischemic areas. At the present time, 6 years later, the patient remains clinically stable and neurologically intact. The extensive workup for suspected collagenopathy, including genetic research for the type 4 Ehlers-Danlos and collagen biopsy, was negative.

7.2. Case 2 (Figures 3 and 4). A 7-year-old roller-skater male was first admitted at a primary medical center with a 4-hour history of acute onset of unstable gait and left-limb weakness during a play fight with his sister, followed by diffuse headache. A brain CT scan was normal. Over the next 12 hours the patient's balance disorder improved, while left-limb weakness remained stable and a mild left cerebellar syndrome. Brain MRI and magnetic resonance angiography (MRA) showed a left cerebellar ischemic stroke and absence of the left superior cerebellar artery (SCA). Cardiac disorders were initially excluded by transthoracic echocardiogram.

The patient was admitted to our institute 5 days after symptoms onset. Anti-platelet treatment was started. Head and neck angio-CT and brain MRI revealed an infarction in the left superior cerebellar hemisphere (Figure 3) and the presence of a possible dissection of the left vertebral artery close to the foramen magnum. The cerebral DSA showed a lumen margin irregularity consistent with a fresh thrombus in the proximal tract of the left SCA. Laboratory findings excluded haematological disorders such as thrombophilias and SCD.

Over the next 7 days the patient's neurological symptoms gradually improved. Then, one week later, he abruptly developed headache, repeated vomiting, disturbance of consciousness with drowsiness, and right limb weakness. Brain MRI demonstrated a new cerebellar ischemic lesion in the superior right cerebellar hemisphere (Figure 4). Anticoagulant medication (low molecular weight heparin) was initiated. Over the following days the patient had



(a) (b)

Figure 6: Anteroposterior view of the left vertebral angiography showing a direct arteriovenous shunt between the anterior temporal branch of the left PCA (white arrow) and a superficial temporal vein with an interposed irregular aneurysmal dilatation (black arrow in (a)). The posttreatment angiography (b) demonstrates the complete resolution of the shunt obtained utilizing detachable platinum coils and histoacrylic glue (arrow in (b)).

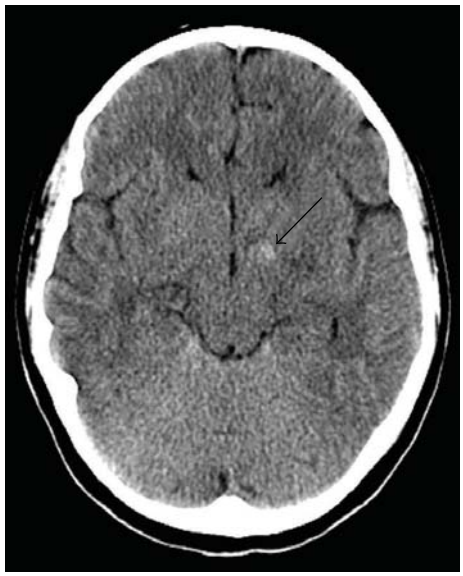


Figure 7: A small, well-defined hyperdense lesion in the left frontal basal area, just below the basal nuclei, is recognizable at the emergency CT (arrow). There is no evidence of subarachnoid haemorrhage.

a dramatic clinical improvement, and neurological examination demonstrated only a mild right cerebellar syndrome. Repeated transoesophageal echocardiography during Valsalva maneuver revealed an atrial septal defect that was repaired via percutaneous endovascular approach due to significant resting shunts. Clinical and neuroradiological followups since then were unremarkable.

7.3. Case 3 (Figures 5 and 6). A 4-year-old female, with a strong family history (father and grandfather) of hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease, was first evaluated at our institute at the age of 3 months for left temporal lobe hemorrhagic lesions detected elsewhere in the neonatal period. Neonatal history was complicated by tremors and generalized seizures that started on the second day of life after normal pregnancy and delivery.

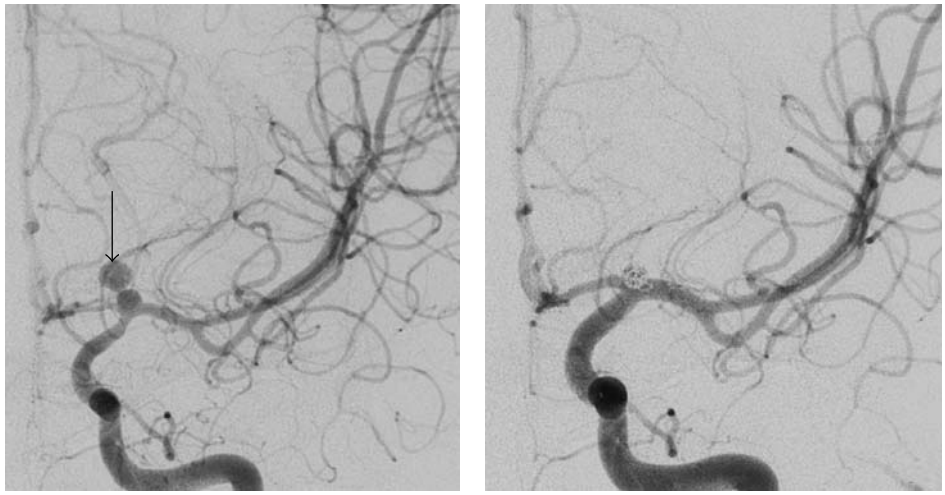
On first admission at our institute, she was severely hypotonic; epilepsy was well controlled by antiepileptic monotherapy. Serial brain MRI and MRA studies (Figure 5) revealed left cortical-subcortical temporo-parietal-occipital gliotic-malacic areas associated with a cortical malformation.

A possible vascular malformation was also suspected in the left temporal hemisphere. Due to the age and the clinical condition of the patient, DSA was not performed at that time.

The patient presented psychomotor and language delay, and at the age of 4 years she started having recurrent episodes of epistaxis. Genetic analysis confirmed the HHT diagnosis with a mutation in the endoglin gene (ENG) on chromosome 9. Abdominal and pulmonary artero-venous malformations were excluded after adequate screening.

Four vessels DSA was then performed under general anesthesia, showing a left temporal arteriovenous shunt with an abnormal vascular dilatation, probably consistent with a venous varix (Figure 6(a)). It was successfully treated via endovascular approach with a superselective catheterization of the left anterior temporal artery, obliterating the venous varix and the shunt, utilizing detachable platinum coils and histoacrylic glue (Figure 6(b)).

7.4. Case 4 (Figures 7 and 8). A 12-year-old girl, who complained of a sudden headache with no other neurological deficit, was brought to the Emergency Room of another hospital. CT scan showed a small, round area of hyperdensity in the left basal frontal lobe, just below the basal ganglia (arrow in Figure 7). No subarachnoid blood was depicted. The patient was referred to our hospital for further examinations. At admittance, the patient was awake, well oriented, with no neurological deficit, but suffering



(a) (b)

Figure 8: Anteroposterior view of the left internal carotid artery angiography shows a blister-like aneurysm at the intracranial bifurcation (a). Note the small pseudoaneurysm (arrow in (a)) at the dome of the aneurysmal sac, corresponding to the image seen on the CT (Figure 7), and the spasm in the supraclinoid portion of the carotid artery. The posttreatment angiography shows successful obliteration of the aneurysm with stent and a single platinum coil (b).

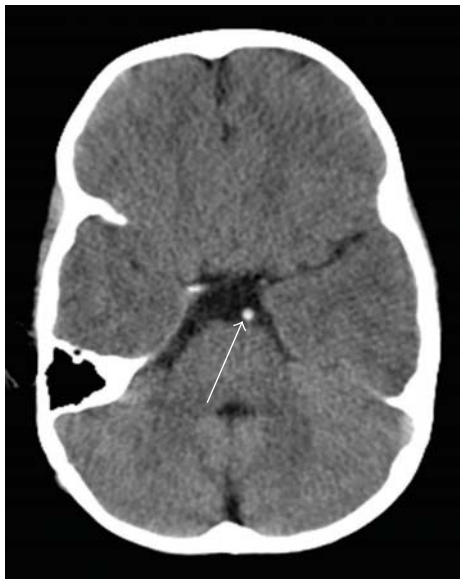


Figure 9: CT at admittance to Emergency Room shows a hyperdensity of the basilar artery, consistent with a thrombus (arrow).

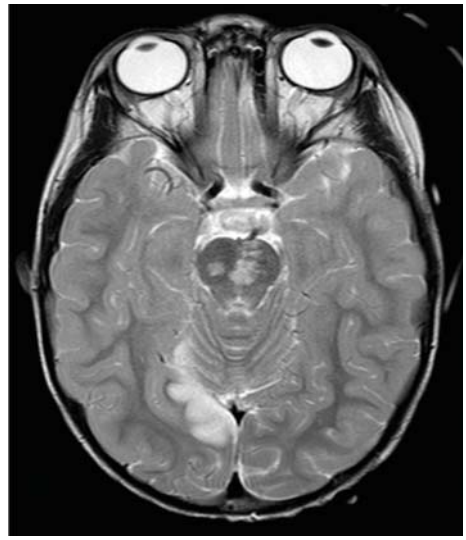


Figure 10: The axial T2 MR study performed 3 days after symptoms onset demonstrates the ischemic lesions in the pons and right occipital cortex.

from intense headache. DSA showed a small "blister-like" aneurysm at the left internal carotid artery bifurcation with a pseudoaneurysm just above it (arrow in Figure 8(a)). The patient was treated by endovascular approach, considering the neurosurgical approach more risky due to the presence of many perforating vessels in the area. Since the neck of the aneurysm was wide, a neuroform stent was deployed and a single platinum coil detached after passing through the struts of the stent. The final control showed the occlusion of the sac and the normal flow in the carotid artery (Figure 8(b)), with contrast stagnation inside the pseudoaneurysm. After the stent deployment, antiplatelet therapy was started and kept for 6 weeks. The patient had no deficit. Headache progressively decreased in the following days.

No recurrence of the aneurysm was observed at the 6-month follow-up angiography.

7.5. Case 5 (Figures 9–11). A 3-year-old African boy presented with sudden onset of nausea and vomiting. He was admitted to the Emergency Room hypotonic, hyporeactive, with abnormal ocular movements and recurrent seizures. In the recent past medical history, only sporadic headache was

reported, after a varicella infection. At brain CT a hyperdense basilar artery was visible (arrow in Figure 9). At MRI with MRA, ischemic lesions in the vertebrobasilar territory with severe obstruction of the basilar and right posterior cerebral arteries were observed. As some hours had already passed from symptoms onset and the experience as well as the literature data on thrombolysis in children were poor, it was decided not to proceed to thrombolysis neither by venous nor arterial route. In addition, clinical conditions, though severe, did not seem to be life-threatening at that moment. Over the next few days, patient clinical conditions slowly but progressively improved. An MRI control at day 3 showed a new lesion in the pons (Figure 10). A DSA performed at day 12 confirmed the MRI findings: occlusion of the basilar artery from the vertebrobasilar (VB) junction to the tip, with good collaterals supplying the brainstem perforators and partial revascularization of the superior cerebellar arteries (arrows in Figure 11).

In the diagnostic workup, a patency of the foramen ovale was found, as the cardiologists did not consider the thromboembolic source causing the occlusion. At day 22, at discharge, no neurological deficits were present except for a very slight difficulty in walking with a preferred use of the left limbs.

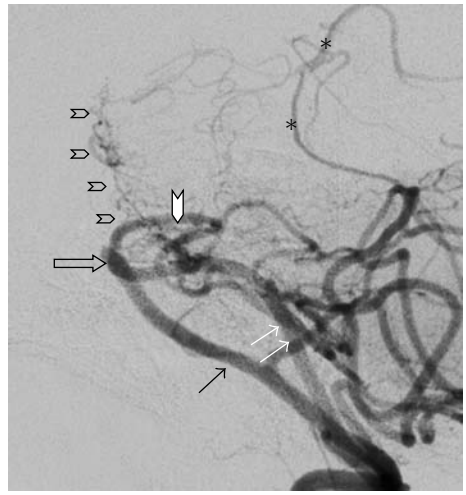


Figure 11: Cerebral angiography (lateral view) with injection of the left vertebral artery (arrow) shows occlusion of the basilar artery (open arrow) at the vertebrobasilar junction, just above the origin of the right superior cerebellar artery (white arrowhead). There are many tiny collaterals that supply the territory of the brainstem perforators (small arrowheads) and wider collaterals that reconstitute the superior cerebellar artery (asterisks). There is also retrograde filling of the right vertebral artery (white arrows) and of the right PICA.

8. Discussion and Conclusion

Stroke in paediatric population is associated with relative high morbidity, mortality, and recurrence rates. Silent stroke can be responsible for neuropsychological disability not otherwise recognizable.

If a stroke is suspected in a child, the diagnostic work-up should include systemic blood tests (haematological disorders, infections), genetic and cardiac examinations (see our case 2). The neuroradiological diagnosis comprehends CT scan, MR imaging, and DSA. CT scan may demonstrate the presence and site of the intracranial bleeding (SAH or intracerebral haematoma) in case of HS. MR imaging with MRA better delineates the brain tissue status, the presence, the nature, and sometime the timing of possible structural lesions, for both HS and IS. They represent crucial tools both for treatment planning and followup. DSA is an invasive exam that should be performed by expert operators and only in selected cases. MRI and DSA in childhood are commonly performed in general anaesthesia to ensure a good quality imaging without any discomfort for the young patient.

In the appropriate setting, besides medical treatment, invasive procedures including endovascular approach should be considered. In cases of structural lesions a thorough risk/benefit analysis in order to decide the best treatment option is mandatory. Timing of invasive treatment can also represent a troublesome factor in a very young patient in whom fluid balance is a critical aspect in the anesthesiological and surgical management. In very small children, for this reason, it may be necessary to delay treatment waiting for a more favourable clinical status such as in our case 3.

In case of aneurysm the endovascular approach includes the obliteration of the fundus utilizing detachable coils associated with an intracranial stent in case of large neck, such as in our case 4. Experience in stent placement in children is limited; double antiplatelet therapy in case of stent deployment is recommended; since there are not specific trials for antiplatelet treatment for intracranial stenting in children, medical treatment is reasonably based on the adult's literature data. Another concern with paediatric intracranial stenting is the ongoing growth of the vessels over the time [11, 12, 23].

Dissecting aneurysm represents a typical vascular malformation in which the treatment must be tailored case by case. In case of a large dissecting aneurysm in a distal vascular territory, the obliteration of the arterial feeder with coils or glue should be taken into consideration. A balloon occlusion test to verify the possible collateral network can be previously performed. In case of a large thrombotic dissecting aneurysm in a vital territory, a precise preoperatory planning should be carried out, balancing benefits and risks. In our case 1, where a nonruptured large partially thrombosed aneurysm of the basilar artery causes a critical stenosis of the vessel, we preferred to delay the management of the aneurysm and of the BA stenosis because of the good clinical condition of the patient. Therefore, we followed the patient with MRI and MRA every 2–4 months. The spontaneous occlusion of the BA with repair of the aneurysm occurred asymptomatically.

Detachable coils and glue can be successfully utilized to occlude arteriovenous fistulas or AVM, such as in our case 3 in whom the direct AV fistula was related to HHT; in fact the presence of a cerebral AVM is one of the four diagnostic criteria for HHT [27].

In childhood, revascularization procedures in thrombotic vessels utilizing an endovascular approach are anecdotic (our case 5), likewise for the new flow-diverters devices that are indicated for aneurysmal repair in adult, and no literature data or specific recommendations are available as already discussed in the Treatment section.

In conclusion, stroke in childhood represents a challenging disease in which a correct diagnostic conduct may lead to the most appropriate treatment. A decision-making process should be carried out case by case by a multispecialist group, including the neuropaediatrician, neurosurgeon, and neuroradiologist. Future trials focused on treatment of vascular diseases in the youngest population are necessary to better understand the disease and, therefore, to improve the treatment.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Current Proceedings of Childhood Stroke

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Stroke is a sudden onset neurological deficit due to a cerebrovascular event. In children, the recognition of stroke is often delayed due to the low incidence of stroke and the lack of specific assessment measures to this entity. The causes of pediatric stroke are significantly different from that of adult stroke. The lack of safety and efficiency data in the treatment is the challenge while facing children with stroke. Nearly half of survivors of pediatric stroke may have neurologic deficits affecting functional status and quality of life. They may cause a substantial burden on health care resources. Hence, an accurate history, including onset and duration of symptoms, risk factors, and a complete investigation, including hematologic, neuroimaging, and metabolic studies is the key to make a corrective diagnosis. A prompt and optimal treatment without delay may minimize the damage to the brain.

1. Introduction

Stroke is defined as the sudden occlusion or rupture of cerebral arteries or veins resulting in focal damage and clinical neurologic deficits. Clinical manifestations of stroke include weakness or paralysis of a limb, or the sudden inability to speak, and the onset of the deficit may be within seconds, minutes, or hours. Stroke is one of the most common neurological causes for admission to a hospital and is the second commonest cause of death in the world [1]. Although stroke is still a disease of the senescence and the incidence of stroke for old people is approximately 12/1,000, [2–4] stroke in the young people is relatively rare. The annual incidence rate for stroke in children is 2-3/100,000 [5]. The incidence of neonatal stroke is much rarer, approximately 1 in 4000 term live births. There was a slight female predominance [6–8]. The prevalence of stroke in the east countries is different from that in the West, and this difference has been attributed to differences in urbanization, change of diet, lifestyles, and healthcare facilities [9, 10]. Stroke is particularly tragic because of much longer expected lifespan ahead leasing to a long-term burden for the victims, their families, and community, emphasizing the need for a high degree of clinical suspicion toward the stroke in the young. The current review focuses on pediatric strokes.

2. Etiologies

Contrary to adults in whom arteriosclerosis is the leading cause, risk factors of pediatric strokes are multiple [11], including cardiac disorders, infection, prothrombotic disorders, moyamoya disease and moyamoya syndrome, and others.

2.1. Cardiac Disorders. Congenital heart disease (CHD) and other cardiac problems are still recognized as presumed risk factors for pediatric stroke [12]. In the presence of an atrial or ventricular septal defect with intermittent right-to-left intracardiac shunting including patent foramen ovale [13–15], systemic venous clots can reach the cerebral circulation. In addition, stroke is highly related to procedures such as surgery of catheterization [12, 16, 17] and Fontan surgery [18–20]. Prosthetic heart valves are an important source of emboli [21, 22]. Therefore, most congenital heart lesions should be repaired to improve cardiac function and reduce the risk of subsequent stroke. All children with strokes

of undermined causes should have an echocardiogram performed.

2.2. Infection. Varicella is reported to be related to pediatric ischemic strokes [23–27]. Radiographic features of postvaricella angiopathy include basal ganglion infarctions and self-resolving unilateral stenosis of the distal internal carotid or proximal anterior, middle, or posterior cerebral arteries [28, 29]. Several viruses have been linked to arteriopathies and strokes in children, but paradoxically, not so many children have strokes as minor viral infections are so common in children. It is still not clear how viral infections contribute to arteriopathies and strokes.

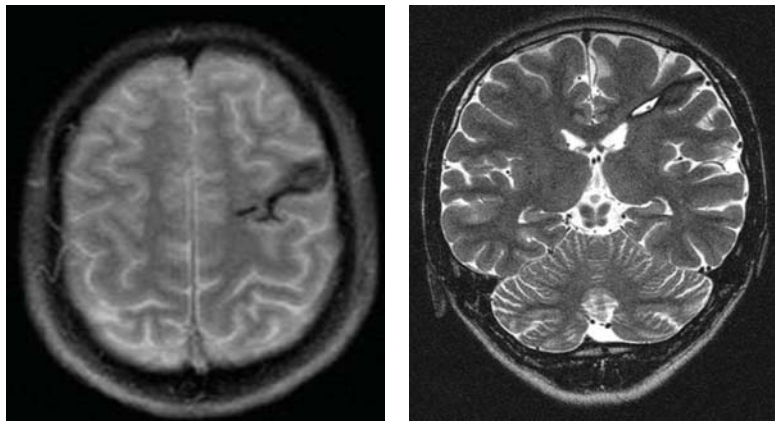
2.3. Prothrombotic and Hematologic Disorders. Inherited or acquired prothrombotic or coagulation disorders can predispose children to strokes [30, 31]. Most common prothrombotic abnormalities include deficiencies of protein C [32], protein S [33], antithrombin III [34], plasminogen [35], anticardiolipin antibody [33], lupus anticoagulant [33], homocystein [34] and antiphospholipid antibodies [34], prothrombin 20210A gene [36], and mutated Factor V [37] and mutated methyl-tetrahydrofolate reductase (MTHFR) [38]. Coagulation studies should be performed in any child with stroke without identified risk factors. Abnormal results on samples taken within several weeks of the stroke should be confirmed by testing parents, if the abnormality is a hereditary coagulation abnormality, or the child should be retested several months later.

2.4. Moyamoya Disease and Moyamoya Syndrome. Moyamoya disease is a nonatherosclerotic, noninflammatory, and nonamyloid vasculopathy characterized by chronic progressive stenosis or occlusion of the terminal internal carotid arteries and/or the proximal portion of the anterior cerebral arteries and/or middle cerebral arteries [39]. Moyamoya disease is more common in girls [40] and peaks in both the first and fourth decades of life [41]. The definitive method for diagnosis is conventional angiography, which may show a pattern of "hazy, cloudy puff of smoke." The underlying reflects an abnormal network of small collateral vessels in response to the stenosis (Figure 3). In Japanese, the term "moyamoya" represents the appearance of radiographic features [42]. The clinical course may be stable, may appear recurrent transient ischemic attacks (TIAs), and may manifest strokes with progressive neurologic impairment or alternate hemiplegia [43, 44]. Partial and secondary generalized seizures are common in younger children [45]. No specific medical therapy can effectively halt the progression of moyamoya disease. Complications of moyamoya disease include intellectual impairment and permanent motor deficits [46]. The moyamoya syndrome shows radiographic features of moyamoya disease but different underlying etiologies, such as sickle cell disease or postradiation vasculopathy. Revascularization including anastomosis of the superficial temporal artery to the cerebral artery, encephalomyosynangiosis, and encephaloduroarteriosynangiosis [47] is promising because it is associated with a reduced stroke rate [48].

2.5. Other Risk Factors. Hyperlipidemia is one of the most common risk factors for stroke in a Chinese young stroke study [49]. Mild trauma or exertion causing cerebral arterial dissection may lead to pediatric stroke [8]. Hsu et al. [50] reported a child suddenly experienced left hemiparalysis after performing repeated backward somersault resulting in an isolated middle cerebral artery dissection (Figure 4). When the dissection of carotid or vertebral arteries occurs, this event may result from a tear to the arterial wall often related to trauma. However, this tragedy may occur spontaneously in children [51] or be caused by nonaccidental traumas and strangulation. If there is any unexplained subdural hemorrhage (SDH) in infants (Figure 2), nonaccidental traumas should be considered, and retinal hemorrhage may provide a supportive clue of shaken baby syndrome. Migraine is also a dangerous risk factor because literature shows that women who had experienced onset of migraine within the previous year had 6.9-fold higher odds of stroke compared with women without a history of migraine [52]. Vasculitis, such as polyarteritis nodosa [53], Takayasu's arteritis [54], mixed connective tissue disease [55], and systemic lupus erythematosus [56], has all been reported in childhood strokes. An elevated homocystein level appears to be associated with strokes in young Asian patients [57]. Patients with Fabry's disease, a lack of alpha galactosidase, may have multiple lacunar cerebral infarcts in affected boys during the teenage and early adult years [58]. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) in children present with episodes of nausea, vomiting, headache, seizures, hemiparesis, and cortical blindness. Infarct-like lesions in the cerebral cortex, basal ganglia, and brainstem are confirmed by autopsy [59]. Cranial CT or MRI shows areas of infarctions that do not correspond to major vascular distributions. A3243G mutation affecting the rates of mitochondrial translation and respiration consequently causes the mitochondrial dysfunction [60]. Children with neurofibromatosis may have complications of cerebral arteriopathies [61]. History of use of oral contraceptives and illicit drugs (amphetamines, cocaine) is a risk factor for strokes in the young people.

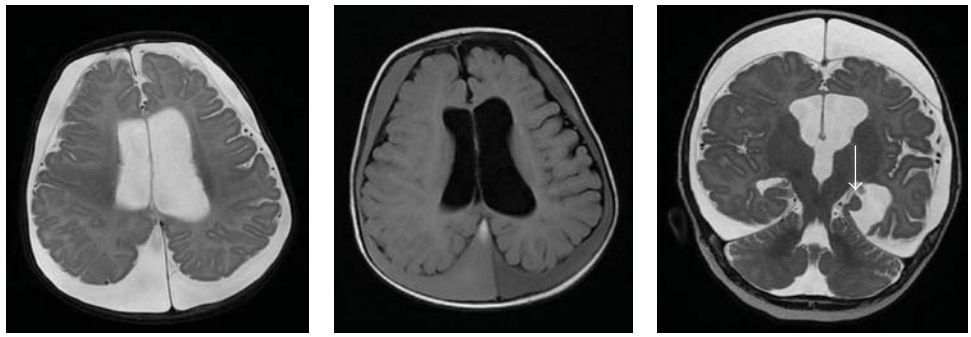
3. Clinical Features

Seizures, irritability, or altered consciousness are common in infants and young children, but hemiparesis is difficult to recognize in this age group [11]. Older children typically present with speech, visual, focal sensory, or coordination abnormalities. Dystonia is more common in children with basal ganglia infarction than in adults. TIAs are increasingly recognized in children and infants [11]. Even so, the recognition of cerebral infarction in children is often delayed due to the low incidence of stroke and the lack of awareness of pediatricians to this entity [62]. Hence, clinical features obtained from the history and physical examination can provide significant information. For instance, a recent head or neck injury suggests dissection. A recent varicella infection should lead to consideration of postvaricella angiopathy.



(a) (b)

Figure 1: A 17-year-old boy was presented with seizures one month after a prior head injury. Axial T1-weighted image (a) and coronal T2-weighted image (b) showed the hemosiderin deposition and a small CSF-filled cavity of the left middle frontal gyrus.



(a) (b) (c)

Figure 2: A 4-month-old infant was presented with a large head circumference followed by seizure-like episodes. Axial T2-weighted image (a) showed hydrocephalus and prominent CSF space along bilateral cerebral convexities. The fluid was subdural hematomas because the signal intensity of the fluid is different from that of CSF on FLAIR T2-weighted image (b). Coronal T2-weighted image showed hypoplasia of the left hippocampus.

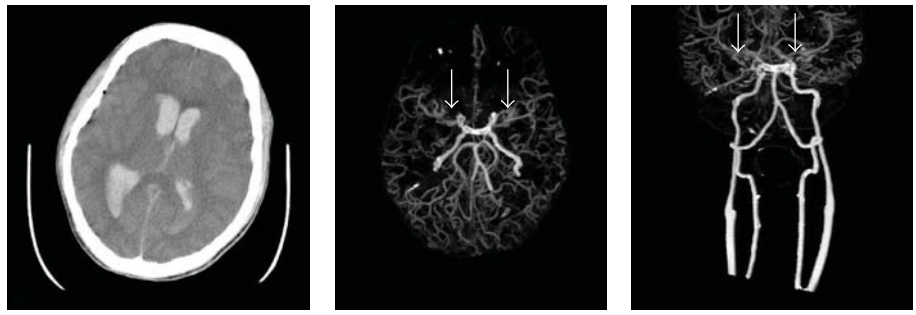
Migraine and oral contraceptive, amphetamine, or cocaine use all predispose to infarction. A family history of stroke [63], heart attack, lipid problems, and calf deep vein or pulmonary thrombosis at young ages may be associated with increased stroke risk. Physical examination such as head or neck bruits, cardiac murmurs or skin lesions of tuberous sclerosis, Neurofibromatosis or Fabry's disease may also provide additional clues.

4. Classification

Strokes can be subdivided into two types: ischemic and hemorrhagic.

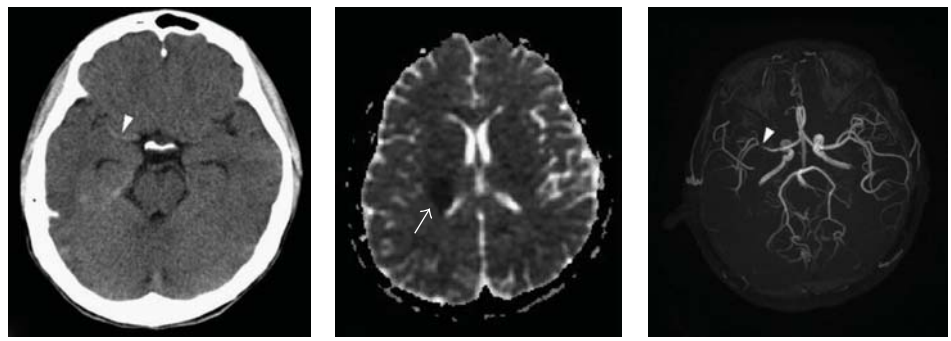
4.1. Hemorrhagic Stroke. Hemorrhagic stroke is as common as ischemic stroke in childhood, and nearly half of pediatric strokes are hemorrhagic [64]. There are two major types of hemorrhagic stroke which reflect the anatomic site of the bleeding and are classified as "intracerebral hemorrhage (ICH)" and "subarachnoid hemorrhage (SAH)." They can coexist in individual patients, such as when rupture of an arteriovenous malformation (AVM) produces both SAH and ICH. In contrast to ischemic stroke, definitive treatment for hemorrhagic stroke frequently requires neurological intervention [65, 66].

4.2. Intracerebral Hemorrhage (ICH). ICH devastates children with death reported in up to 33% and permanent deficits in up to 40%, including seizures and cognitive and motor impairment [65, 67]. ICHs result from the rupture of cranial vessels and are classified as extradural, subdural, subarachnoid, intracerebral, or intraventricular. Compared with adults, pediatric ICH is more likely to result from a bleeding diathesis due to inherited hemophilic or thrombocytopenic disorders [68]. In acquired conditions, ICH is present in at least 9% of infants undergoing extracorporeal membrane oxygenator (ECHO) procedure and occurs early after initiation of bypass in 85% [69]. Trauma is the common cause for ICH in children (Figure 1). Typical clinical features in children are seizures,



(a) (b) (c)

Figure 3: A 17-year-old boy was presented with sudden loss of consciousness and generalized seizure attack. Nonenhanced CT study (a) showed acute intraventricular hemorrhage. CT angiography (b, c) disclosed occlusion of bilateral prebifurcation M1 segment of middle cerebral arteries with some moyamoya vessels (arrows).



(a) (b) (c)

Figure 4: A 15-year-old boy suddenly experienced acute right-sided headache and dizziness followed by drowsy consciousness and left-sided weakness after practicing backward somersaults. Nonenhanced CT image of the brain (a) showed increased attenuation at the M1 segment of the right MCA (white arrowhead). Apparent diffusion map of the brain (b) delineated a 2.4-cm low-signal area in the posterior limb of the right internal capsule, consistent with a hyperacute infarct (arrow). Magnetic resonance angiography of the brain (c) showed focal stenosis of the right MCA with decreased flow and number of distal branches (white arrowhead).

decreasing levels of consciousness, and IICP. It is unusual for infants to present bulging fontanel and splayed sutures and focal signs resulting from the increasing volume of intracranial blood, edema, or secondary hydrocephalus because infants with nonfused cranial sutures can accommodate to increase in brain volumes with raised ICP. The periventricular germinal matrix of preterm neonates is extremely vulnerable to hypoxia. Once hemorrhage occurs, blood may extend into the ventricular system and cause extension of hemorrhage because the unmyelinated brain of infant offers relatively less mechanical resistance than the adult brain. Available evidence shows that pediatric ICH is caused by hematologic abnormalities and infratentorial hemorrhage location [70], and ICH volume [71] is associated with poor outcome.

4.3. Subarachnoid Hemorrhage (SAH). SAH is a neurologic emergency characterized by the extravasation of blood into the spaces covering the CNS that are filled with CSF [72]. Ruptures of aneurysms, AVMs, and head trauma are the major causes for SAH. The underlying cause for neonate SAH is usually hypoxia in preterm or trauma in term infants. Trauma is the common cause for SAH in children [73]. Rupture of an aneurysm accounts for 80% of cases [74]. In infants, most aneurysms tend to rupture less than 2 years of age or in children older than 10 years [75]. Typical presentations of SAH include a sudden and severe onset of headache, a stiff or painful neck, vision loss, inability to move an arm or leg, numbness, speech difficulty, and/or loss of consciousness in adults, and there may be intermittent seizures or no symptoms on a well baby. SAH is occasionally detected on CT, MRI, or postmortem in neonates after a normal or minor traumatic vaginal delivery. Lumbar puncture should be performed in any patient with suspected SAH and equivocal results on head CT scanning. MRI and MRA can provide good visualization of aneurysms, but angiography is more reliable. Treatment of patients with aneurysmal SAH not only involves securing the aneurysm by endovascular coiling or surgical clipping but also prevention and treatment of the medical and neurological complications, including symptomatic vasospasm [76], hydrocephalus [77], and rebleeding [78]. More than half of survivors report problems with memory, mood, or neuropsychological function [72]. The average

case mortality rate for SAH is 51% [79]. Early identification and therapy of cerebral and systemic complications are very important to preserve and improve functional outcome.

4.4. Cerebral Sinovenous Thrombosis (CSVT). CSVT is defined by the presence of thrombus or flow interruption within cerebral veins or dural venous sinuses. More rapid rates of occlusion of cerebral venous structures lead to a rise in cerebral venous pressure that are more likely to produce infarction and occasionally may interfere regional perfusion. CVST is rare in children and the incidence is 0.67 per 100,000 children per year with over 40% occurring in newborn [80]. CSVT has been reported in neonates with asphyxia, lethargy, jitteriness, and seizure without focal signs [80–83] and in 25% of children with pseudotumor cerebri [84]. Iron-deficiency anemia has been increasingly reported in pediatric patients with CSVT [85–87]. In septic CSVT, a bacterial infection adjacent to the sinuses spreads directly into the sinus, provoking thrombophlebitis. Dehydration is a dangerous signal for SVT because of increased hemoconcentration impairing laminar flow. In neonates, the increased risk for CSVT may be due to the location of the major dural sinuses along the bony suture lines and their consequent mechanical distortion during calvarial molding in the birth process [88]. In older children, head trauma or cranial surgery may damage the dural sinuses, leading to CVST [89, 90]. The diagnosis of CVST requires neuroimaging evidence of thrombus or lack of flow in the cerebral veins or venous sinus. However, brain CT scan may yield false-positive results, particularly in neonates. Spiral CT imaging can delineate vascular flow, enabling noninvasive cerebral CT venography [91]. MRI can clearly visualize both absent flow and the presence of thrombus, clot progression, and resolution over time as well as associated parenchymal lesions have made MRI the diagnostic study of choice in CSVT [84, 92, 93]. Cerebral angiography is still the gold standard especially when CT or MRI is not definitive. Treatment of SVT includes general supportive measures and antithrombotic and nonantithrombotic therapies. Studies showed that anticoagulants were used in up to 50% of childhood CSVT patients without significant hemorrhagic complications [80, 94]. For neonates with CSVT, unfractionated heparin or low-molecular-weight heparin given for 7 days followed by low-molecular-weight heparin alone for 6 to 12 weeks is indicative. For older infants and children, unfractionated heparin or low-molecular-weight heparin given for 7 days, followed by Coumadin for 3 to 6 months, is a treatment option. If significant ICH is associated with SVT, the use of anticoagulants is controversial. Septic SVT requires antibiotics and may need surgical removal and drainage of the infection. Regular cranial ultrasound can monitor and screen the course of CSVT. The long-term outcome in adults with SVT is quite good, but mortality rate in pediatric CSVT is reported to be 6 to 30% [95, 96]. Therefore, children with CSVT should be closely monitored.

5. Diagnosis

The diagnosis of stroke relies mainly on a detailed history, careful neurological examination and astute suspicion, and its differentiation from other conditions that mimic stroke's presentations. The confirmation requires laboratory investigations including (1) a full blood count (CBC) to detect polycythemia, thrombocytosis, or anemia; (2) ESR to exclude arteritis or bacterial endocarditis; (3) levels of urea and electrolytes to reveal any electrolyte disturbance that can mimic stroke; (4) level of blood glucose; hyper-and hypoglycemia can mimic stroke, and diabetes mellitus is a risk factor; (5) serum cholesterol; a well-known risk factor for strokes and heart attack; (6) syphilis serology as syphilis is a rare but treatable cause of stroke; (7) blood cultures should be performed if there is any suspicion of bacterial endocarditis. EKG may detect cardiac sources of ventricular hypertrophy and/or arrhythmia. Chest X-ray can demonstrate cardiac sources of emboli, ventricular hypertrophy, and/or any organic lesions. Doppler ultrasound can detect large vessel vasculopathy in carotid and intracranial arteries. CT scans, CT spiral angiography, and MRI may navigate clinicians the anatomy of each major artery in the brain and localize hemorrhages and damaged tissue. MRI is far superior to CT in detecting small and multiple infarcts, especially in the brainstem and cerebellum. Modifications of MRI include diffusion-weighted imaging, perfusion MR imaging, proton spectroscopic imaging, and MRA, that have improved the early detection and specificity of ischemic injury. Moreover, single-photon emission computed tomography (SPECT) scanning can detect areas of hypoperfusion that may occur earlier than other radiographically detected defects in the arterial ischemic stroke.

6. Treatment

In acute stage, newborns with arterial ischemic stroke rarely require antithrombotic treatment; children with stroke should be stabilized promptly and transferred to a tertiary care centers with expertise that can provide specialized pediatric neurovascular care, because their autoregulation of CNS vascular system is dysfunction [97]. Optimal treatment, including antithrombotic therapies, thrombolytics agents, neuroprotective agents, neurosurgical procedures, and careful monitor of blood pressure, body temperature, and biochemical data such as hemoglobin and blood glucose and careful fluid management, should be given to minimize the damage to the brain.

6.1. Heparin. Heparin, a large heterogenous polysaccharide complex, cannot cross the placenta. The mechanisms of Heparin are those that enhance the rate by which antithrombin III neutralizes the activity of several activated clotting proteins, especially factor Xa and thrombin in turn prevent clot extension or new clot formation [98]. The average $t_{1/2}$ of intravenous heparin is about 60 minutes in adults and can be as short as 30 minutes in the newborn. Heparin is commonly used in children for deep vein thrombosis and pulmonary embolism. Heparin has been the standard

therapy for acute anticoagulation following stroke [99]. Heparin is given at maintenance dose of 28 units/kg/hour in infants, 20 units/kg/hour in children older than 1 year of age, and 18 units/kg/hour in older children. The target activated partial thromboplastin time is 60 to 85 seconds or 1.5 to 2 times of the baseline value. A recent central nervous system hemorrhage; bleeding from inaccessible sites; malignant hypertension; bacterial endocarditis; recent surgery of the eye, brain, or spinal cord; current administration of regional or lumbar block anesthesia are contraindicated in the anticoagulation treatment with heparin. Because heparin can be neutralized by protamine sulfate, specific heparin levels should be obtained so that the heparin level is 0.35–0.70 Unit/mL by antifactor Xa assay or 0.2–0.4 unit/mL by protamine sulfate assay. Low-molecular-weight (LMW) heparin has become the first choice for acute anticoagulation therapy because adults with arterial infarcts treated with low-molecular-weight (LMW) heparin may have a better outcome [100] and so as to that in children [101]. However, adult patients receiving LMW heparin usually do not need to have their heparin levels monitored, but in pediatric patients, monitoring is critical to ensure that a therapeutic level is achieved, which for antifactor Xa is 0.5 to 1.0 units/mL in a sample drawn 4 to 6 hours after the subcutaneous dose.

6.2. Warfarin. Warfarin is an oral anticoagulant drug that reduce the activity of the vitamin K-dependent coagulation factors: II, VII, IX, and X, as well as protein C and protein S. Prothrombin time (PT) is the clotting test used to assess warfarin anticoagulation. Warfarin is used in adults for the secondary prevention of stroke in situations in which aspirin therapy has failed. In children with cerebrovascular disorders, including severe hypercoagulable states, arterial dissection [102], cardiogenic embolism [102], cerebral sinovenous thrombosis (CSVT) [103], and ischemic stroke or TIA [104], the international normalized ratio (INR) for standard treatment of thrombosis is 2.0-3.0. The most serious side effect of warfarin is hemorrhage. Contraindications to Warfarin anticoagulants are essentially the same as those for heparin therapy.

6.3. Thrombolytic Agents. Thrombolytic agents include streptokinase, urokinase, prourokinase, and recombinant tissue-type plasminogen activator (rTPA). Natural streptokinase is isolated and purified from streptococci. Streptokinase is not a protease and has no enzymatic activity; however, it forms a complex with plasminogen that releases plasmin [105]. Urokinase is occasionally referred to as urinary-type plasminogen activator (uPA) because it is formed by kidneys and is found in urine [106]. One benefit over streptokinase is that urokinase is nonantigenic; however, this is offset by a much greater cost. Lack of fibrin specificity makes streptokinase and urokinase less desirable thrombolytic drugs than rTPA compounds. Single-chain urokinase-type plasminogen activator or prourokinase is a zymogen with an intrinsic catalytic activity which is greater than that of most of the other zymogens. Intra-arterial prourokinase administration has been proved to be beneficial in clinical trails in adults within 6 hours of the onset of acute ischemic stroke caused by MCA occlusion which significantly improved clinical outcome at 90 days [107], and the risk of symptomatic intracranial hemorrhage was increased in the presence of acute hyperglycemia [108]. rTPA is a purified glycoprotein produced by recombinant DNA technology. It has the property of fibrin-enhanced conversion of plasminogen to plasmin and is successfully used in acute myocardial infarction [109] and ischemic stroke [110]. Although studies show that the intravenous rTPA administration is effective in reducing disability and possibly decreasing the size of the infarct [110, 111], many patients are left with moderate to severe neurological deficits in this manner. Intra-arterial treatment is proposed for its higher rates of recanalization, lower doses of thrombolytics used compared with intravenous therapy, and lower rates of intracerebral hemorrhage (ICH) [112, 113]. However, the US Food and Drug Administration only approves the use of intravenous rTPA in adults with acute ischemic stroke, and the condition for this thrombolytic agent is that the duration between onset of symptoms and the time for the use of rTPA is within three hours and can be extended to four and half hours in certain patients [114]. Clinical trials evaluating the feasibility and efficacy of intravenous and intra-arterial rTPA therapy for pediatric strokes are difficult because of the frequent delay in diagnosis and the lack of safety data. A study on the safety and effectiveness of a low dose of rTPA for thrombolysis in children with arterial and venous thrombi is under investigation and the results are promising [115].

6.4. Neuroprotective Agents. Accumulative evidence supports that hypothermia can protect against brain damage, especially in neonates with hypoxic ischemic encephalopathy [116, 117]. Hypothermia in adults with stroke may be associated with serious sequelae, such as hypotension, arrhythmia, and pneumonia [118]. Early use of antiepileptic drugs in children with seizures associated with arterial ischemic stroke is essential to prevention from recurrent seizures that may worsen the infarct volume [119].

6.5. Neurosurgical Procedures. Emergent decompression with hemicraniectomy may save a patient's life when a huge amount of hemorrhage and/or hematoma causes herniation.

6.6. Rehabilitation Therapy. Compared with old patients with strokes, infant and young children have additional rehabilitation difficulties, including feeding dysfunction related to speech therapy and ongoing modification therapies when they grow and develop age-related skills over time. Hemiatrophy limbs can cause orthopedic problems, such as leg length discrepancy. Moreover, these patients may develop learning and behavior problems and require intervention by specialized pediatric rehabilitation and education teams. It is necessary to encourage patients' families and remind them of avoiding overprotection. What is more important is to treat the affected child as normally as possible.

7. Conclusion

With half of the world's population, stroke in Asia is important globally. With an aging population, there is an expected rise in numbers of stroke and a corresponding increase in the burden of stroke in Asia. Indeed, tremendous efforts have been made to increase public recognition of adult stroke, and similarly most of the studies have been directed to understanding and evaluating prevention and treatment strategies in adult stroke. In fact, there are important differences between adult and pediatric stroke that limit the applicability of data from adult research to this population. Therefore, multicenter collaborative databases are needed to have a global view on the causes, treatment approaches, and outcome of the stroke in the young people. In fact, strokes in the young still remain less noticeable even among clinicians. Given the far better potential for outcome and longer duration of disability in children with stroke compared with adults, further studies are needed to refine our understanding of underlying mechanisms and improve the development of rational therapies for pediatric stroke.

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Research Article

Does Stroke Impair Learning in Children?

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Objective. To assess cognitive development and learning in children who have had strokes. *Method*. Twenty-nine stroke patients and 18 children with no brain lesions and no learning impairments were evaluated. For the cognitive assessment, Piaget's clinical method was used. Writing, arithmetic, and reading abilities were assessed by the school performance test. *Results*. The mean age at evaluation was 9.6 years. Among the 29 children, 20 had early lesions (mean of 2.4 years old). The stroke was ischemic in 18 subjects; there were 7 cases of recurrence. Six children could not answer the tests. A high index of cognitive delay and low performance in writing, arithmetic, and reading were verified. Comparison with the control group revealed that the children who have had strokes had significantly lower performances. *Conclusion*. In this sample, strokes impaired cognitive development and learning. It is important that children have access to educational support and cognitive rehabilitation after injury. These approaches may minimise the effects of strokes on learning in children.

1. Introduction

A childhood stroke is defined as a cerebrovascular event that occurs between 29 days and 18 years of age [1]. Its incidence varies from 2.3 to 13/100,000 children/year [2–9]. Although it is considered rare, the childhood stroke is among the ten main causes of death. Around 5% to 10% of the patients die, mostly in the first year of life [1, 10]. In general, children who survive strokes will live with sequelae for the rest of their lives, and these conditions may cause impairments in other aspects of their personal and familiar lives.

Over the last decade, research investigating the cognitive evolution of children [11–20] has shown that the learning also deserves special attention. In regard to school-based learning, there is evidence that these children need specialised educational assistance (at regular schools or other special education institutions) and are more likely to have school failures [13, 14, 21–24]. However, data are scarce, which justifies the development of new studies in this area. The main objective of this study was to investigate cognitive development and the writing, arithmetic, and reading abilities in children who have had strokes.

2. Method

The present study was submitted to and approved by the Ethics Research Committee of the State University of Campinas Medical Sciences Faculty (Process no. 638/2003). Parents were informed about the research content and gave signed consent.

2.1. Participants. Children ranging in age from zero to fifteen years old are followed at the Childhood and Adolescence Cerebrovascular Disease Research Outpatient Unit of the Clinics Hospital (HC), State University of Campinas (Unicamp). Patients of 15 years old or younger who had been treated for ischemic or hemorrhagic strokes were included in this study. Diagnosis was made through clinical, laboratory, and neuroimaging examinations. Patients who have had strokes caused by hypoxic-ischemic encephalopathy, head trauma and Down syndrome were excluded. The group of children who had strokes was labelled the experimental group (EG).

A control group (CG) was composed of subjects similar in age and gender to the EG. The children of this group

Age of child	CN	CM	CCQ	OC-Fl	OC-Fr	OS	CW	CV	Minimum score child should achieve
Up to 7 years									1
Up to 8 years									2
Up to 9 years									3
Up to 10 years									6
Up to 11 years									7
Up to 12 years									8

CN: Conservation of number task
CM: Conservation of mass task
CCQ: Conservation of continuous quantity task
OC-Fl: Test on objects classification (flowers)
OC-Fr: Test on object seriation (fruits)
OS: Test on object seriation
CW: Conservation of weight
CV: Conservation of volume

Figure 1: Grading criteria for Piaget's operation tasks.

attended public schools in the Campinas, São Paulo (Brazil) region, had no history of cerebral lesion and had no learning problems according to their teachers.

The evaluation of all children was done individually in an appropriate room, free from outside interferences. The EG was assessed at HC/Unicamp and the CG at the school they attended.

2.2. Cognition Functioning. The cognitive development was evaluated through Piaget's clinical method [25]. Five conservation tasks (number, mass, continuous quantity, weight, and volume), two tests on object classification, and one test on object seriation were used. The following criteria were used for grading the tests: 1 point for correct responses, 0.5 points for partial correct responses, and 0 points for incorrect responses. Figure 1 describes the scores expected in relation to age.

The total score obtained by the child was compared to the total score expected for chronological age. The final classification of cognitive development complied with the following criteria: an adequate level if the score was equal to or higher than the expected score for the child's age; mild delay if the score was up to two points below the expected score; severe delay if the score was between 7 and 8 points below the expected score.

To evaluate writing, arithmetic, and reading performances, the school performance test [26], which is a developed and standardised tool for the Brazilian population, was used.

The data were analysed and compared. Statistical analysis was conducted through the SAS System for Windows (version 8.02) and SPSS for Windows (version 10.0.5) programmes. The significance level adopted was $P < .05$.

3. Results

3.1. Baseline Characteristics. There were 13 girls and 16 boys. Eighteen patients had ischemic strokes, and 11 had haemorrhagic strokes. The mean age at stroke onset was 2.4 years old (range of 1 month to 10 years old) with a median age of 1.66 years old. Twenty patients had early strokes (occurred in the time from birth up to the second year of life), and there were 7 cases of recurrence. Most of the lesions were seen in the right hemisphere, and 13 patients had cortical and subcortical lesions. The mean age of the patients at assessment was 9.6 years old (range of 7 to 12 years old), with a median age of 10 years and 1 month old (Table 1). The mean follow-up time of the EG was 7.6 years (range of 4 months to 12 years), with a median of 7 years.

At followup, neurological examination showed no dysfunction at all in 3 children (of the 29 examined). All physical sequelae are listed in Table 2.

3.2. Educational Aspects. Six patients of the EG demonstrated severe neurological impairment. For this reason, they were not capable of performing the proposed tasks. Five of these patients attended a specialised educational institution. The only child who attended a regular school was too impaired cognitively to acquire elementary learning (such as acknowledging colours). In Table 3, the school data for the other 23 children are listed.

It is important to highlight that despite a policy of continuous progression in regular education in Brazil, 14 out of the 23 children were held back (in relation to age and school year) (Table 3). All of the CG children were attending public regular schools and did not experience school delays.

3.3. Cognitive Evaluation. Cognitive evaluation using Piaget's clinical method [25] assessed 23 children of the EG and 23 of the CG. Eight in the EG had adequate performance. All of the other children had either mild (3/23), moderate (4/23), or severe (8/23) delays (Figure 1). The stroke type (ischemic or haemorrhagic), injured hemisphere (right, left, or bilateral), and recurrent stroke (occurred or did not occur) were not determinant factors for the best or worst performance of the EG children on operation tasks.

In the CG, 11 children had adequate performance. The other children (12/23) had a mild delay (Figure 2). The comparison between the CG and the EG showed that the performances of children who had strokes were significantly inferior to those of the control ($P = .000$, Mann-Whitney's test).

Table 1: Experimental group characteristics.

Subject	Gender	Stroke Type	Stroke onset (y + m)	Age at assessment (y + m)	Affected hemisphere	Lesion area
1	F	I	7 + 2	7 + 10	B	L: C R: S
2	F	I	2 + 11	8 + 4	L	S
3	M	H	0 + 1	8 + 1	R	S
4	M	H	11 + 8	12 + 0	L	C/S
5	M	H	1 + 0	7 + 1	B	L: C R: CB
6	M	I	2 + 6	8 + 10	B	L: C/S R: S
7	F	I	2 + 4	10 + 2	R	C/S
8*	F	I	0 + 5	9 + 5	B	L: C R: C
9	M	I	4 + 10	10 + 9	L	C/S
10*	F	I	1 + 2	9 + 7	B	L: S R: S
11	M	I	1 + 8	12 + 0	L	S
12	M	H	10 + 2	12 + 7	L	BS
13	M	H	0 + 2	7 + 0	R	S
14*	M	I/H	4 + 8	12 + 5	L	BS
15	M	H	0 + 9	8 + 1	R	S
16	M	H	3 + 8	9 + 10	R	C
17	M	I	0 + 7	7 + 7	R	C
18*	F	I	1 + 0	12 + 4	B	R: C/S L: C
19	F	I	0 + 2	11 + 5	R	C/S
20*	F	H/I	2 + 8	8 + 4	R	C/CB
21*	F	H	0 + 2	12 + 4	B	R:C/S L: S
22	F	I	1 + 3	10 + 3	B	L: C/S R: S
23	F	H	0 + 9	10 + 1	B	R: C/CB L: C/S
24	F	I	2 + 11	8 + 9	L	C
25	M	I	7 + 0	10 + 9	R	C/S
26	F	H	0 + 9	12 + 8	R	C/S
27*	M	I	4 + 10	12 + 4	B	C/S
28	M	I	0 + 11	11 + 11	L	C/S
29	M	I	6 + 5	8 + 6	R	S

*: recurrent stroke; F: female; M: male; H: haemorrhagic, I: ischemic; y: years, m: months; B: bilateral; R: right; L: left; C: cortical, S: subcortical; CB: cerebellum; TC: brainstem.

Table 2: Physical sequelae at followup.

Physical sequelae	Ischemic stroke ($n = 18$)	Haemorrhagic stroke ($n = 9$)	Ischemic and haemorrhagic stroke ($n = 2$)
Motor (hemiparesis and tetraparesis)	17	6	1
Speech dysfunction	6	2	—
Visual deficit	4	1	1
Seizures	10	4	1
Conduct disorder	3	1	—
Global development retardation	4	1	—

3.4. Writing, Arithmetic, and Reading Evaluation. The school performance test (SPT) [26] was given to only 18 patients from the EG because five children were severely behind in school and were not capable of doing the test. Among these children, four had strokes at an early developmental stage.

Data analysis of the SPT showed that most of them had weaker performances in writing (9/18), arithmetic (12/18) and reading (10/18), (Figures 3 and 4).

In this sample, there was no relationship between the stroke type (ischemic or haemorrhagic), injured hemisphere

Table 3: School data of the 23 children in the experimental group.

Type of education	Ischemic stroke ($n = 13$)	Haemorrhagic stroke ($n = 8$)	Ischemic and haemorrhagic stroke ($n = 2$)
Specialised institution	1	—	—
Public school (regular classroom)	9	6	2
Public school (special classroom)	2	2	—
Private school (regular classroom)	1	—	—
School delay (in relation to age)	8	5	1

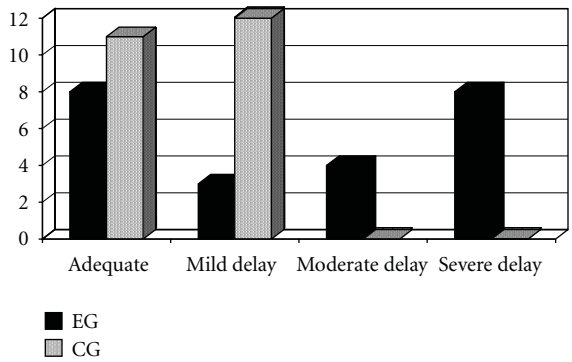

Figure 2: Cognitive evaluation outcomes of the experimental and control groups (EG: control group; CG: control group).

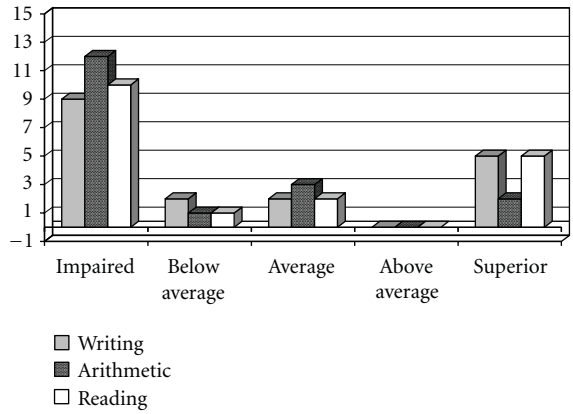

Figure 3: Performance of the experimental group (EG) on the writing, arithmetic, and reading test.

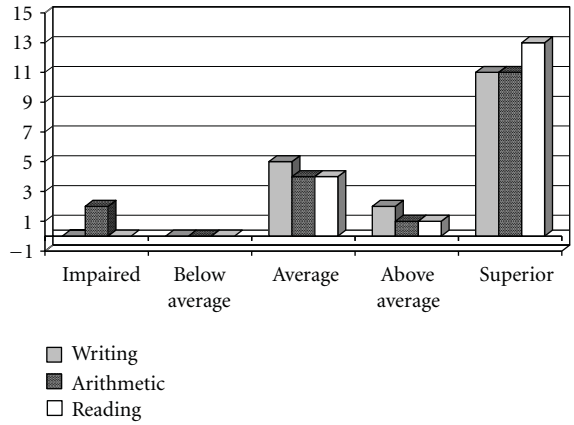

Figure 4: Performance of the control group (CG) on the writing, arithmetic, and reading test.

and recurrent stroke (occurred or did not occur) and the writing, arithmetic, and reading subtest performances. However, there was a positive relationship between vascular injury at an early age and weaker performance on the test. Among the 10 children who had early strokes, six had impaired performances on the three subtests (writing, arithmetic, and reading).

The hypothesis that stroke might have negatively influenced writing, arithmetic and reading abilities was strengthened when the results were compared to those from the CG. The children who had strokes had performances significantly inferior (Mann-Whitney test) compared to those of the CG (Figure 5).

4. Discussion

This study aimed to understand cognitive development and learning in children who had strokes. In a previous study [17], cognitive delay was already observed in 15 children with ischemic stroke when they were compared to other children of the same gender and age. In the present study, an increase in the sample size and the inclusion of children with haemorrhagic stroke added important data that can be highlighted.

Among the children who were able to perform the tests, half of them demonstrated severe or moderate delays on Piaget's operation tasks, and most of them had inferior outcomes on the tests that assessed basic writing, arithmetic, and reading abilities. Furthermore, comparison with the control group revealed the significantly inferior performance of children with cerebrovascular disease. The consequences of poor performance were evident when educational aspects were analysed. Among the patients who attended regular schools, most showed learning disabilities and had repeated histories of school failure. This evidence has also been reported in other researchs [13, 14, 21–24].

The stroke type and affected hemisphere were not determinants for the impaired performances of the children in this study. However, there was a positive relationship between the

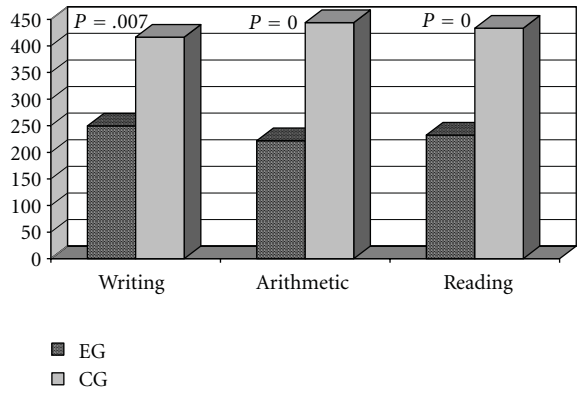

Figure 5: Comparison of EG and CG performances on the three subtests (writing, arithmetic, and reading) of the school performance test.

onset of cerebrovascular injury and inferior performances on the tests.

Among the 29 children in the study, 20 had strokes in the time from birth up to the second year of life. Among these 20 children, 6 had cognitive impairments severe enough to exclude them from the assessment group for not responding to the tests. Another 5 children could not respond to the school performance test [26]. From the 9 patients who accomplished this test, most of them had low performances in writing, arithmetic, and reading.

Some authors have also drawn attention to the relationship between early stroke and impaired cognitive evolution [14, 21, 23, 27]. The first years of life are part of the most dynamic period for brain development. Lesions that occur in this period produce more severe impairments because they interfere with the reorganisation of the development of superior mental functions [23].

It is very important to emphasise that language is fundamental to the development of higher cortical functions. A large capacity for brain reorganisation is identified in early brain injury. Thus, adaptive plasticity is evident in the early stage of development. However, pathological plasticity (or maladaptive plasticity) could also occur, leading to a decrease in verbal and nonverbal skills and neuropsychological morbidity. After the first year of life, brain reorganisation is more limited but is more organised and is less likely to produce secondary sequelae [28]. Thus, children with cerebrovascular injury in later life would have less involvement in learning. This was confirmed in this study.

The concept of functional hierarchy [29] can also explain why children who have lesions at an early development stage have increasingly worse cognitive impairments. Initially, the primary zones of the brain that receive unimodal stimuli are fully active. In the case of primary zone lesion, there might be impairment in the development of multimodal areas (secondary and tertiary) due to a trophic stimulus deficit from sensorimotor activities [30]. Children who have had strokes generally have good motor development. Despite the hemiparesis, patients walk independently (with or without ortheses or other assistive devices). However, performance in other areas, such as daily life activities, communication, and socialisation, is less adequate in these patients [21]. Seizures that occurred after onset were also important because studies show that this clinical condition is related to cognitive impairment [13, 14, 18]. In this sample, 15 children had seizures, which corroborates the data reported by other studies.

5. Conclusions

Since the last decade, several studies have shown that childhood stroke can impair learning in children. This was evidenced in the present study.

Our data have shown that childhood stroke can impair cognitive development and learning in children. The lesion onset age seems to be an important factor for cognitive function development. Therefore, special attention must be given to patients who have had strokes in the initial developmental stage. Early cognitive rehabilitation might minimise the effects of the injury and provide a better quality of life for the children and their families.

Conflict of Interests

There was no conflict of interests in this study.

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Review Article

Incidence of Stroke in Young Adults: A Review

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Introduction. Stroke in the young may have a dramatic impact on the quality of life in survivors. This study was aimed to evaluate incidence of first-ever stroke in the young by means of a systematic review. *Materials and Methods*. All papers on incidence of stroke in the young published after 1980, were identified by electronic search of Medline and manual search of reference lists. Only studies recruiting subjects under 44 years of age and with a lower age limit not higher than 20 years were included. Incidence rates were standardized to the 2000 European population according to the direct method. Poisson regression analysis was used to compare studies. *Results*. 29 studies including 3548 participants were identified. Incidence rates, after excluding a few outliers, ranged between 8.63 and 19.12 for crude rates and between 8.70 and 21.02 for standardized rates. Heterogeneity among studies was statistically significant but improved after excluding 4 studies. Few studies reported the proportions of stroke subtypes. *Conclusions.* Stroke in subjects under 45 years of age is not such a rare disease and requires specific preventive programs.

1. Introduction

According to available data, fewer than 5% of all strokes occur in subjects under 45 years of age, in Western countries [1]. Higher proportions, between 19 and 30%, were reported in developing countries [2, 3]. Stroke incidence studies in the young were reported in several surveys and a few community-based studies that used different methodology and results were often very different [1, 3–30]. Moreover, in many studies, reported incidence rates had wide confidence intervals because of the small number of incident cases in the young [1, 3–30].

This study was aimed to evaluate incidence of first-ever stroke in the young by means of a systematic review of the literature.

2. Materials and Methods

In the present review, data were identified by searches of Medline and from the references of relevant articles published after 1980. Different subsets of studies were potentially eligible for different parts of this review. The search terms "population-based," "community-based," "community," "epidemiology," "epidemiological," "incidence," "survey," "surveillance," "stroke," "isch(a)emic stroke," "intracerebral," "intraparenchymal," "subarachnoid," and "h(a)emorrhage" were used. Only papers published in English were reviewed. Only papers reporting incidence rates of first-ever stroke in a lifetime in subjects under 45 years of age were included. Moreover, studies were included if the lower age limit was less than 20. Stroke had to be defined according to the WHO definition, that is the occurrence of rapidly developing signs of focal or global disturbance of cerebral function, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin.

Two of the authors reviewed all published data of selected studies and assessed age and sex distribution of population at risk and of cases of first-ever stroke occurring in those populations.

Repeated reporting of the same studies were excluded, so that each data set was considered only once. Stroke type classification was considered only in those studies where CT, MRI, or autopsy findings were available for at least 80% of stroke cases. Strokes were classified into four major types: ischemic stroke (if CT or MRI within 30 days of stroke

Table 1: Studies on incidence of stroke in the young.

Study	Person* year	Crude rate	95% CI		Adjusted rate*
			LL	UL	
Stockholm	4,712,240	15.56	14.43	16.68	17.25
Benghazi	158,348	39.79	29.96	49.61	48.51
Lund-Orup	97,283	9.25	3.21	15.30	9.28
Denmark	13,144,499	14.94	14.28	15.60	11.21
Dijon	75,880	26.36	14.81	37.91	31.42
Florence	531,597	8.84	6.31	11.37	8.88
OCSP	226,936	9.64	5.60	13.68	9.74
Russia†	350,432	19.12	14.54	23.70	19.13
Baltimore whites	388,532	13.64	9.97	17.31	14.14
Baltimore blacks	272,464	30.83	24.24	37.42	34.20
Reggio Emilia	212,646	13.64	8.67	18.60	13.95
Aosta 1988	67,784	13.28	4.60	21.95	13.26
Rochester	1,297,209	8.63	7.03	10.23	14.21
Malmö†	127,581	11.76	5.81	17.71	10.06
Israel	2,170,500	5.76	4.75	6.77	6.14
Auckland	456,667	20.15	16.03	24.26	21.02
Perth	93,086	20.41	11.23	29.59	13.83
Warsaw	230,108	16.51	11.26	21.76	13.51
Belluno	126,513	10.28	4.69	15.86	16.70
Innherred†	73,862	12.18	4.22	20.15	12.02
Northern Sweden	774,608	11.36	8.99	13.73	11.17
South London	327,384	10.69	7.15	14.23	11.48
L'Aquila	874,375	10.18	8.06	12.29	10.23
OXVASC	178,071	8.99	4.58	13.39	13.12
Erlangen	62,453	16.01	6.09	25.94	14.58
Northen Manhattan†	321,739	23.00	17.76	28.24	23.03
Aosta 1997†	66,698	16.49	6.75	26.24	16.38
Melbourne	84,888	20.03	10.51	29.55	19.25
Brazil	844,378	11.55	9.26	13.85	8.70

CI indicates confidence interval.
*Standardized to the 2000 European population.
†Standardized only by sex.

Table 2: Estimated incidence rates stratified by age and sex.

Age class	Males	Females
0–14 yr	0.99	0.73
15–24 yr	4.20	2.95
25–34 yr	10.68	7.67
35–44 yr	30.66	23.99

showed infarct or no relevant lesion and/or autopsy showed ischemic stroke), primary intracerebral haemorrhage (if shown on CT, MRI, or autopsy), subarachnoid haemorrhage (classified by characteristic findings in CSF analysis and/or autopsy, CT, or cerebral angiography), and undetermined stroke (no CT, MRI, autopsy, cerebral angiography, or [for subarachnoid haemorrhage only] CSF examination was done).

The incidence of first-ever stroke was calculated per 100,000 person-years. Age standardisation was performed with the direct method using the 2000 European population as the reference population [26]. Age-standardised incidence rates were plotted with the corresponding 95% CI for each study to facilitate comparison. Poisson regression analysis was used to compare incidence rates from different studies. Fitted values were assumed as the best estimates of the true stroke incidence in the young at the various age classes. Sensitivity analysis was performed by excluding those studies that produced a significant deviance change when removed from the model.

3. Results

During the review period we identified 29 studies including altogether 3548 patients under 45 years of age with

Table 3: Proportion of different stroke types in the included studies.

	IS		ICH		SAH	
Study	%	95%CI	%	95%CI	%	95%CI
Stockholm	21.0	18.1–24.0	22.0	19.0–25.0	55.4	51.8–59.0
Benghazi	77.9	67.7–88.2	12.6	4.4–20.8	9.6	2.3–16.8
Lund-Orup	67.5	48.1–87.0	16.7	1.2–32.2	15.8	0.6–31.0
Florence	38.5	24.5–52.4	21.5	9.7–33.2	36.2	22.5–49.9
OCSP	66.7	48.9–84.4	3.7	0–10.8	29.6	12.4–46.9
Baltimore whites	77.4	66.1–88.6	22.6	11.4–33.9	—	—
Baltimore blacks	70.2	60.5–80.0	29.8	20.0–39.5	—	—
Reggio Emilia	58.7	40.7–76.6	20.5	5.8–35.2	20.5	5.8–35.2
Malmö	53.3	28.1–78.6	20.0	0–40.2	13.3	0–30.5
Perth	47.5	32.0–63.0	20.0	7.6–32.4	32.5	18.0–47.0
Belluno	30.8	05.7–55.9	38.5	12.0–64.9	30.8	5.7–55.9
Innherred	55.6	23.1–88.0	33.3	2.5–64.1	11.1	0–31.6
L'Aquila	57.3	47.0–67.6	20.2	11.9–28.6	22.5	13.8–31.1
OXVASC	66.7	48.9–84.4	3.7	0–10.8	29.6	12.4–46.9
Erlangen	70.0	41.6–98.4	10.0	0–28.6	20.0	0–44.8
Northen Manhattan	43.5	32.2–54.8	30.4	20.0–40.9	26.1	16.1–36.1

CI indicates confidence interval.
IS indicates ischemic stroke; ICH indicates intracerebral hemorrhage; SAH indicates subarachnoid hemorrhage.

a diagnosis of stroke. Person-year at risk, crude incidence rates, and rates standardized to the 2000 European population are reported in Table 1. Crude rates ranged from 5.76/100,000 to 39.79/100,000 and standardized rates ranged from 6.14/100,000 to 48.51/100,000. However, after excluding 4 outliers (Benghazi, Dijon, Baltimore-blacks, and Israel, ranges became much tighter (8.63 to 19.12/100,000, for crude rates, and 8.70 to 21.02, for standardized rates). Figure 1 shows that rates were approximately similar among studies.

Poisson regression analysis revealed a significant heterogeneity among studies ($P < .0001$). However, after excluding the above mentioned outliers, heterogeneity markedly reduced, although was still statistically significant ($P = .021$). Fitted values for each age class of both sexes are reported in Table 2 and show rates clearly higher in men than in women.

The distributions of stroke types were reported by half of the papers only, mostly without age and sex stratification (Table 3). The proportion of ischemic stroke ranged between 21.0% and 77.9%, the proportion of intracerebral hemorrhage ranged between 3.7% and 38.5%, and the proportion of subarachnoid hemorrhage ranged between 9.6% and 55.4%.

4. Discussion

In subjects under 45 years of age the annual crude incidence rate of first-ever stroke is usually considered low. However, it is usually higher than that of other invalidating neurological disease.

The strength of the present study relies on the inclusion of a large number of studies and of participants. However, studies were rather heterogeneous on the basis of methodology and ethnicity. Higher rates were reported by few studies with less accurate identification of the study population [2, 29, 30]. Rates were higher in USA black people and in developing countries. Racial composition of the study population is an important component of incidence variability since young blacks and hispanics have been shown to have greater stroke incidences than young whites [3, 11]. Nevertheless, in some developing countries higher rates may reflect life style and inaccurate control of risk factors.

The proportion of ischemic strokes, ranging between 21.0% and 77.9%, was much lower than that reported for stroke of all ages. This finding probably depended on the occurrence of hemorrhagic strokes due to vascular malformations, and illicit drug use as well as on the lower prevalence of atherosclerosis in young subjects.

Although stroke was a rare event in the young, due to the longer expected survival at this age, young patients accounted for as much as 20% of the years of potential life lost because of the stroke [31]. Primary prevention is likely to be the principal strategy to fight stroke in the young. In addition to conventional stroke risk factors, young patients have special risk factors inherent to genetic and environmental elements, such as cardiac abnormalities, thrombophylic states, migraine, the use of oral contraceptives and illicit drugs that should be identified and adequately controlled [32]. The high proportion of subarachnoid and intracerebral hemorrages in patients under 45 years reported by some studies, makes mandatory tailored preventive strategies, mainly focused on early detection and treatment of hypertension and possibly including neuroimaging studies for the screening of aneurysms and arteriovenous malformations in subjects at risk.

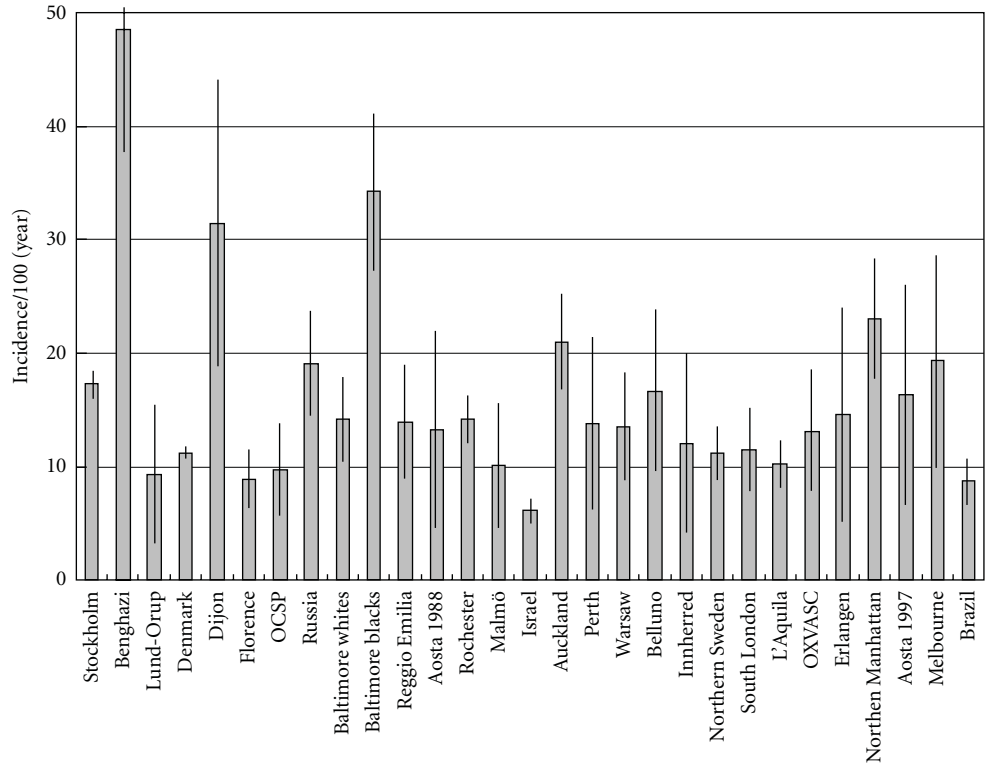

Figure 1: Incidence rates of stroke in the young (rates are adjusted for age and sex to the 2000 European population).

5. Conclusion

Studies on incidence of stroke in the young provide comparable rates showing that stroke in those subjects is not such a rare condition and requires tailored prevention programs.

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Review Article

Epidemiology and Etiology of Young Stroke

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Introduction. Stroke in people under 45 years of age is less frequent than in older populations but has a major impact on the individual and society. In this article we provide an overview of the epidemiology and etiology of young stroke. *Methods*. This paper is based on a review of population-based studies on stroke incidence that have included subgroup analyses for patients under 45 years of age, as well as smaller community-based studies and case-series specifically examining the incidence of stroke in the young. Trends are discussed along with the relative frequencies of various etiologies. *Discussion*. Stroke in the young requires a different approach to investigation and management than stroke in the elderly given differences in the relative frequencies of possible underlying causes. It remains the case, however, that atherosclerosis contributes to a large proportion of stroke in young patients, thus, conventional risk factors must be targeted aggressively.

1. Introduction

Stroke incidence rises steeply with age; therefore, stroke in younger people is less common; however, stroke in a young person can be devastating in terms of productive years lost and impact on a young person's life. As will be outlined below, some causes of stroke are more frequent in adults under 45 years of age compared to more aged populations [1]. We here provide an overview of the incidence and etiology of young stroke.

While a specific definition of "young stroke" is lacking, the vast majority of authors consider "young stroke" to pertain to individuals under 45 years of age. Hence, this paper is based on a review of population-based studies on stroke incidence that have included subgroup analyses for patients under 45 years of age, as well as smaller community-based studies and case-series specifically examining the incidence and etiology of stroke in the young. Individual studies and reviews were found by performing a medline search (1948-present) using the search terms "young stroke," "ischaemic stroke and young," "ischemic stroke and young," "haemorrhagic stroke and young," "hemorrhagic stroke and young," as well as "epidemiology and young stroke" and "etiology and young stroke." We also collected papers by examining the references cited in these articles and selecting those pertaining to the epidemiology of young stroke. Finally, we examined prevalence in large population registries that provided subgroup analyses for patients younger than 45 years of age. These were identified using the search terms "epidemiology and stroke" and "population-based studies and stroke." Again, references were examined to identify other stroke registries, which were examined with regard to prevalence among young patients under age 45.

2. Incidence of Young Stroke

Differences in methods of reporting the incidence of young stroke make it difficult to draw geographical comparisons. While the majority of population-based studies report rates for all stroke combined (ischaemic and haemorrhagic, including subarachnoid haemorrhage), a few report rates for ischaemic stroke alone. Furthermore, referral bias needs to be considered when hospital-based registries as opposed to community-based studies are used to examine the relative proportion of young stroke, as is often the case in developing countries. Moreover, incidence has been examined at different time points over several decades and incidence rates

may change overtime. Finally, where authors have reported incidence rates by age decile, it is apparent that even within the "young stroke" category, incidence increases sharply with age, particularly among the 34 to 44 year old age group [2–12].

Despite these difficulties, some general trends are apparent. Overall incidence rates under the age of 45 range from 7 to 15 in 100 000 people/year for all stroke (ischaemic and haemorrhagic) [13–17], with higher rates reported in some countries [18]. A few studies reporting similar incidence rates have examined all stroke in the 15 to 44 year old age group [19, 20] or ischaemic stroke only in the 15 to 49 year old age group (6.6 to 11.4 in 100 000 people/year) [21–23]. Under the age of 35, rates are less than 10 in 100 000 people/year (ranging from 0 to 9) [3, 4, 9, 24]. Within the 35 to 44 year old age range, rates range from 22 to 45 in 100 000 people/year [2–12]. There may be a greater incidence of stroke in developing countries, such as Libya with a reported rate of 47 in 100 000 people/year for all stroke under the age of 45 [18]. High rates have also been observed in Japanese adults (70 in 100 000 in the 35 to 44 year old age group) [25], Hispanics (26 in 100 000 in the 22 to 44 year old age group) [26], and American blacks with a relative risk of 5 for all stroke reported for blacks compared to whites (96 in 100 000 versus 19 in 100 000) within the 35 to 44 year old age group in the Greater Cincinnati/Northern Kentucky Stroke Study from 1993-1994 (an RR of 2.2 was observed in the 0 to 34 year old age group) [24, 27]. This trend is supported by the results of the Northern Manhattan Stroke Study demonstrating a nonsignificant trend of increased risk among blacks aged 22 to 44 years old [26], as well as the Baltimore Washington Co-op Young Stroke study [28, 29]. Interestingly, two studies of Caribbean blacks demonstrate similar stroke rates to those reported in other young stroke populations [9, 11], suggesting that the increased risk among young blacks in the United States might be related to socioeconomic variables, although high rates are observed in South African blacks of all ages [30, 31]. Very high young stroke rates were also observed in a rural population from Northern Portugal [32].

With regard to sex differences in the incidence of young stroke, rates are greater among men than women in the 35 to 44 year old age group [2, 4, 10, 14]. Some population-based studies demonstrate an increased incidence among women under 30 years old [22, 33, 34], as do several case-series [34–36].

3. Etiology of Young Stroke

While a greater proportion of strokes are due to subarachnoid haemorrhage and intracranial haemorrhage in young adults (40–55%) compared to the general stroke population (15–20%), [17, 26, 37], cerebral infarction is still most common. An increased risk of cerebral infarction among young adults with conventional vascular risk factors is observed, particularly in developing countries due to increasing smoking rates and urbanization [38], as well as among young blacks and Taiwanese patients with more adverse risk factor profiles resulting in a greater relative contribution of small vessel disease to young stroke [39, 40]. However, other causes of stroke in young adults differ in frequency from those observed in the elderly [41]. This holds particularly true in adults under 30 years of age.

In terms of etiology and relative strength of risk factors, most data comes from clinical series and case-control studies. The majority of these have examined adults less than 45 years of age, while the Helsinki Young Stroke registry examined etiology in adults under 49 years of age [21]. In as many as 35% of cases, the underlying etiology remains unclear [21, 23, 29, 33, 34, 36, 42–44]. Importantly, while atherosclerosis remains an important risk factor (accounting for 15–25% of strokes in young adults [36], and an even greater proportion among certain ethnicities) [40, 45], cardioembolic stroke is more common among younger patients (15–35% of cases) [21, 29, 33, 34, 36, 42, 43, 45]. Other causes that are more frequent in young people include extracranial artery dissection (2–25% of cases) [21, 29, 36, 40, 42, 46], migraine (up to 20% of cases [42], although thorough studies excluding alternate possible causes suggest migraine contributes to just 1–5% of cases [23, 29, 33–36]), and drug use (up to 5% of cases, depending on the frequency of use in a given population [29]). Oral contraceptive use has been implicated in up to 8% of cases of young stroke in some populations [43]. Apart from antiphospholipid antibody syndrome (5–10% of cases) [23, 29, 33, 34, 36, 42, 45], inherited coagulation disorders do not appear to play a large role in young stroke in the absence of right to left venoarterial shunting [47]. Sickle cell disease, in which 7 to 10% of affected individuals experience strokes before the age of 20 [48], and rheumatic valvular heart disease are important in some populations, with as many as 32% of cases of young ischaemic stroke attributable to rheumatic heart disease in Iran [49]. Cerebral venous thrombosis is an uncommon cause of young stroke (i.e., <1% of cases [50]), as are rare causes of nonatherosclerotic arteriopathies (although they contribute to 15–35% of cases of young stroke as a collective group [36]). These include Sneddon's syndrome; Moyamoya disease (responsible for 6–15% of cases due to nonatherosclerotic arteriopathy (22–27% of all young ischaemic stroke) in Asian populations [40, 45]); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); vasculitis; prior chemoradiotherapy; HIV infection (up to 7% of cases of young stroke in Nigeria [51]); and neoplasm. While only specifically examined and demonstrated in young patients in South Africa, in addition to sickle cell disease and rheumatic heart disease, a higher prevalence of stroke secondary to vasculitis due to infection likely occurs in developing countries [38].

With regard to stroke in women, oral contraceptive use is associated with a 2- to 5-fold increased risk of stroke of all subtypes, depending on the estrogen content, although there is some controversy as to whether pills with a low estrogen content (i.e., less than 50 micrograms of ethinyl estradiol) are truly associated with an increased risk given the discrepancy in results between cohort studies, which do not support a link, and a large number of case-control studies that do [52]. This risk is increased in smokers and in

those who experience migraine with aura [53]. Less common causes of stroke that are more common in women include systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APLAS), central venous thrombosis (CVT), reversible cerebral vasoconstriction syndrome (RCVS), Susac syndrome, Takayasu's arteritis, Moyamoya disease, Sneddon's syndrome, and fibromuscular dysplasia. In addition, women are particularly susceptible to stroke in the puerperium.

4. Cardioembolic Stroke

Different frequencies of the various causes of cardioembolic stroke are reported, and geographical variation is seen. The methods and criteria that are used to identify potential causes also vary. Mitral valve disease, which accounts for a significant proportion of cardioembolic stroke in young patients, is more common in some populations due to a high prevalence of rheumatic heart disease [49]. The relative contribution of rheumatic heart disease (in the presence or absence of synthetic valve prosthesis) and mitral valve prolapse to cardioembolic stroke varies widely among different geographical regions and stroke registries from 40–70% in most studies [33, 36, 40, 43, 49], and far less in the Helsinki registry given the virtual disappearance of rheumatic fever in Finland [21]. The prevalence of dilated cardiomyopathy also demonstrates geographical variation in light of the increased prevalence of Chagas disease in South America (also associated with intramural thrombi) [54], as well as the increased prevalence of alcohol abuse among certain populations. Rates range from 4–17% [21, 36]. Reports identify atrial fibrillation in 2–20% of young patients who have experienced a cardioembolic stroke [21, 33, 37, 38, 40, 47], more commonly in the setting of rheumatic heart disease [49], which is still less than that observed in older populations [43]. Other potential causes of cardioembolic stroke include acute myocardial infarction and subacute bacterial endocarditis. Rarely, aortic valve disease or left ventricular thrombi are implicated. The relationship between presence of a patent foramen ovale and ischaemic stroke is complex.

5. Patent Foramen Ovale (PFO) and Stroke

The potential link between PFO and young stroke remains a controversial subject. Somewhere in the area of twenty-five percent of the population have a PFO, which in itself is not associated with an increased incidence of first ever stroke in large population studies [55], although a nonsignificant trend toward an association has been observed, particularly among individuals under the age of 60 with an atrial septal aneurysm (ASA) [55–57]. PFO is, however, a more common finding among young patients who present with cryptogenic stroke [55]. A meta-analysis of nine case-control studies (566 patients and 459 nonstroke controls), the majority of which examined patients under 55 yo, found that young patients with cryptogenic stroke had an OR of 6.0 for having a PFO compared to young patients with a known cause of stroke (the OR of having a PFO was 3.0 for all young stroke pts) [55, 56]. The concurrent presence of an ASA, found in 2.2% of the population [55], likely adds further risk [55, 57]. Reports examining whether the presence of large septal defects might confer additional risk have yielded contradictory results [55].

6. Thrombophilia in the Setting of PFO and Stroke

With the exception of APLAS, while thrombophilia on its own is probably not associated with ischaemic stroke, there is some evidence to suggest that the prothrombin gene mutation, in particular, might confer a greater risk of ischaemic stroke in the setting of a PFO. As nongenetic laboratory assays in the assessment of coagulopathies may be unreliable in the acute phase of stroke [58], the most reliable studies use genetic testing to identify patients with inherited thrombophilias.

In the largest case-control study examining this issue ($n = 125$; mean age 34.7), an increased incidence of the prothrombin gene mutation in particular (as well as more than one thrombophilic defect) was found among young stroke patients with a PFO compared to those with infarction unrelated to presence of a PFO [47]. The results of three smaller case-control studies are inconsistent [59–61]. The role of FV61691A and TT MTHFR mutations is even less clear with weak or no demonstrated link observed in the absence of more than one defect [47, 59]. Two retrospective reviews of recurrent stroke in patients referred for PFO closure have demonstrated a greater incidence of recurrent stroke among those with thrombophilia; however, the thrombophilic groups have included patients with APLAS (for which there is a known association with stroke) and evidence of thrombophilia on biochemical testing alone, making it difficult to tease out the relative contribution of genetically-determined inherited thrombophilias to the observed increased risk [62, 63].

7. Migraine and Stroke

The weight of evidence from case-control studies suggests that migraine, particularly migraine with aura, is associated with an increased risk of ischaemic stroke in young women under 45 years of age [53, 64–69]. The pathophysiological mechanism underlying this remains unclear. For one, it is difficult to tease out the relative contribution of cases in which migraine precedes ischaemia (i.e., in which stroke occurs secondary to cerebral hypoperfusion during the aura phase), comprising a migrainous infarct, from cases in which migraine with aura is experienced secondary to ischaemia. True migrainous infarcts are probably rare and tend to affect the posterior circulation [53]. It is also possible that young patients with a history of migraine have an increased incidence of stroke due to a shared underlying etiology which predisposes to both. Migraine as a risk factor for future ischaemic stroke seems to apply mostly to young women, and the relative risk may be as high as 3-fold in those who experience migraine with aura [53]. Several associations which might predispose to stroke in migraineurs have been identified in a small number

of case-control studies, including carotid artery dissection [70, 71] and the presence of a patent foramen ovale [72–75]; however, this does not explain the observed sex difference in the frequency of ischaemic stroke among migraineurs [53]. What is known is that there is an additive risk of stroke in women who experience migraine with aura that smoke, with a greater than 3-fold increase in risk, as well as in those who use the oral contraceptive pill, in whom the risk is quadrupled [53]. An OR of 34 to 35 has been reported for young women who smoke, use the oral contraceptive pill, and experience migraine with aura [53].

8. Stroke in the Puerperium

Stroke complicates an estimated 34 in 100 000 deliveries [76], although reported incidence rates vary from 4 to 210 in 100 000 deliveries ($RR = 3$) [77–80], contributing to at least 12% of maternal deaths [81–83]. Some reports suggest that ischaemic and haemorrhagic stroke occur in roughly equal proportions [81, 84, 85], although ischaemic stroke was more common in one study [86]. Treadwell et al. propose that this may be due to differences in patient subgroup selection since some studies exclude stroke secondary to cerebral venous thrombosis, which contributes to a significant proportion of ischaemic strokes in the puerperium (38% in one series [86], although lower and higher rates have been reported [87, 88]). Nonetheless, arterial occlusion remains most common [86, 88]. Most strokes occur peri- or postpartum [86, 89] with a relative risk of 8.7 for ischaemia in the first six weeks postpartum [82, 85], during which cerebral vein thrombosis is also more common [81, 89, 90], and a relative risk of 5.6 for intracerebral haemorrhage during pregnancy [81, 91]. Looking at intracerebral and subarachnoid haemorrhage combined, a 2.5-fold increased risk of haemorrhagic stroke has been reported in pregnancy, and a 23.8-fold increased risk postpartum [81, 91]. Half of cases of aneurysmal rupture in women under the age of 40 occur in pregnancy [81, 92]. Causes of stroke in pregnancy include haemorrhagic and ischaemic stroke in the setting of pre-eclampsia and eclampsia (25–45% of patients with pregnancy-related stroke) [81, 85, 91], arterial dissection, peripartum cardiomyopathy, paradoxical embolism, amniotic fluid embolism, postpartum cerebral angiopathy, and cerebral vein thrombosis. Cerebral haemorrhage is the most common cause of death in patients with eclampsia but associations between pre-eclampsia and eclampsia and ischaemic stroke are also observed [76, 85, 93]. Subarachnoid haemorrhage is the third leading cause of nonobstetric-related maternal death [77, 81], often secondary to aneurysmal rupture [85, 91]. Whether or not the presence of a patent foramen ovale alone is associated with an increased stroke risk in pregnancy has not been properly examined, nor has the incidence of pregnancy-related stroke in association with peripartum cardiomyopathy. Post-partum angiopathy, a reversible cerebral vasoconstriction syndrome usually occurring in the first week postpartum, may be more common than initially thought, although the exact incidence is unknown. It may or may not be associated with pre-eclampsia or eclampsia and cases have also been seen in association with vasospastic drugs, such as ergonovine and bromocriptine during pregnancy [78, 79, 81].

9. Antiphospholipid Antibody Syndrome

Ischaemic stroke was the most common presentation of arterial thrombosis in 1000 patients (mean age 42 ± 14 years) fulfilling the Sapporo criteria [80, 94] for antiphospholipid syndrome (stroke was the incident event in 13% of patients and TIA in 7%) in a large cohort study [95]. There is little doubt that such patients are at increased risk. However, although case-control studies have uniformly demonstrated a higher prevalence of antiphospholipid antibodies among young people who have experienced ischaemic stroke [96–100], studies documenting the persistence of antiphospholipid antibodies following ischaemic stroke in the young are lacking. Ischaemia may transiently induce antiphospholipid antibodies, and prospective studies examining the stroke incidence among patients found to have antiphospholipid antibodies in the absence of an incident event have not been performed [101]. Whether or not the presence of lupus anticoagulant poses a greater risk than other antiphospholipid antibodies remains unclear. Consistent associations between young ischaemic stroke and the presence of lupus anticoagulant and anticardiolipin antibodies are seen [96–100, 102, 103], although there are conflicting reports regarding the significance of anticardiolipin antibodies in older stroke populations [104–106]. Interpretation is complicated by methodological differences and the use of different cut-off values with stronger associations observed at higher titre cutoffs.

With regard to the increased incidence of young stroke among patients with systemic lupus erythematous found to have antiphospholipid antibodies, lupus alone is associated with an increased incidence of cerebrovascular events, which can be mediated by targeting conventional risk factors. As such, it is difficult to tease out the relative contribution of antiphospholipid antibodies in these patients.

10. Nonatherosclerotic Vasculopathies

Cervical artery dissection, migraine, vasculitis, including primary cerebral angiitis, infection (including HIV), radiation vasculopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), reversible cerebral vasoconstriction syndrome (RCVS), Moyamoya, Sneddon's syndrome, Fabry's disease, and malignancy, all come under the heading of nonatherosclerotic arteriopathies. The most common of these in young stroke patients is cervical artery dissection (CAD), which has been implicated in up to 20–25% of cases of young stroke [21, 23, 42], followed by vasculitis related to infection (up to 7% of cases depending on the geographical region [51]), Moyamoya in Asian populations (6–15% of cases of nonatherosclerotic vasculopathy [40, 45]), and migraine (probably closest to 1–5% of cases [21, 23, 29, 33–36]). While, as

a collective group, the remaining nonatherosclerotic vasculopathies contribute to 7–25% of cases of young stroke along with CAD, migraine, infection, and Moyamoya [36, 40, 43, 45], each is responsible for less than 1% of cases. Many of the nonatherosclerotic vasculopathies demonstrate ethnic, geographical, and genetic links making them more common in some populations than others. Similar to Moyamoya, Takayasu's arteritis is more common in Asian females for example (approximately 1% of cases of nonatherosclerotic arteriopathy in Korea) [45]. Vasculitis related to infection as a cause of young stroke is more common in developing countries and in geographical regions with a high prevalence of HIV [51]. Primary cerebral angiitis, a rare cause of stroke, is more common in middle-aged men [107], and MELAS is a maternally inherited mitochondrial disorder. Reversible cerebral vasoconstriction syndrome, which may be underrecognized, is more common in females [108], as is Sneddon's syndrome [109], while both familial and sporadic cases of CADASIL have been described [110, 111].

It should be noted that, apart from primary cerebral angiitis, systemic vasculitides rarely involve the intracranial vessels to produce stroke. Rather, concurrent atherosclerotic disease (and rarely nonbacterial thrombotic endocarditis) is a much more important cause of stroke in patients with systemic lupus erythematosus, for example.

11. Extracranial Arterial Dissection

Cervical artery dissection (CAD) accounts for up to one fifth of ischaemic strokes in young and middle-aged patients [23, 112, 113]. In a majority of cases, the specific etiology remains unknown. Trauma, infection, migraine, fibromuscular dysplasia, and a range other causes have been linked with CAD but evidence to support strong links is limited [112, 114].

With regard to CAD epidemiological observations suggest that some as-yet unrecognized predisposing factors could be heritable [112, 115–117]. A recent meta-analysis has observed a probable link with Ehlers-Danlos but no other consistent associations, although there is little doubt that genetic factors play a role given the high proportion of connective tissue defects noted on specimens and the observed clustering of CAD in families [112]. Environmental triggers, such as infection, are likely also important [112].

12. Haemorrhagic Stroke

The largest studies indicate that subarachnoid and intracranial haemorrhage comprise 25–55% of all strokes under the age of 45 [17, 26, 118, 119] with reported incidence rates ranging from 3 to 6 in 100 000 people/year for subarachnoid haemorrhage, and 2 to 7 in 1 000 000 people/year for intracranial haemorrhage under the age of 45 [18, 20, 26, 120] (the greatest reported incidence rates are for adults aged 20 to 44 in the Northern Manhattan Stroke Study, while other studies have examined adults from age 15 to 44).

The known association between hypertension and intracranial haemorrhage may explain the increased rate of intracranial haemorrhage observed among young blacks in America [26, 39], with one study specifically demonstrating an increased incidence of hypertensive intracranial haemorrhage among young blacks [39]. A relatively high proportion of intracranial haemorrhage has also been noted in young Nigerians, although the analysis was hindered by the inability of many patients to afford a CT scan [51]. An increased risk of intracerebral haemorrhage has also been observed in Hispanics in the Northern Manhattan Stroke Study [26]. This issue has not been well examined among young Asians, apart from a study in North India that did not find an increased proportion of haemorrhagic to total strokes (i.e., only 14% of cases were haemorrhagic) [121] compared to Western countries (with reported proportions in the range of 40–55% of all young strokes [17, 26, 119]). A relatively low proportion of haemorrhagic stroke has also been observed in Saudia Arabia (13% of cases) [122]. Larger scale population studies are required to explore this further. Vascular malformations (aneurysms and arteriovenous malformations) were found in 49% of patients in a retrospective evaluation of 200 cases of intracranial haemorrhage in a tertiary medical centre in Mexico [123]. A high proportion of haemorrhagic stroke secondary to vascular malformations has also been reported in developing countries, although formal angiography is less accessible and reported frequencies are somewhat lower [121].

An important consideration in young persons presenting with intracerebral haemorrhage is the possibility of illicit drug use. In a large American population-based study examining drug use among young patients hospitalized with haemorrhagic ($n = 937$) or ischaemic ($n = 998$) stroke, increased young haemorrhagic stroke rates were observed in association with increased rates of amphetamine and cocaine abuse over a period of three years. An odds ratio of 5 (95% CI 3.24–7.55) for young haemorrhagic stroke in the setting of amphetamine abuse, and 2.33 (95% CI 1.74–3.11) in the setting of cocaine abuse was observed. Cocaine abuse was also associated with an increased rate of ischaemic stroke (OR 2.03; 95% CI 1.48–2.79) [124]. There is now a convincing body of evidence to suggest a high prevalence of underlying cerebrovascular abnormalities among patients experiencing ICH or SAH in association with cocaine and other drug abuse [125].

13. Conclusion

In summary, stroke in the young requires a different approach to investigation and management than stroke in the elderly given differences in the relative frequencies of possible underlying causes. Haemorrhagic stroke is common, and vascular imaging is recommended given a high frequency of underlying vascular anomalies. It is also important to explore the possibility of illicit drug use in these cases. With regard to ischaemic stroke, the increased frequency of dissection mandates a high index of suspicion for imaging the extracranial and intracranial vessels. Whilst the commonest cause of cardioembolic stroke in the elderly is atrial fibrillation, in a young patient transoesophageal echocardiography looking for the presence of a patent foramen ovale ± an atrial septal

aneurysm will have a higher yield. One must not forget, however, that atherosclerosis still contributes to a large proportion of stroke in young patients and likely explains at least some of the ethnic differences noted in the incidence of stroke, emphasizing the need for aggressive risk factor management. This, as well as differences in the prevalence of other causative etiologies, such as rheumatic fever and infection, combined with a younger background population age distribution, may contribute to an increased incidence of young stroke in developing countries. Finally, the incidence of stroke appears greater in women than men under the age of 30, and women are at increased risk of haemorrhage and infarction in the puerperium. Additional history, including use of the oral contraceptive pill, and testing for antiphospholipid antibodies is important in young women.

There is a need for further research in young stroke, particularly population-based studies utilising standardised methodology. These will provide clarity by enabling comparison of incidence rates between countries and trends overtime, and insights into underlying etiological mechanisms.

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Case Report

Intravenous Thrombolysis of Occlusion in the Middle Cerebral and Retinal Arteries from Presumed Ventricular Myxoma

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Background. Although thrombolytic therapy has been shown to be beneficial to stroke patients, the effectiveness of intravenous thrombolysis in ischemic stroke patients with ventricle myxoma is unknown. *Case Description*. A 22-year-old woman with left hemiplegia was sent to the emergency department at a teaching hospital. The magnetic resonance angiography showed occlusion of the right middle cerebral artery, and the echocardiography showed a mass in the left ventricle. Intravenous recombined tissue plasminogen activator (rt-PA) was administrated, and the postthrombolysis transcranial Doppler exam showed that her right middle cerebral artery was circulative. The patient's condition improved gradually, and no complication was observed up to 16 months of follow-up. *Conclusion*. Intravenous rt-PA is a reasonable treatment for stroke patients with ventricle myxoma.

1. Introduction

Myxoma represents 50% of primary cardiac tumors. Embolic stroke is the most common neurological manifestation of cardiac myxoma [1, 2], but the role of thrombolytic therapy in the treatment of stroke patients with cardiac myxoma is unknown. Considering that thrombolytic therapy has a 3-hour time-window only, physicians seldom performed a complete cardiac evaluation when applying the thrombolytic therapy to stroke patients. We hereby report a patient with left ventricle myxoma who received an intravenous recombined tissue plasminogen activator (rt-PA) treatment and showed gradual symptom improvement without complications up to 16 months of followup.

2. Case Report

The patient was a 22-year-old, 53 Kg, right-handed woman with a history of exertional dyspnea who had suffered from three episodes of syncope. There was no family history of stroke. She had no history of headache, smoking, or drinking and no history of taking birth control pills. She suddenly developed left-side limbs weakness and was brought to the emergency department at a teaching hospital within one hour of stroke onset. At the emergency department, her blood pressure was 104/68 mmHg, and she had a regular heart rate of 72 with normal heart sounds. She was conscious and well oriented. Her eyes were deviated to the right side, and her right eye vision was lost. She had a severe left-side hemiparesis and a left central type facial palsy. Her National Institutes of Health-Stroke-Scale (NIHSS) score was 12, and her modified rankin score (mRS) was 4. Results of her hematologic and biochemistry tests were normal, and her chest roentgenogram revealed a normal heart size. The brain computerized tomography (CT) showed no abnormal density, and the electrocardiogram (ECG) revealed sinus rhythm. There was no carotid bruit. Intravenous administration of rt-PA (0.9 mg/Kg) was given between 125 to 185 min after the stroke onset.

On the next day, her blood sugar, cholesterol, triglyceride, protein C, protein S, antithrombin, antinuclear antibody, anticardiolipin, and homocystein values were normal.

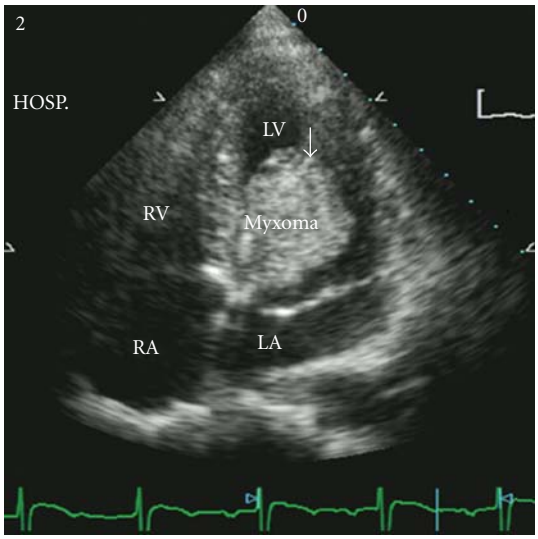

Figure 1: Transthoracic echocardiogram from apical 4-chamber view showed one myxoma (arrow) in the left ventricle with diameter 3×4 cm and stalk on middle interventricular septum.

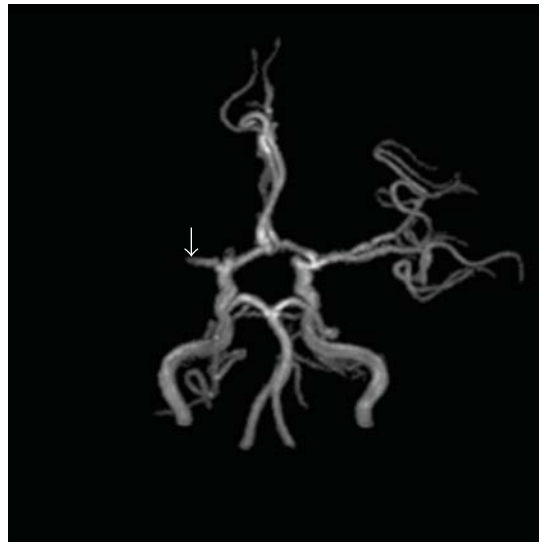

Figure 3: MRA shows right proximal middle cerebral artery (MCA) occlusion (arrow).

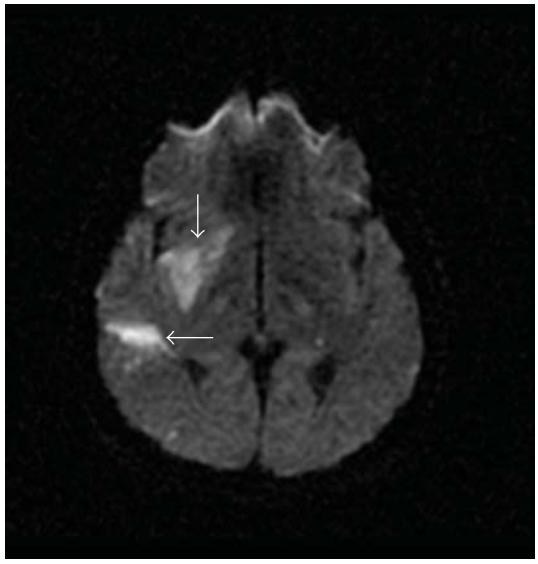

Figure 2: MRI of brain shows infarct in right putamen and temporal lobe (arrows).

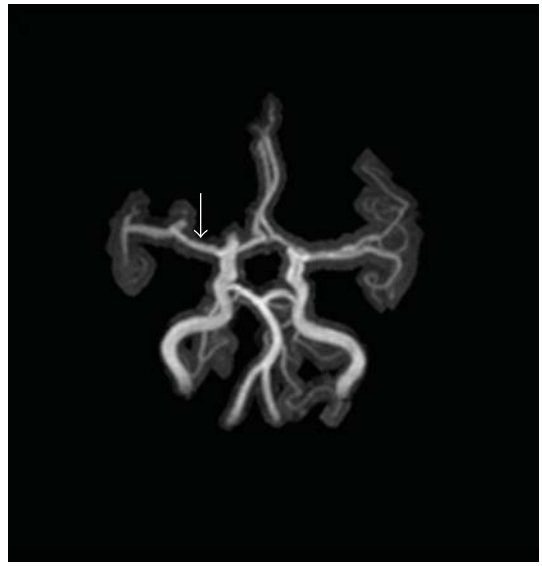

Figure 4: Sixteen months after thrombolytic therapy, MRA shows right middle cerebral artery recanalization (arrow).

A neurological examination showed a mild improvement, with NIHSS of 11 and mRS of 4, but no change in muscle power or facial palsy. Her transthoracic echocardiogram revealed a large (3×4 cm) homogenous mass with a stalk attached to the left interventricular septum (Figure 1), but her carotid duplex ultrasonography was normal. A transcranial Doppler (TCD) exam showed a decrease in blood flow in the right middle cerebral artery. From T2 and diffusion-weighted magnetic resonance image (MRI), infarcts in right basal ganglion and temporal lobe were observed (Figure 2). Magnetic resonance angiography (MRA) showed occlusion of the right middle cerebral artery in the proximal section (Figure 3). No adverse effects following the thrombolytic therapy were observed.

The patient received a tumor resection, and the pathological examination confirmed the diagnosis of left ventricle myxoma. The postoperation clinical course was uneventful without further syncope episodes. Her neurological symptoms improved gradually, but her visual acuity had no improvement. Ten months after the thrombolytic therapy,

her NIHSS was 5 and mRS was 2. Sixteen months after the therapy, the MRA showed right middle cerebral artery recanalization (Figure 4).

3. Discussion

Approximately 75% of cardiac myxomas are located in the left atrium, and only 2.5% of them occur in the left ventricle [3, 4] Clinical manifestations of cardiac myxoma include constitutional, obstructive, and embolic symptoms. Constitutional symptoms (recurrent fever, malagia, and weight loss) occur in 34 to 90% of patients, and obstructive symptoms (fatigue, weakness, dyspnea, and syncope) occur in 54 to 95% of patients. Embolic symptoms were reported in 10 to 45% of cases [2]. Neurological symptoms present in 12 to 45% of patients, and embolic cerebral infarct is the most common event [1, 5].

Thrombolysis with intravenous rt-PA treatment within three hours of ischemic stroke is now widely applied because it has been found to be beneficial to patient's outcome. In this patient, acute occlusions of the right middle cerebral artery and retinal artery were likely to be caused by embolism from the left ventricle myxoma. This patient had received a complete dose of rt-PA before her myxoma was diagnosed by transthoracic echocardiography. After the thrombolytic therapy, the patient's neurological symptoms improved. Although MRA did not show recanalization of the right middle cerebral artery, TCD showed that the right middle cerebral artery was circulative. Approximately 41% of cardiac myxomas have surface emboli, and systemic embolization related to myxoma surface thrombus is most likely [5]. Because cases of embolic stroke following thrombolytic therapy of myocardial infarction were reported [6], cardiac myxoma was once considered as a contraindication for thrombolytic therapy, but such an argument has not been well established [7].

Successful thrombolytic therapy with rt-PA in acute ischemic stroke patients with cardiac thrombus has been reported [8, 9], and intra-arterial thrombolysis of cerebral artery occlusion with urokinase has been demonstrated to be capable of causing partial recannalization [10]. However, a previous report showed that thrombolytic therapy in patients with ventricular thrombous may cause embolic stroke [6]. The response to intravenous thrombolysis by myxomatous embolic stroke patients is unpredictable.

Using "ventricular myxoma," "thrombolytic therapy," "stroke," and "cerebrovascular disease" as key words, we did not find any reports on similar cases in the PubMed databases. Intravenous thrombolytic therapy in acute ischemic stroke patients, caused by left atrial myxoma, had been reported to be an effective treatment [11]. However, thrombolytic therapy in patients caused by ventricular myxoma has not been reported. Therefore, the case described in this paper is probably the first reported evidence of a successful thrombolytic therapy in a stroke patient with presumed left ventricular myxomatous embolism. Based on this case, thrombolytic therapy with IV rt-PA is reasonable for ischemic stroke patients with ventricular myxoma.

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Review Article

Ischemic Stroke during Pregnancy and Puerperium

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Ischemic stroke during pregnancy and puerperium represents a rare occurrence but it could be a serious and stressful event for mothers, infants, and also families. Whenever it does occur, many concerns arise about the safety of the mother and the fetus in relation to common diagnostic tests and therapies leading to a more conservative approach. The physiological adaptations in the cardiovascular system and in the coagulability that accompany the pregnant state, which are more significant around delivery and in the postpartum period, likely contribute to increasing the risk of an ischemic stroke. Most of the causes of an ischemic stroke in the young may also occur in pregnant patients. Despite this, there are specific conditions related to pregnancy which may be considered when assessing this particular group of patients such as pre-eclampsia-eclampsia, choriocarcinoma, peripartum cardiomiopathy, amniotic fluid embolization, and postpartum cerebral angiopathy. This article will consider several questions related to pregnancy-associated ischemic stroke, dwelling on epidemiological and specific etiological aspects, diagnostic issue concerning the use of neuroimaging, and the related potential risks to the embryo and fetus. Therapeutic issues surrounding the use of anticoagulant and antiplatelets agents will be discussed along with the few available reports regarding the use of thrombolytic therapy during pregnancy.

1. Introduction

Ischemic stroke is more common in men than in women until advanced age, when a higher incidence is observed in women [1]. When younger patients are considered, females usually exceed males under 35, a period that coincides with the prime child-bearing years [2, 3]. Pregnancy and puerperium may partly contribute to this increased rate.

Ischemic stroke during pregnancy is a rare occurrence but it could be a serious and stressful event for mothers, infants, and also their families.

A conservative approach is frequently adopted because of concerns of any adverse effects of treatment and etiological investigations on the mother and the unborn fetus.

This article describes the physiological changes that may increase the risk of cerebral complications and deepens specific mechanisms, risk factors for ischemic stroke, and management of this subgroup of patients.

2. Maternal Changes during Pregnancy Predisposing to Ischemic Stroke

Maternal physiological alterations occur during pregnancy as a consequence of the variations of the hormonal status, involving the haemostatic and hemodynamic systems. Wether this adaptation could affect the risk of an ischemic stroke is still unclear and the relationship is likely complex.

2.1. Haemostatic Adaptations. Pregnancy is normally associated with significant changes in venous flow and in the molecular mediators of haemostasis, to the extent that the overall balance shifts towards a hypercoagulant effect [4] (Table 1).

Procoagulant changes are more marked around term and in the immediate postpartum period, presumably related to the expulsion of the placenta and release of thromboplastic

Table 1: Modifications of haemostatic factors during pregnancy.

Procoagulant factors	
Fibrinogen (factor I)	↑
von Willebrand factor	↑
Factors VII, VIII, IX, X, XII	↑
Factors V, XIII	↑↓
Factor XI	C
Factor II	C
Coagulation inhibitors	
Protein S	↓
Protein C, antithrombin III	=
Fibrinolytic factors	
Tissue plasminogen activator	↓
Plasminogen activator inhibitor 1 and 2 (PAI-1, PAI-2)	↑
Thrombin activatable fibrinolysis inhibitor (TAFI)	↑
Others	
Platelet count	↓
Prothrombin fragment 1+2	↑
Thrombin-antithrombin complex	↑
D-dimer, fibrinopeptide-A	↑

↑: increase; ↓: decrease; =: no significant change; ↑↓: early increase followed by decrease; C: controversial data.

substances at the site of separation. Blood coagulation and fibrinolysis get back to those of the nonpregnant state approximately 3 weeks after delivery [4].

This resulting hypercoagulable state in association with a venous stasis condition may likely account for an increased risk of thromboembolic complications, in particular, during the third trimester and the puerperium.

2.2. Hemodynamic Adaptations. In the first 10 weeks of pregnancy, a volume shifting develops with an increase of total body water, that remains stably increased until 1 to 2 weeks after delivery, after which it gradually returns to normal.

This hypervolemic state combined with an increasing circulatory demands of fetus and placenta results in a rise of 30% to 50% of cardiac output, stroke volume, and heart rate. Half of this change occurs during the first 8 weeks of pregnancy, reaching a peak at 25–30 weeks. During labour, there is a dramatic change in cardiac output which increases progressively as labour advances increasing by a mean value of 30%. Heart rate also increased consistently.

Then, in the first days after delivery, there is a strong fall of stroke volume and heart rate and cardiac output gradually decreases to 50% above prepregnancy level within 2 weeks after delivery and returns to normal by 6 to 12 weeks [5].

As a consequence of decrease in systemic vascular resistance, blood pressure starts to lower around the seventh week, hits the lowest levels at 24 to 32 weeks, and then increases progressively to prepregnancy levels at term.

Venous compliance increases throughout pregnancy, leading to decreased blood flow, increased stasis, and a tendency toward orthostatic pressure drops.

A remodelling in arterial composition with a reduction in collagen and elastin contents and a loss of distensibility that partially normalizes near term has been also observed during pregnancy [6].

3. Epidemiology

In hospital-based and community-based reports, the incidence for ischemic strokes associated with pregnancy or puerperium varies considerably raging from 4.3 to 210 per 100,000 deliveries [7].

Potential explanations for this variability are: (1) differences in study designs, (2) small sample size of most studies, (3) inadequate consideration of referral bias, and (4) different definitions of strokes and stroke subtypes. Studies are also not uniform in definition of postpartum period. Moreover, estimation of incidence is influenced by those studies reported before neuroimaging use became widely available [8, 9]. When data published since 1985 are considered [7, 9–16], the incidence rates is reduced ranging from 4 to 41 per 100,000 pregnancies and decreases more considering only the three population-based studies, with a range from 4 to 11 cases per 100,000 deliveries [7, 9, 12] (Table 2).

The risk of stroke varies according to pregnancy stages. Kittner and coworkers estimated a relative risk of cerebral infarction of 0.7 (95% CI, 0.3 to 1.6) during pregnancy, which increased to 5.4 (95% CI, 2.9 to 10.0) during the six weeks after pregnancy (after a live birth or stillbirth) [12]. In hospital–based series, the frequency of ischemic stroke has been observed to be higher in the third trimester, with a peak in the first postpartum week [7, 14, 15].

In a large Swedish cohort of over 650,000 women with over 1 million deliveries in an eight-year time period, the greatest risk of ischemic and hemorrhagic stroke was found around delivery [33,8 (95% CI 10.5 to 84.0), two days before and one day after with an increased but declining risk over the subsequent six weeks [8.3 (95% CI, 4.4 to 14.8] [17].

The reason of a clustering of events around delivery and postpartum period is not clear but implies a possible link with the coagulation profile of this stage. The large reduction of blood volume or the rapid hormonal changes following delivery have also been suggested to influence this stroke risk timing, perhaps through hemodynamic, coagulative, and vessel-wall changes [12].

4. Risk Factors and Associated Conditions

Data from the Nationwide Inpatient Sample in United States for the period from 2000 to 2001 showed that several medical conditions resulted associated with stroke in pregnancy such as hypertension, diabetes, heart disease, sickle cell disease, anemia, thrombocytopenia, and thrombophilia. Among lifestyle factors, alcohol, smoking, and substance abuse were found to be significantly associated to stroke in pregnancy [18]. Pregnancy and delivery complications such as infection, transfusion, postpartum hemorrhage, and fluid

Table 2: Studies of pregnancy-related stroke since 1985.

Author, year	Methodology	Study period	Postpartum period	Deliveries N°	Total stroke N°	Ischemic stroke N°	Ischemic stroke incidence (per deliveries)	Mortality N° (%)	Ischemic stroke mortality	Notes
Wiebers and Whisnant, 1985	Retrospective population-based study	1955–1979	NR	26099*	1	1	NR	NR	NR	*Live births
Simolke et al., 1991	Retrospective single hospital-based study	1984–1990	NR	89913	15	7	1 in 10000'	2 (13,3)	1 (14,3)	*Including also cerebral venous thrombosis
Awada et al., 1995	Retrospective hospital-based study	1983–1993	15 days	NR	12	9	NR	4 (33)	1 (11,1)	
Sharshar et al., 1995	Retrospective and prospective multihospital-based study	1989–1992	2 weeks	348295	31	15	4,3 per 100 000	4 (13)	0	
Kittner et al., 1996	Retrospective population-based study	1988–1991	6 weeks	141243	31	17*	11 per 100 000	NR	NR	*Including cerebral venous thrombosis (1 patient)
Witlin et al., 1997	Retrospective single hospital-based study	1985–1995	4 weeks	79301	24	5	NR	7 (29,2)	NR	
Jiagobin and Silver, 2000	Retrospective single hospital-based study	1980–1997	6 weeks	50711	34	21*	41 per 100 000	3 (9)	0	*Including cerebral venous thrombosis (8 patients);
Skidmore et al., 2001	Retrospective hospital-based study	1992–1999	12 weeks	58429	36	21	NR	1 (2,7)	1 (4,7)	
Ros et al., 2001	Retrospective, records from birth register, Sweden	1987–1995	6 weeks	1003489	NR	NR	4 per 100 000	NR	NR	
Jeng et al., 2004	Retrospective single hospital-based study	1984–2002	6 weeks	49796	49	16	32,1 per 100 000	10 (20)	2 (13)	
Liang et al., 2006	Retrospective single hospital-based study	1992–2004	6 weeks	66781	26	11*	16,5 per 100000	5 (19)	1 (9,1)	*Including cerebral venous thrombosis (3 patients)

NR: not reported.

and electrolyte imbalance were also linked to pregnancy-related stroke [18]. However, this study was limited to data derived from discharge record abstraction and no precise information on stroke ischemic subtype were available.

Although the risk of pregnancy-related stroke is resulted to be higher among women aged 35 years and older [18], ischemic subtype has been associated with a younger maternal age [12] and a mean age under 30 has been reported in patients with pregnancy-related stroke in hospital-based series (Table 3).

Migraine headaches have been associated with a 17-fold increased risk of stroke in pregnancy [18], a relation which is stronger with ischemic subtype (OR 30.7, 17.4 to 34.1) [19]. However, difficulties in differentiating between migraine as a manifestation or as a consequence of an ischemic stroke and others conditions such as severe pre-eclampsia, and migraine as an independent risk factor for ischemic stroke during pregnancy, limit the external validity of these findings.

Caesarean delivery has been shown to be associated with a 3–12 times increased risk of peripartum and postpartum stroke [20, 21]. Ischemic stroke risk was found to be significantly increased in women with Cesarean delivery and up to 6 months postpartum [22]. However, an increased number of caesarean delivery among patients with previous stroke or with conditions that can increase the risk of stroke such as preeclampsia-eclampsia may confound this association.

5. Etiology of Ischemic Stroke in Pregnancy

As several causes of ischemic stroke in the young have been reported in pregnancy and the puerperium [23], in most cases it is quite difficult to distinguish whether pregnancy is coincidental or plays a role in the occurrence of the cerebral infarction. Notwithstanding, there are specific conditions related to pregnancy which may lead to ischemic stroke such as preeclampsia and eclampsia, and most rare disorders such as choriocarcinoma, amniotic fluid embolism, peripartum cardiomyopathy, and postpartum cerebral angiopathy. Since most studies included small numbers of patients and authors defined strokes and stroke etiologies differently, a comparison of the conditions that contribute to ischemic stroke in pregnancy is limited. However, while a high proportion of cases, ranging from 28% to 46%, has resulted to be undetermined, preeclampsia-eclampsia and cardioembolic causes represent the conditions that mainly contribute to ischemic stroke (Table 3).

6. Pregnancy-Specific Causes of Ischemic Stroke

6.1. Preeclampsia and Eclampsia. Preeclampsia-eclampsia, also known as toxemia, is a multisystem disorder that occurs in the later stages of pregnancy and in the first 6 to 8 weeks after delivery, accounting for a substantial maternal and perinatal mortality [24].

Pre-eclampsia is characterized by the presence of elevated gestational blood pressure, proteinuria, and oedema. Although this condition is usually asymptomatic, patients may complain of headaches, visual abnormalities, confusion, and impairment of consciousness. The onset of seizures or coma defines eclampsia [24]. About 2% to 12% of patients with eclampsia develop a HELLP syndrome [25], a life-threatening condition characterized by hemolytic anemia (H), elevated liver enzymes (EL), and low platelet count (LP). Preeclampsia occurs in about 6% to 8% of all pregnancies, whereas eclampsia has an incidence of 1/1000 to 1/2000 deliveries in the United States [26].

Preeclampsia-eclampsia increases the risk of stroke [12, 22, 27]. The proportion of patients with ischemic stroke related to preeclampsia-eclampsia during pregnancies varies from 6% to 47% (Table 3). Moreover, preeclampsia is also founded to increase the risk of stroke later in life suggesting that these patients may be closely monitored and controlled for stroke risk factors also beyond the postpartum period [27].

Patients with severe pre-eclampsia or eclampsia may manifest focal neurological deficits, consistent with a clinical diagnosis of stroke and on neuroimaging both ischemic or hemorrhagic stroke may be found.

Clinical signs and neuroradiological lesions frequently reverse completely within a few days or weeks. Brain computed tomography (CT) and magnetic resonance imaging (MRI) show subcortical white matter lesions often with posterior predominance and, to a lesser extent, in the cortical grey matter predominantly affecting the parietooccipital region, consistent with the presence of reversible vasogenic edema. The appearance of cerebral edema on brain imaging is thought to be the consequence of disturbed cerebral autoregulation with cerebral endothelial leakage in the setting of severe hypertension. These findings are similar to those found in other vasculopathies associated to pre-eclampsia such as the posterior reversible encephalopathy syndrome (PRES). MR angiography may also show reversible vasospasm of the large and medium-sized vessels.

The pathogenesis is complex and not completely understood. This condition is characterized by abnormal vascular response to placentation and by endothelial cell dysfunction which represents common response leading to instability of vascular tone with vasospasm in various organs and activation of the coagulation system with microthrombi formation [24, 28, 29] with the consequence of ischemic damage in many organs.

The management of pre-eclampsia is aimed at delivery of the fetus and placenta and drug therapy of hypertension. Magnesium sulphate should be used for the treatment of seizures and in prophylaxis may prevent or reduce the rate of eclampsia and its complications in pre-eclamptic patients [24, 30].

6.2. Choriocarcinoma. Choriocarcinoma is a malignant neoplasm that arises from placental trophoblastic tissue, usually following a molar pregnancy but also term delivery, abortion, and ectopic pregnancy. It has a tendency to early metastasize, especially to the lungs, brain, liver, and vagina [31]. Brain metastases are relatively common complication involving about one-fifth of patients. The clinical presentation of cerebral involvement includes headache, focal neurological

Table 3: Etiologies of ischemic stroke complicating pregnancy and the puerperium.

Author, year	Mean age, yrs	N° case	Large artery disease	Cardiac disease N° (%)	Coagulopathy N° (%)	Other causes N° (%)	Pre-eclampsia eclampsia N° (%)	Other pregnancy N° (%)	Unkown N∘ (%)	Notes
Awada et al., 1995	30	9		3 (33%)*		1(11%)**	1(11%)		4(45%)	*2 valvular heart disease, 1 postpartum cardiomyopathy with atrial fibrillation, *Nephrotic syndrome
Sharshar et al., 1995	30,2	15			1(6,6%)*	1(6,6%)**	7(47%)	2(13,2%)***	4(26,6%)	*Protein S deficiency; **vertebral artery dissection; ***1 postpartum cerebral angiopathy, 1 amniotic fluid embolism
Kittner et al., 1996	27	17		1 (5,9%)*		6 (35,3%)**	4 (23,5%)		6 (35,3%)	*Mitral valve prolapse; **2 primary CNS vasculopathy, 1 cerebral artery dissection, 1 cerebral venous thrombosis, 1 postherpetic vasculitis, 1 thrombotic thrombocytopenic purpura;
Jiagobin and Silver, 2000	30	13	1 (8%)*	4 (30,7%)**	2 (15,3%)***		3 (23,1)****		6 (46%)	*Carotid artery dissection; *valvular heart disease, coronary artery disease, patent foramen ovale; ***deficiencies of protein C, protein S, activated protein C resistance; ****preeclampsia-eclampsia was considered as a risk factor
Skidmore et al., 2001	26,9	21		5 (23,7%)*	2 (9,6%)**	5 (23,7%)***	3 (14,4%)		6 (28,6%)	*1 pedunculated cardiac mass, 2 rheumatic heart disease, 1 valvular heart disease, 1 peripartum cardiomyopathy, **1 protein S deficiency, 1 factor VII anomaly, ***1 cerebral vasculitis, 1 migrainous infarct, 1 mucormycosis, 1 hypotension, 1 thrombotic thrombocytopenic purpura

Table 3: Continued.

Author, year	Mean age, yrs	N° case	Large artery disease	Cardiac disease N° (%)	Coagulopathy N° (%)	Other causes N° (%)	Pre-eclampsia eclampsia N° (%)	Other pregnancy N° (%)	Unkown N∘ (%)	Notes
Jeng et al., 2004	28,9	16		9 (56%)*	3 (19%)**	1 (6%)***	1(6%)		2 (13%)	*7 rheumatic heart disease, 2 other heart diseases; **protein S deficiency; ***giant cerebral aneurysm
Liang et al., 2006	31,5	11	1 (9%)	4 (36%)*		3 (27%)**	2 (18%)	1 (9%)***		*2 congenital heart disease, 1 rheumatic heart disease, 1 atrial mixoma; **cerebral venous thrombosis; ***amniotic fluid embolism;

deficits, seizures, encephalopathy, signs of elevated intracranial pressure, and excessively elevated serum β human choriogonadotrophic hormone level [32, 33].

Choriocarcinoma is a highly vascular tumor and is extremely prone to hemorrhage. In the brain, trophoblasts may invade blood vessels, just as they would in the uterus. Cerebral ischemic damage may be the result of thrombotic process in damaged vessels or consequence of trophoblastic cerebrovascular embolism [23].

6.3. Amniotic Fluid Embolism. Amniotic fluid embolism (AFE) is a rare complication of pregnancy, related more frequently to advanced age and multiparity. AFE occurs in the setting of a disrupted barrier between the amniotic fluid and maternal circulation. Why this entry into maternal circulation occurs in some women and not in others is not clearly understood.

The mortality rate varies from 61 to 86% and accounts for approximately 10% of all maternal deaths in the United States [34]. AFE usually presents at term during labour and should be suspected in any pregnant patient, specifically those with ruptured membranes, who develop sudden onset dyspnea with hypoxia, acute hypotension, and/or cardiac arrest followed by a profound coagulopathy**;** a large percentage of survivors has a permanent hypoxia-induced neurological damage [34]. Paradoxical cerebral amniotic fluid embolism is possible [23]. Seizures is present in 10%–20% of cases and may be at times the first manifestation.

6.4. Postpartum Cerebral Angiopathy. Postpartum cerebral angiopathy is characterized by prolonged but reversible vasoconstriction of the cerebral arteries, usually associated with acute onset, severe, recurrent headaches, with or without additional neurologic signs and symptoms. It has been described using various labels, including postpartum angiopathy [35, 36], postpartum angiitis [37], and puerperal cerebral vasospasm [38]. Although the pathophysiology is scarcely understood, a disturbance in the control of cerebral vascular tone seems to be a critical element, features similar to those observed in preeclampsia or eclampsia [39]. Most patients have a history of uncomplicated pregnancy and normal labor and delivery, followed within days to a few weeks by acute onset of headache with or without various neurologic signs and symptoms. The brain MRI in patients with postpartum angiopathy may show areas of T2/FLAIR hyperintensity in any location, but especially in watershed areas between vascular territories. Multifocal segmental narrowing of large and medium-sized cerebral arteries may be present on both magnetic resonance angiography (MRA) and CT angiography. Arterial abnormalities are better visualized with CT angiography and conventional invasive catheter angiography; both of which require the use of iodinated contrast material. The MRI and MRA features may normalize with time, although extensive infarction may develop [36].

6.5. Peripartum Cardiomyopathy. Peripartum cardiomyopathy is a rare dilating cardiomyopathy, that develops in the last gestational month of pregnancy or in the first 5 months after delivery, with no identifiable cause for heart failure and in the absence of heart disease. Early development of a cardiomyopathy during pregnancy has also been described with similar clinical presentation and maternal outcome but with a higher incidence in twin pregnancies, shorter duration of pregnancy, and lower birth weight [40].

The true incidence of this condition is unknown; the reported rate is of 1 in 3000 to 1 in 4000 live births in the United States but there are geographical differences being rare in Europe and more common in Africa [41–43].

Risk factors include advanced age (>30 years), multiparity, obesity, twin pregnancies, preeclampsia, and severe hypertension during pregnancy [40, 44, 45]. The etiology remains uncertain. Suggested hypotheses include myocarditis, abnormal immune response to pregnancy, maladaptive response to the hemodynamic stresses of pregnancy, stress activated cytokines, viral infection, and prolonged tocolysis.

Clinical features consist of heart failure with dilated cardiac cavities. However, the diagnosis remains a challenge because many normal women in the last month of a normal pregnancy experience dyspnea, fatigue, and pedal edema, symptoms similar to early congestive cardiac failure. Peripartum cardiomyopathy is a diagnosis of exclusion, distinguished by rapid onset, occurrence in the peripartum period, and significant improvement in up to 50% of affected women.

Systemic and pulmonary embolization is frequently associated with this condition with an estimated incidence ranging from 25% to 40% [23]. Neurologic deficits caused by thromboembolism can rarely be the presenting symptoms [46–48]. The incidence of ischemic stroke is about 5% [23]. Additionally, cerebral infarction may result more rarely from cerebral hypoperfusion secondary to cardiac failure [49]. Prognosis is dependent on recovery of systolic function. The majority of patients recover partially or completely but the mortality rate is high and the rate of heart transplantation is about 11% [50]. Recurrences during subsequent pregnancies are common.

7. Brain Imaging Ischemic Stroke during Pregnancy

Imaging studies as part of the workup should be based on neurological indications but several concerns about fetal exposure to radiation arise for the clinician. The harmful effects of radiation depend on the stage of gestation at which the fetus is exposed, the total dose of radiation absorbed, and the rate at which the dose is absorbed [51]. Fetal exposure to ionizing radiation from CT of the maternal head is extremely low. Potential risk of birth defects due to radiation are limited to the first few weeks, the embryogenesis period, when the patient may not be aware of the pregnancy. Radiation-protection precautions for the developing fetus should be used whenever the question of pregnancy arises.

A CT perfusion study should be avoided due to a significant increase of the X-ray exposure and to the necessity

of administering intravenous contrast unless the information is critical to guide therapy. The use of iodinated contrast material during pregnancy may pose some risk to the fetus.

There are no evidence of adverse fetal effects in humans to the magnetic field exposure for magnetic resonance imaging (MRI). It has been hypothesized that some risk for the fetus may raise due to exposure to very powerful magnetic fields, minimal increases in body temperature, and loud tapping noises of the coils [52]. Although a possible teratogenic effect has been found in some studies on animal models [53, 54], MRI is the preferred imaging option in pregnancy.

Regarding the use of gadolinium during MRI study, toxic effects are not known but depositions of the gadolinium ions in fetal tissue raises concerns. Moreover, animal reproduction studies showed that gadolinium at high dose have teratogenic effects [52, 55]. Therefore, the use of gadolinium should be avoided in a pregnant woman unless specifically indicated in particular situation where the decision must be made after a well-documented and thoughtful risk-benefit analysis [56, 57].

8. Treatment of Ischemic Stroke during Pregnancy

The choice of therapy for an ischemic stroke in pregnancy is complicated by potentials of fetal toxicity, in particular during the first trimester when the risk of teratogenicity is the highest. Therapeutic intervention is influenced by the identification of underlying etiology and the related effectiveness of the treatment, the possibility of adverse outcomes both to the mother and the fetus, and by the consideration of the term of pregnancy.

8.1. Prevention Treatment. Therapeutic decision is made difficult by the lack of randomized controlled trials that adequately compare treatment options for this group of patients. Therefore, the choice of agents for prophylactic strategies is largely based upon inferences from others studies, primarily on prevention of deep vein thrombosis and the use of anticoagulants in women with high-risk cardiac conditions.

According to the American Heart Association (AHA) guidelines for pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions such as coagulopathy and mechanical heart valves, three possible therapeutic alternatives may be considered: (a) adjusted-dose unfractionated heparin (UFH) throughout pregnancy, (b) adjusted-dose low molecular weight heparins (LMWHs) throughout pregnancy, (c) either UFH or adjusted-dose LMWHs until week 13, then restarted from the middle of the third trimester until delivery and warfarin at other times [58]. For lower risk conditions, either UFH or LMWH therapy is recommended in the first trimester, followed by lowdose of aspirin for the remainder of the pregnancy [58].

8.2. Anticoagulant Treatment. UFH and LMWH do not have teratogenic effects since they do not cross the placenta and are not causes of fetal hemorrhage, although bleeding at the utero-placental junction is possible. Several studies strongly suggest that UFH/LMWH therapy is safe for the fetus [59–62]. By contrast, warfarin cross the placenta and can cause bleeding and malformation in the fetus [61, 63]. This agent is probable safe if administered during the first 6 weeks of gestation, but confers a risk of embryopathy if given between 6 weeks and 12 weeks of gestation [63]. In addiction, warfarin cause an anticoagulant effect in the fetus, which is a concern, particularly at the time of delivery, when the combination with the trauma of delivery can lead to bleeding in the neonate. Therefore, warfarin is best avoided during pregnancy.

A major bleeding was reported in about 2% of the pregnant women treated with UFH [62], which is consistent with the observed rate in nonpregnant women receiving UFH and warfarin therapy. Since the possibility of a persistent anticoagulant effect (for up to 28 hours after the last injection of heparin), the use of UFH prior to labor may complicate the delivery increasing the risk of bleeding and contraindicates epidural analgesia. By contrast, LMWH therapy is rarely related with bleeding complications and in particular, it is not associated with an increased risk of severe peripartum bleeding [64]. LMWH has also the advantages of producing a more stable coagulant response and lower incidence of osteoporosis. In about 3% of non pregnant patients, the UFH therapy can cause the development of the heparin-induced thrombocytopenia (HIT), an acquired immune condition IgGmediated, which is frequently complicated by extension of the preexisting thrombotic phenomena or new arterial thrombosis [60]. In pregnant women who developed HIT and require ongoing anticoagulant therapy, use of the heparinoid danaparoid sodium is recommended because it is an effective antithrombotic agent, does not cross the placenta, and has much less cross-reactivity with UFH and, therefore, less potential to produce recurrent HIT than LMWH [65].

Heparin and LMWHs do not reach the maternal milk and can be safely given to nursing mothers [65]. The use of warfarin is also safe during breastfeeding [65].

8.3. Antiplatelet Treatment. Wether treatment with aspirin during the first trimester of pregnancy is safe remains unclear. Although some retrospective studies reported an increased risk of fetal malformations in pregnant women using aspirin during first months, prospective studies did not confirmed this result.

A meta-analysis of eight studies (seven observational and one randomized) evaluated whether aspirin use during the first trimester of pregnancy is associated with an increased risk of congenital malformations and found no evidence of an overall increase in rates of major congenital malformations, suggesting that aspirin is safe even when used early in pregnancy [66]. This analysis, however, showed that exposure to aspirin may be associated with an increased risk of gastroschisis, but the reliability of this result should be biased because of the limitations of the studies involved related to the use of other drugs, the selection of control

Table 4: Case reports describing the use of thrombolytic treatments in ischemic stroke during pregnancy and puerperium.

Author, year	Thrombolysis	Dosage	Maternal age	Gestational age	Maternal complications	Fetal outcome	Associated conditions
Dapprich, 2002	IV rt-PA	0,9 mg/kg	31 y	12 week	minor hemorrhagic imbition of infarct area	good	Protein S deficiency
Elford, 2002	IA rt-PA	15.5 rng	28 y	I week	hematoma in basal ganglia	good	Ovarian hyper-stimulation syndrome
Johnson, 2005	IA rt-PA	15 rng	39 y	37 week	none	good	Undeterminated cause Elevated IgG and IgM anti-cardiolipin
Leonhardt, 2006	IV rt-PA	0,9 mg/kg	26 y	23 week	basal ganglia infarction	good	Antibodies
Murugappan, 2006	[a]IV rt-PA	0,9 mg/kg	37 y	12 week	intrauterine hematoma	MTP	Mitral valve replacement
	[b]IV rt-PA	0,9 mg/kg	31 y	4 week	none	MTP	decreased protein S activity
	[c]IV rt-PA	0,9 mg/kg	29 y	6 week	death from dissection during angioplasty	died	Aortic valve replacement
	[d]IA rt-PA	21 rng	43 y	37 week	none	good	AT III, protein C and S deficiencies
	[e]IA UK	600 000 U	28 y	6 week	buttock hematoma	good	protein C and S deficiencies, PFO
	[f]local UK	700 000 U	25 y	frrst trimester	asymptomatic ICH	SA	bacterial endocarditis
Wiese, 2006	IV rt-PA	0,9 mg/kg	33 y	13 week	none	good	mitral valve replacement
Mendez, 2008	IA UK	100 000 U	37 y	fifteen hours after cesarean delivery 6 days after	none		Undeterminated cause
Ronning, 2010	IA rt-PA	20 rng	29 y	delivery	none		Peripartum cardiomyopathy

IV: intravenous; IA: intra-arterial; rt-PA: recombinant tissue plasminogen activator; UK: urokinase; ICH: intracerebral hemorrhage; MTP: medical termination of pregnancy; SA: spontaneous abortion.

subjects, and failure to definitively confirm the diagnosis in all patients [66]. Potential complications of aspirin therapy in late pregnancy include fetal and maternal bleeding, premature closure of the ductus arteriosus, prolongation of labour, and delay in the onset of labor. According to data reported in another meta-analysis of 14 randomized studies including a total of 12,416 women, there is no evidence of fetal and maternal adverse effects of low-dose aspirin therapy (60 to 150 mg/d) administered during the second and the third trimester of pregnancy in women at risk for pre-eclampsia [67].

Therefore, available evidence suggests that low-dose aspirin (<150 mg/die) can be used safely during the second and third trimester; by contrast, the safety of higher dose of aspirin and/or aspirin ingestion during the first trimester is controversial.

Clopidogrel has not been found to cause significant fetotoxicity in animal studies at high doses, but there are no adequate and well-controlled studies in pregnant women so far. Only few case reported pregnant women who had successful outcome while taking clopidogrel [68, 69]. Thus, there are insufficient data to evaluate its safety in this setting.

Although dipyridamole has not been found to cause significant fetal adverse effects, there are no adequate data regarding safety or effectiveness of dipyridamole in humans during pregnancy.

8.4. Thrombolytic Treatment. No data are available about the use of thrombolytic treatment in pregnancy since this conditions was an exclusion criteria from clinical trials that validated these therapies. To date, the experience is limited only to case reports and case series, including different thromboembolic conditions such as pulmonary embolism, thrombosis of cardiac valve prosthesis, myocardial infarcts, and deep venous thrombosis, but also ischemic stroke [70]. Due to its large molecular size, recombinant human tissue plasminogen activator (rt-PA) does not cross the placental barrier and studies on animal model have not shown teratogenic effects [71, 72]. However, fetal adverse effects remain largely unknown. Obstetric concerns are also raised by the possible effects on the placenta resulting in premature labor, placental abruption, or fetal demise.

In the last years, thrombolysis for acute ischemic stroke in pregnancy has been described in only 11 patients [70, 73–77] (Table 4). In most cases, patients received thrombolysis during the first trimester, sometimes inadvertently. One of six patient treated with systemic rt-PA died; the other five women were treated with catheter-based therapy (three intra-arterial rt-PA, one intra-arterial urokinase, and one local urokinase). Four patients did not have complications, while three had cerebral hemorrhage with clinical worsening in one case. Hemorrhagic complications also included intrauterine hematoma in one case and buttock hematoma in another one. Two women had an elective therapeutic abortion and one a spontaneous miscarriage.

Moreover, thrombolysis in the postpartum period was also reported, within fifteen hours after a cesarean delivery in one case and after six days from delivery in another one, without complications for the patients [78, 79].

However, because of the differences in etiologies, as well as in thrombolytic agents used and in the way of administration, it is difficult to draw any conclusion regarding safety or effectiveness although favorable maternal outcome was shown in many cases. Therefore, thrombolytic therapy should not be withheld for potentially disabling stroke during pregnancy, but in each clinical situation, since experience is limited, the ultimate choice of therapies must be based on careful assessment of the maternal and fetal risks and benefits.

9. Prognosis and Recurrence

In a previous study of late sixties, the maternal mortality immediately after stroke was reported to be 26% [8]. Subsequently, maternal mortality following cerebral infarction has been reported not to exceed 14% and some studies reported no maternal deaths secondary to an ischemic stroke [7, 14]. However, a reliable estimate is difficult as a consequence of small number of events and different characteristic of published studies (Table 2).

In the Ile de France study, about half of the patients had a mild to moderate residual neurological deficit, with a modified Rankin score raging from 1 (3 patients) to 2 (2 patients) [7]. Skidmore and coworkers reported that 73% of the patients were discharged home [15]. Fetal outcome showed a death rate of about 12% [7].

Data regarding the influence of pregnancy on the risk of recurrent stroke are scarce, thereby making difficult to counsel women with a history of ischemic stroke about future pregnancies.

A multicenter French study on a group of 489 consecutive women aged 15 to 40 years with a first-ever arterial ischemic stroke or cerebral venous thrombosis showed that the risk of stroke recurrence associated with subsequent pregnancies is relatively small [80]. In this study, twenty-eight patients (of 373 with arterial ischemic stroke) had the initial ischemic event during pregnancy or the puerperium. During a mean followup period of 5 years, 13 of the whole cohort had a recurrent stroke but only two of these occurred in a subsequent pregnancy, related to rare definite causes of stroke such as essential thrombocythemia and primary antiphospholipid syndrome. No woman whose initial stroke occurred during pregnancy had a recurrent stroke during subsequent pregnancies. The postpartum period, not the pregnancy itself, is associated with an increased risk of recurrent stroke (RR 9.68, 95% CI 1.2, 78.9), but these results may be limited by small number of observed events, lack of prospective record of recurrent events and subsequent pregnancies, and by a selection bias related to follow-up lost.

In line with these results, a descriptive study of a series of 23 patients with a history of a previous ischemic stroke showed no recurrence of ischemic stroke during subsequent pregnancy or after delivery [81].

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Review Article

Preeclampsia and Stroke: Risks during and after Pregnancy

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Preeclampsia and stroke are significantly related, both pathologically and temporally (across the life span) in women. Cerebrovascular events can complicate preeclampsia, and can also manifest later in life. A history of preeclampsia is associated with long-term risk for hypertension, stroke, and heart disease. Cerebrovascular complications occur in only a small proportion of women with severe preeclampsia, but with high morbidity and mortality. Endothelial dysfunction and impaired cerebral autoregulation, and severe hypertension in the setting of preeclampsia are likely the cause of many strokes during pregnancy. The relationship between preeclampsia and stroke involves shared risk factors for both disorders, including chronic endothelial dysfunction and increased risk for long-term hypertension following preeclampsia (one of the major risk factors for stroke). This overlap provides insights into underlying pathophysiology and potential preventive strategies for both preeclampsia and stroke. For example, aspirin may prevent both disorders. The current review will describe the current data regarding these relationships and suggest future research to investigate remaining knowledge gaps. These are important topics for neurologists, who are likely to be involved with the care of severely ill preeclamptic patients with neurologic complications, as well as women at increased risk of stroke due to a history of preeclampsia.

1. Introduction

While stroke is a leading cause of death in postmenopausal women, it is a relatively uncommon occurrence during pregnancy. However, its morbidity and mortality are disproportionately high, especially in young women and newborn or unborn children. The incidence of stroke during pregnancy including cerebral venous thrombosis ranges from 10 to 34/100,000 deliveries [1–3]. One of the most common risk factors for stroke in pregnancy, particularly postpartum, is preeclampsia/eclampsia [2, 3]. In the most recent Nationwide Inpatient Sample epidemiological study of stroke in pregnancy, preeclampsia/eclampsia was associated with a 4-fold increased risk of stroke [2]. Preeclampsia is potentially of interest to neurologists because it shares common pathophysiology and risk factors with stroke, including endothelial dysfunction, dyslipidemia, hypertension, hypercoagulability, and abnormal cerebral vasomotor reactivity. It is not surprising then, that a history of preeclampsia during pregnancy would lead to an increased risk of stroke later in life, as well [4]. The purpose of this review is to describe what is currently known about the epidemiology of preeclampsia as it related to risk factors for stroke during pregnancy and in later life. We will also identify areas where further research is needed.

2. The Spectrum of Preeclampsia/Eclampsia

Preeclampsia is classified as one of the hypertensive disorders of pregnancy. It is generally defined as new onset hypertension with proteinuria during pregnancy, although the term is also used to describe worsening blood pressure and proteinuria in women with a history of chronic prepregnancy

hypertension [5]. The maternal syndrome consists of hypertension and proteinuria, which may also include multisystem abnormalities such as hemolysis, elevated liver enzymes, or low platelets (HELLP) syndrome; disseminated intravascular coagulation (DIC); acute renal failure; seizures; pulmonary edema [6]. The fetal syndrome includes fetal growth restriction, small-size-for-gestational-age (SGA), reduced amniotic fluid, and placental insufficiency leading to fetal hypoxia and hypoperfusion. Preeclampsia can occur near or before term, with or without fetal complications [6].

Preeclampsia is categorized as mild or severe. Mild preeclampsia is defined as blood pressure of at least 140 mm Hg systolic or at least 90 mm Hg diastolic on at least two occasions and at least 4 to 6 hours apart after the 20th week of gestation in women without prepregnancy hypertension, with proteinuria (defined as ≥300 mg protein in a 24 hour urine specimen) [6]. Severe preeclampsia is defined as blood pressure at least 160 or 170 mm Hg systolic, 110 mm Hg diastolic, or both, accompanied by ≥5 g of proteinuria per day. When symptoms such as severe headache, visual disturbance, epigastric pain, vomiting, multiorgan system involvement, fetal morbidity or mortality, onset before 34 or 35 weeks or eclampsia (seizures) are present, preeclampsia is also classified as severe (see Table 1). Eclampsia, defined as tonic-clonic seizures in a pregnant or recently delivered woman not attributable to other causes than preeclampsia or gestational hypertension, complicates about 1 to 2% of all cases of severe preeclampsia [7]. It is important to note that published guidelines for preeclampsia diagnostic criteria vary among different professional societies [7].

3. Epidemiology of Preeclampsia

Preeclampsia is part of the spectrum of hypertensive disorders in pregnancy, which also includes gestational hypertension (GH). GH is defined as elevated blood pressure of at least 140 mm Hg systolic or at least 90 mm Hg diastolic without proteinuria in a woman after 20 weeks' gestation, which resolves postpartum [10]. Hypertensive disorders in pregnancy affect 8%–12% of all pregnancies, and this rate is even higher in developing countries. About three quarters of cases of preeclampsia in women are classified as mild, with onset at or near-term [6]. Adverse outcomes are generally rare in mild preeclampsia. However, it is important to note that mild preeclampsia is a retrospective diagnosis. Mild hypertension in pregnancy can evolve quickly and unpredictably to fulminant severe preeclampsia. African American women appear to be at higher risk for the development of preeclampsia, although it is not clear whether this relationship is due to a higher prevalence of hypertension in African American women or other risk factors. Women living at high altitude are also known to be at higher risk for preeclampsia.

4. Risk Factors for Preeclampsia

Multiple risk factors for preeclampsia have been identified through clinical and large cohort studies. Many of these risk factors overlap with those for stroke and cardiovascular disease (CVD), such as family history, prepregnancy hypertension, diabetes, obesity and insulin resistance, preexisting thrombophilia, renal disease, and collagen-vascular disease [11]. Some pregnancy-specific and maternal risk factors include maternal infections, extremes of maternal age, multiple gestation, maternal low birthweight, hydrops fetalis, and preeclampsia in a prior pregnancy [7, 12] (see Duckitt et al. for comprehensive review). An unusual protective factor against preeclampsia is maternal smoking, for unclear reasons.

Immune and paternal factors may also affect women's risk for preeclampsia. In a large birth cohort in Norway, the rate of preeclampsia was 3.4% in women with their first pregnancy, whereas the rate of preeclampsia in the second pregnancy with the same father was 1.7%; other studies have noted an increase in the risk for preeclampsia with a change in paternity, limited sperm exposure with the same partner, or increased duration of time between pregnancies [13]. These findings suggested that an immune tolerance mechanism contributes to the pathogenesis of preeclampsia [14]. This theory has recently been challenged by findings that preterm preeclampsia is more likely to recur than term preeclampsia, which is not consistent with an immune-mediated mechanism. Preterm preeclampsia is also more likely to be associated with long-term CVD, which implicates maternal factors as being important in its pathogenesis [15]. Other paternal factors have been shown to contribute to the risk for preeclampsia. In the Norwegian study cited above, men who fathered one preeclamptic pregnancy were 1.8-fold as likely to father a preeclamptic pregnancy in a different woman (OR 1.8; 95% CI 1.2–2.6) [14]. Preeclampsia has a clear genetic component. In an intergenerational study of paternal and maternal contributions to the risk of developing preeclampsia, women whose mothers had preeclampsia were more likely to have the condition in their own pregnancies. Men born after a pregnancy complicated by preeclampsia were more likely to father a pregnancy complicated by preeclampsia, and for both women and men, familial preeclampsia was associated with more severe preeclampsia in the index pregnancy [16].

A novel risk factor for preeclampsia may be migraine. There is a growing body of literature to suggest an association between migraine and preeclampsia, although no cause and effect has been established. The symptomatology of both conditions may overlap, since severe preeclampsia may involve headache with visual scotoma [7], similar to migraine with aura. A review of all cross-sectional, case-control, and cohort studies published prior to 2006 revealed 10 studies that examined the association between migraine and preeclampsia, 8 of which showed a positive and significant relationship [17]. Since then, at least 2 additional studies have been published. In a large study of delivery hospitalization discharges in the Nationwide Inpatient Sample, over 34,000 women had a primary or secondary discharge diagnosis of peripartum migraine [18]. The association between preeclampsia and migraine (OR 2.29, 95% CI 2.13–2.46) was so robust that preeclampsia diagnosis codes had to be excluded in order to analyze the association

Table 1: Criteria for classification of severe preeclampsia [8, 9].

Severity Criteria	Recommendations from SOGC and ASH
Gestational age at onset	Less than 34 to 35 weeks' gestation
Maternal symptoms	Persistent or new/unusual headache; visual disturbances; persistent abdominal or right upper quadrant pain; severe nausea or vomiting; chest pain or dyspnea
Maternal signs of end-organ dysfunction	Eclampsia; severe hypertension (>160/110 mm Hg); pulmonary edema; suspected placental abruption; severe diastolic hypertension (>110 mm Hg); heavy proteinuria (3 g/day) or oliguria
Abnormal maternal laboratory testing	Raised serum creatinine; increased AST, ALT, or LDH with symptoms; platelet count $<100 \times 10^9$/L; or serum albumin <20 g/L; decreased glomerular filtration rate
Fetal morbidity or mortality	Oligohydramnios; intrauterine growth restriction; absent or reversed end-diastolic flow in umbilical artery by Doppler velocimetry; intrauterine fetal death; any fetal morbidity (non-reassuring fetal testing)

SOGC: Society of Obstetricians and Gynaecologists of Canada; ASH: American Society of Hypertension; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase.

between migraine and stroke [18]. A case control study from Peru showed an incrementally stronger relationship between preeclampsia and any headache before or during pregnancy (OR 2.4, 95% CI 1.7–3.3), migraine prior to pregnancy (OR 3.5, 95% CI 1.9–6.4), and migraine during pregnancy (OR 4.0, 95% CI 1.9–9.2) [19]. The mechanism for this association is currently unknown, but may relate to endothelial dysfunction, widely recognized as important in the pathophysiology of both conditions [17–20].

5. Risks of Cerebrovascular Disease in Women with Preeclampsia

Fewer than 1% of women with preeclampsia suffer from stroke during the puerperium (the first six weeks postpartum). However, among women with stroke during pregnancy, preeclampsia/eclampsia is an important risk factor for both ischemic and hemorrhagic strokes. For example, in a French case series of 31 women with stroke during pregnancy, about half ($n = 15$) were ischemic, with preeclampsia/eclampsia accounting for 6 cases or 47%. Of those with hemorrhagic strokes, 7 (44%) had eclampsia, in addition to HELLP syndrome or disseminated intravascular coagulation [21]. A Canadian case series reported that 7 of 34 or 21% of women with peripartum stroke had preeclampsia [1]. In Taiwan, 7 of 19 or 37% of women with peripartum stroke had preeclampsia/eclampsia or hypertensive intracerebral hemorrhage [22]. These single-center case series are limited due to the small sample sizes, but larger cohort studies have confirmed this association. The Nationwide Inpatient Sample analysis from 2000 to 2001 reported that preeclampsia was associated with a 4-fold increase in stroke during pregnancy (OR 4.4; 95% CI 3.6–5.4) [2]. A limitation of this study, as with most administrative databases, was the need to rely on correct assignment of ICD-9 codes and the inability to review medical records to collect individual level patient details.

Hemorrhagic stroke is the most common stroke type associated with pregnant or postpartum women with preeclampsia/eclampsia. Data from the Nationwide Inpatient Sample examining women aged 15 to 44 showed that most cases of pregnancy-associated hemorrhagic strokes occurred postpartum [23]. The risk factors independently associated with hemorrhagic stroke included preexisting hypertension (OR 2.6; 95% CI 1.34–5.07), gestational hypertension (OR 2.41; 95% CI 1.62–3.59), and preeclampsia/eclampsia (OR 10.4; 95% CI 8.3–13.0) [23]. The in-hospital mortality was 20% [23]. In a detailed series of 27 women with preeclampsia and subsequent stroke, 25 (89%) had hemorrhagic and 2 (7%) had ischemic stroke; 96% of these women had headache, 63% with nausea and vomiting, 71% had symptoms attributable to the central nervous system (e.g., focal weakness, seizure, syncope, decreased level of alertness), and 37.5% had visual problems [24]. Similar to the Nationwide Inpatient Sample analysis, the majority (57%) of strokes occurred postpartum. Another striking feature in this series was that 96% of these women had prestroke systolic blood pressures ≥160 mm Hg, whereas only 21% of women had diastolic blood pressures >105 mm Hg. Not surprisingly, given the high rate of hemorrhagic strokes, the mortality was 54% [24]. The important message from this case series was that, in contrast to current management protocols which base treatment decisions on elevated diastolic blood pressures, women with severe preeclampsia and high isolated systolic blood pressures should be considered at high risk for hemorrhagic stroke and that antihypertensive therapy should be considered in these patients [24].

Besides ischemic and hemorrhagic stroke, preeclampsia is often associated with the syndrome of reversible posterior leukoencephalopathy syndrome (RPLS; also known as posterior reversible encephalopathy syndrome or PRES) [25]. This disorder differs pathophysiologically from ischemic or hemorrhagic stroke because it is associated with reversible vasogenic edema seen on CT or MRI, usually in the occipital or parietal lobes [26, 27]. This disorder is thought to be similar to hypertensive encephalopathy and is associated with seizures, headaches, encephalopathy, and reversible imaging features. RPLS may occur in the setting of preeclampsia due to impaired cerebral autoregulation from endothelial damage. Large changes in blood pressure (rather than the absolute blood pressure) can then result in an imbalance of the capillary and cellular perfusion pressures, leading to vasogenic edema [27, 28]. The treatment of this disorder includes blood pressure lowering and antiepileptics, although most patients do not require treatment for seizures beyond the acute syndrome.

Imaging in women with RPLS associated with the puerperium has been described as diffuse or multifocal segmental

vasoconstriction (or vasospasm) [28]. As this disorder is increasingly recognized there are features that are considered atypical compared with the original definition. For example, in the largest case series of RPLS to date, over half of the patients had significant frontal involvement, in addition to 5% that included hemorrhage and confluent vasogenic edema [26]. Also, about one quarter of these cases had permanent injury, although the lesions were small on repeat MRI. The imaging abnormalities resolved completely in about two-thirds of cases in this series, which means that there are still a considerable number of patients with residual abnormalities [26].

A similar disorder that occurs in association with preeclampsia is reversible cerebral vasoconstriction syndromes (RCVS). The classical presentation of RCVS, also known as Call Fleming Syndrome, is a thunderclap headache, with or without additional neurologic signs [29]. Diagnostic imaging reveals multifocal segmental vasoconstriction of the cerebral arteries, which usually resolves within days to weeks. Besides occurring during the pregnancy or puerperium, this syndrome can occur as an idiosyncratic response to medications or illicit drugs, or without any identifiable cause. Although the pathophysiology of all of the vasoconstriction syndromes is not fully understood, it involves a disturbance in the control of cerebral vascular tone. In the setting of preeclampsia/eclampsia, the syndrome of RCVS usually occurs postpartum (often labeled postpartum angiopathy) [29], and in severe cases of eclampsia, superimposed cytotoxic edema and chronic infarction may also occur [30]. Based on imaging, this diagnosis may be difficult to differentiate from central nervous system vasculitis, thus analysis of spinal fluid may be helpful. Clinically, however, vasculitis usually involves an insidious headache rather than the thunderclap headache characteristic of RCV. The treatment of RCVS is not standardized because it is not known whether the rapid resolution of symptoms may be due to the natural history of the syndrome or therapeutic strategies that are empirically initiated. In confirmed cases with imaging, calcium channel blockers may be initiated, such as nimodipine or verapamil, although caution should be employed to maintain cerebral perfusion in watershed regions of a constricted artery [29]. Other medications have included high-dose glucocorticoids [31] or magnesium sulfate [32].

The amount of overlap between RPLS and RCVS is unclear because some of the larger case series of RPLS did not include arterial imaging [26, 27]. We propose that there is likely to be overlap in the pathophysiology and therefore imaging characteristics of many of the cerebrovascular syndromes associated with preeclampsia/eclampsia, as shown in Figure 1. The primary difference between RPLS and RCVS is in the clinical symptoms. RCVS manifests in a thunderclap headache, whereas RPLS is more likely to include seizures and encephalopathy with nonthunderclap headache. As noted above, because many women do not undergo brain imaging, the true prevalence of cerebrovascular complications such as RPLS and RCVS is unknown. In addition, guidelines recommend recognition and treatment of severe preeclampsia, whether it includes severe hypertension or the onset of severe headache or neurologic signs of any kind [7]. Therapeutic maneuvers such as administration of magnesium sulfate, glucocorticoids, antihypertensive therapy, or delivery of the baby may also effectively treat the reversible syndrome and its clinical symptoms, resulting in the inability to distinguish the two disorders. Because of the urgency of delivering the infant and stabilizing the mother, imaging may also not be performed commonly unless clinically indicated. Therefore, it is possible that the incidence of milder, subclinical forms of either RPLS or RCVS on imaging is much higher than currently recognized. Carefully designed pregnancy registries with detailed clinical and neurological details may provide some insights into the incidence of these disorders. In addition, noninvasive monitoring with ultrasound, such as transcranial Doppler, may also allow evaluation of the cerebral hemodynamics of severe preeclampsia, although it is currently unclear which parameters are most important to measure [33, 34].

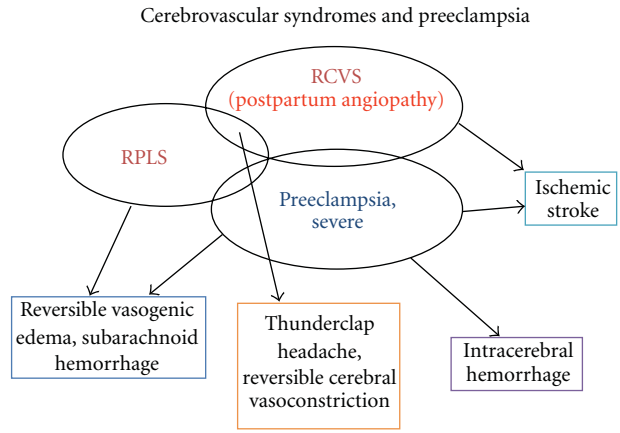

Figure 1

6. Proposed Pathophysiology of Preeclampsia

The underlying cause of preeclampsia is still unknown, but there are well-recognized combinations of placental, immune, and vascular factors that lead to the condition. The placenta is central to the pathophysiology of preeclampsia, since the latter does not occur in its absence. Preeclampsia is thought to occur in 2 stages [15]. In the first stage, abnormal placentation and maternal vascular remodeling lead to placental underperfusion, hypoxia, and/or oxidative stress, with placental release of factors which causes the second stage of endothelial dysfunction and other manifestations of preeclampsia. In the first stage, defective trophoblast differentiation and immune mechanisms related to interactions between maternal T cells and placental cytotrophoblast are hypothesized to be involved with the inadequate placentation early in pregnancy. This leads to inadequate remodeling of the spiral arteries during the first 12 weeks of pregnancy. In the second stage, the onset of systemic endothelial activation involving imbalance between angiogenic and antiangiogenic cytokines occurs as a result of insufficient placental perfusion via the spiral arteries [35]. Another hypothesis involves abnormal syncytiotrophoblast shedding into the maternal circulation, which incites an inflammatory reaction [36].

Consistent with the role of angiogenesis in the pathophysiology of preeclampsia, several blood biomarkers of angiogenesis have been studied to determine their predictive value for the development of preeclampsia later in pregnancy. Soluble flt1, also known as soluble vascular endothelial growth factor receptor 1 (sVEGFR1), is a protein produced by the placenta which binds to placental growth factor (PlGF) and VEGF, both of which are proangiogenic. Levels of sFlt1 are low in early pregnancy but rise steadily thereafter. It is hypothesized that the balance between these factors regulates placental angiogenesis, with increasing levels of sFlt1 and decreasing levels of PlGF and VEGF exerting a restraining effect on placental vascular growth via a net antiangiogenic effect [37]. Endoglin is a coreceptor for transforming growth factor beta 1 and beta 3, which is highly expressed on endothelial and syncytiotrophoblast surfaces. Soluble endoglin is also antiangiogenic and increased in preeclampsia [38]. The combination of these biomarkers was studied using a nested case control cohort of the Calcium for Preeclampsia Prevention Trial [39]. When using a cutoff for high versus low levels of both markers, the combination of high endoglin and high sflt1:PlGF ratios at 21 to 32 weeks gestation was associated with 31.6-fold odds of preterm preeclampsia and 30.8-fold odds of term preeclampsia [39]. These markers appear to be promising for identifying women early enough during pregnancy to provide early intervention.

7. Risks of Stroke Later in Life

Although women with cerebrovascular manifestations of preeclampsia are thought to be out of danger when the baby is delivered, accumulated data show that women with preeclampsia are at risk for stroke and cardiovascular disease well after the postpartum period and child bearing years [40–46]. A meta-analysis investigated the link between preeclampsia and cardiovascular disease, stroke, and relevant risk factors [4]. The cumulative odds ratios nicely illustrate the association. For example, there is nearly a 4-fold odds of developing hypertension (OR 3.7, 95% CI 2.70–5.05) and a 2-fold risk of ischemic heart disease (OR 2.16, 95% CI 1.86–2.52) in women with preeclampsia. For fatal and nonfatal stroke, the meta-analysis included 4 studies [43, 44, 47, 48] with over 64,000 women with preeclampsia and about 900 ischemic strokes. The relative risks ranged from 1.39 to 5.08. The cumulative relative risk was 2-fold with preeclampsia (RR 2.16, 95% CI 1.86–2.52) [4].

In addition to maternal risk, children born to mothers with preeclampsia pregnancies may also be at increased risk for neurological problems and stroke. The Helsinki Birth Cohort traced offspring of the original cohort born between 1934 and 1944 in Helsinki, Finland [49]. The hazard ratio for all forms of stroke in offspring of mothers with preeclampsia was 1.9 (95% CI 1.2 to 3.0), and the hazard ratio was 1.4 for those born to women with pregnancies complicated by gestational hypertension (95% CI 1.0–1.8). There was no increased risk of coronary heart disease, however. Severe preeclampsia was also associated with a reduced head circumference at birth [49].

In addition to the risk of cardiovascular events, the prevalence of cardiovascular risk factors and abnormal vascular markers appears to be higher in women with a history of preeclampsia. For example, women with a history of preeclampsia about 20 years before being studied (mean age at assessment 43 years) had higher diastolic blood pressure and were more likely to be menopausal than women without preeclampsia [50]. Although there were no differences in lipids, biomarkers of endothelial dysfunction such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were elevated in the preeclampsia group [50]. Other studies have shown that women with a history of preeclampsia are more likely to have higher insulin levels compared to controls [51]. However, not all studies have shown consistent differences in markers for cardiovascular risk. Vickers et al. reported no differences in levels of C reactive protein (CRP), von Willebrand factor, or fibrinogen in women with a history of preeclampsia or gestational hypertension compared with controls [52]. As described in the meta-analysis and other longitudinal studies, hypertension is the risk factor for cerebrovascular disease that women with a history of preeclampsia and gestational hypertension are most likely to develop [4, 43].

Women with a history of preeclampsia have also been shown to have abnormal endothelial function well after the puerperium. In a study of women in a minimum of 3 months following pregnancy, those with a prior history of preeclampsia had lower brachial artery flow mediated dilation responses than women with normal pregnancies (0.9% for those with multiple preeclamptic episodes, 2.7% for single episode, and 4.7% for controls) [53]. Preeclampsia was an independent predictor of flow mediated dilation, even after adjustment for family history, cardiovascular risk factors such as cigarette smoking, lipids, glucose, and systolic blood pressure [53]. Interestingly, when brachial artery diameter in response to nitroglycerin, an endothelium-independent response, was measured, there was no difference between groups [53]. Based on these results, preeclampsia appears to have a chronic deleterious effect on the endothelium, regardless of other risk factors. Similarly, the association between preeclampsia and impaired flow mediated dilation was also demonstrated in a separate, smaller cohort measuring flow mediated dilation 6 to 12 months postpartum [54]. Another study of women with early preeclampsia assessed 3 to 11 months postpartum reported impaired microvascular skin reactivity, whereas endothelial-independent activity was not significantly different from controls [55]. More importantly for future risk of stroke, in a study of visually evoked cerebral blood flow responses in the posterior cerebral artery measured with transcranial Doppler ultrasound, women with a history of preeclampsia have a dampened response to this stimulus [56]. Taking into account the time from preeclampsia to the testing, there also appeared to be diminishing cerebral hemodynamic function over time associated with a history of preeclampsia. Alternatively, this could represent worse function at baseline [56]. In either case these findings provide another important pathophysiologic basis for an increased risk for stroke in women with a history of preeclampsia.

8. The Duke Birth Database

There are very few studies of women followed prospectively after preeclampsia other than with administrative databases, and many of the studies were limited to Caucasian race/ethnicity. We performed an Institutional Review Board-approved search of the Duke Perinatal Health Services Outcomes Database, a medical record database of 42,263 women admitted to Duke University Medical Center from 1979 to 2005 by ICD-9 codes for preeclampsia (642.4–642.7) and stroke (437.3–437.7) [42]. After confirming with medical record review that the timing of stroke was greater than 6 weeks postpartum at onset, 23 women met the inclusion criteria for having had preeclampsia and a later admission for stroke. The median age at stroke onset was 38 (range 21–62), 18% or 78% were African American, and just over half had ischemic stroke (13 ischemic strokes/TIAs, 8 hemorrhagic strokes, and 2 subarachnoid hemorrhages). The majority (70%) of women were between the ages of 18 and 34 at the time of the last preeclamptic pregnancy (9% < age 17 and 22% over age 35). When preeclampsia was divided into mild and severe, there was no association with stroke type, age at stroke onset, or race/ethnicity. In terms of risk factors, 70% of these women had hypertension, 26% diabetes, 30% hyperlipidemia, 59% smoked tobacco, 13% used illicit drugs, and 39% had had miscarriages [42]. In addition, 100% of the women with hemorrhagic strokes had prepregnancy hypertension, compared with 60% of the women with ischemic stroke. We also found that the age of onset of hypertension was not associated with the age at stroke [42]. This study was limited because of the small cohort size, the lack of controls, and the inability to track hospitalizations outside of the center where delivery occurred. However, this was a novel longitudinal case series because these data can provide guidance for how additional cohort studies could be ideally designed to investigate the relationships between stroke types and hypertension in women with a history of preeclampsia. For example, based on this database, future cohorts should enroll women who are no more than 5 years from delivery with preeclampsia at baseline. The ongoing HyRAS study is designed to follow women in The Netherlands who are 2.5 years post-preeclampsia for 10 years to track the onset of cardiovascular disease [57]. Future studies that include underrepresented minorities, such as African American women, are needed to better understand the risk of stroke after preeclampsia since these women are at high risk for both preeclampsia and stroke.

9. Prevention of Stroke in Women

Aspirin is an important prevention strategy for ischemic stroke in women. Interestingly, it has also been used for prevention for preeclampsia; therefore prevention with aspirin represents another overlap between these two disorders. A recent meta-analysis combined randomized clinical trials of over 11,000 women randomized to low dose aspirin versus placebo to prevent preeclampsia and intrauterine growth restriction [58]. There was a significant reduction in the rate of preeclampsia with low dose aspirin started at 16 weeks

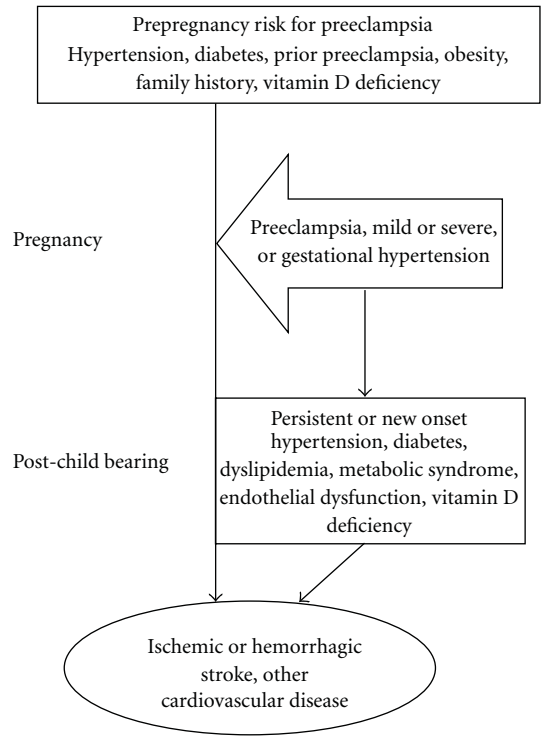

Figure 2

gestation or earlier (RR 0.47, 95% CI 0.34–0.65) in women identified as moderate or high risk. The rate of intrauterine growth restriction was reduced to a similar degree (RR 0.44, 95% CI 0.30–0.65). Since the rate of severe preeclampsia was also reduced, cerebrovascular complications would also theoretically be reduced as well. If aspirin was started after 16 weeks, the reduction in the rate of preeclampsia was no longer significant (RR 0.81, 95% CI 0.63–1.03) [58]. Caution must be exercised in interpreting this meta-analysis, however, since the inclusion criteria for individual trials of aspirin therapy were heterogeneous. In all studies where aspirin had been started before 16 weeks, only women identified as being at moderate to high risk for preeclampsia were included. Although it appears that some cases of preeclampsia can be prevented in women who are pregnant and at high risk for preeclampsia, the best long-term prevention strategy for these young and middle-aged women is currently unknown. For prevention of stroke later in life, the emphasis should be on recognizing and treating cardiovascular risk factors. It is unlikely that treating all young women with aspirin following the occurrence of preeclampsia without any other risk factors would be dangerous because aspirin increases the risk of hemorrhage. More studies are needed to identify women at early risk of stroke, as well as heart disease, and ultimately assess the risks and benefits of various prevention approaches.

Vitamin D deficiency has recently emerged as an important potentially modifiable risk factor for both preeclampsia and stroke. Women who are deficient in vitamin D before or during pregnancy are at increased risk for preeclampsia [59]. Low serum levels of 25(OH)D are very common in

both developed and developing countries. In a population-based study of vitamin D intake and risk of preeclampsia, women with an estimated intake of 600–800 IU of vitamin D per day had reduced odds for preeclampsia compared to women with an estimated intake of less than 200 IU/day (OR 0.76, 95% CI 0.6–0.95). Trials of supplementation with calcium and vitamin D showed inconsistent effects on the risk of preeclampsia [60]. Large ongoing trials of vitamin D supplementation in pregnancy as a strategy to prevent preeclampsia and other adverse pregnancy outcomes are ongoing. In a recent large electronic medical record database analysis, a 51% relative increase in stroke prevalence was noted in patients with very low versus normal vitamin D levels (5.9% versus 3.9%; $P < .0001$) [61]. The association between vitamin D deficiency and increased risk for both preeclampsia and stroke again suggests overlapping pathophysiology for these disorders.

10. Summary

From a clinical perspective, preeclampsia should be regarded as a risk factor for stroke in pregnancy as well as a harbinger of future cerebrovascular disease, although there are many gaps in our knowledge about who is at risk and when, as well as how to best prevent preeclampsia and stroke in women (Figure 2). There are many opportunities to intervene to reduce morbidity and mortality, but the major obstacle currently is our ability to identify women who are at risk for early cardiovascular disease. Given the overlap in risk factors, the potential for early atherosclerosis, and the evidence of lasting endothelial dysfunction (i.e., subclinical vascular disease) from the literature, several screening tests could be done to risk-stratify women with preeclampsia. It is noteworthy that the spectrum of hypertensive disorders in pregnancy parallels the risk for stroke and cardiovascular disease later in life. Therefore, women should be actively screened for a history of pregnancy complications as part of routine preventive care or during evaluation for stroke risk, even though they are well past their child-bearing years. Using this simple historical information is the first step to risk stratification. Further research on the utility of subclinical vascular measurements, such as cerebral or peripheral vasomotor reactivity, carotid intimal medial thickness, coronary calcification, or clinical and biochemical biomarkers, is needed to identify which women with a history of preeclampsia are at increased risk for future stroke.

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Review Article

Hereditary Connective Tissue Diseases in Young Adult Stroke: A Comprehensive Synthesis

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Though the genetic background of ischaemic and haemorrhagic stroke is often polygenetic or multifactorial, it can in some cases result from a monogenic disease, particularly in young adults. Besides arteriopathies and metabolic disorders, several connective tissue diseases can present with stroke. While some of these diseases have been recognized for decades as causes of stroke, such as the vascular Ehlers-Danlos syndrome, others only recently came to attention as being involved in stroke pathogenesis, such as those related to Type IV collagen. This paper discusses each of these connective tissue disorders and their relation with stroke briefly, emphasizing the main clinical features which can lead to their diagnosis.

1. Introduction

Epidemiological studies on stroke, one of the prominent causes of death and disability in the Western world, have revealed a strong genetic influence in its pathogenesis, with conventional risk factors contributing only up to 40%–50% of stroke risk [1]. Often stroke represents a complex polygenetic or multifactorial disease, hampering the identification of causal genes. However, in some individuals—particularly young adults—stroke can result from a monogenic disorder [2, 3]. Next to arteriopathies (Cerebral Autosomal Dominant of Autosomal Recessive Arteriopathy with Stroke-like Episodes and Leucoencefalopathy—CADASIL and CARASIL, resp.) or metabolic diseases (Fabry, homocystinuria), several connective tissue disorders (CTD) can involve ischaemic or haemorrhagic stroke as part of the phenotype in young adults. Moreover, several extracellular matrix (ECM) components have been (suggested to be) implicated in stroke pathogenesis [4].

The connective tissue is a basic type of tissue providing structural and metabolic support for other tissues and organs throughout the body. Its uniqueness, compared to other tissues, lies in its composition of a diverse set of constituents—cells, fibres, blood vessels—scattered around in an ECM. Four types of macromolecules can be distinguished in the ECM: collagen, elastin, glycoproteins and proteoglycans.

Heritable disorders that involve connective tissue are among the most common genetic diseases in humans. Their classification is not without challenge because of the phenotypic variability within and between families which characterizes several of these disorders. Classification also tends to overemphasize the aetiologic differences between severe genetic disorders that are apparent in infants or young children and the more common diseases that appear later in life. Yet these late-onset diseases, such as aneurysms and stroke, can be caused or influenced by single-gene variants. Because of the wide distribution of connective tissues within the human body, diseases that affect connective tissue cells or ECM proteins often have systemic effects. Based on the two major constituents of the connective tissue, collagen and elastin, these disorders can be divided into "collagenopathies" and "elastinopathies" [5, 6].

Awareness for and recognition of such connective tissue disorders has a broad relevance as their identification has implications not only for counselling, recurrence risk and risk for associated manifestations, but also for management and prognosis. This paper attempts to present a comprehensive review of the most important connective tissue

diseases to consider when confronted with stroke in young adults. Also some promising candidate genes encoding ECM proteins will be discussed briefly.

2. Disorders Affecting the Collagens

Collagens are triple helical proteins formed when three polypeptide chains, called alpha chains, wind around each other to form a collagen molecule. The collagen superfamily of proteins is a major component of the ECM and contains the most abundant proteins in the body which are classified into 29 collagen types [7]. A wide spectrum of diseases has been associated with the collagens, caused by mutations in at least 27 different collagen-associated genes [5]. Of them, the Ehlers-Danlos syndromes, osteogenesis imperfecta, autosomal dominant polycystic kidney disease and collagen Type IV can be related to stroke.

2.1. The Ehlers Danlos Syndrome. The Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of connective tissue disorders, affecting approximately 1 in 5000 individuals [8, 9]. It can be catagorized into several types, based on the phenotypical and molecular characteristics (Table 1).

The classic and hypermobility type are characterised by various expression of joint hypermobility and related complications, easy bruising and atrophic scarring. In contrast, the vascular type of EDS (Type IV) presents with a distinct tissue fragility of the vasculature, colon and uterus, while hypermobility and bruising are less prominent [8–10]. Particularly in the latter, autosomal dominant form, haemorrhagic or ischaemic stroke may occur at young age [11].

EDS Type IV (OMIM no. 130050) results from mutations in the *COL3A1* gene, encoding Type III procollagen (chrom. 2q31); the mutation spectrum is broad with novel mutations being a common finding (approximately 50%). The mutant Type III collagen has reduced strength, elasticity and healing properties as well as defective integration into the normal ECM, resulting in the typical EDS IV phenotype [10]. This encompasses a typical facial appearance (thin nose and lips, sunken cheeks, small chin), thin skin and fragile arteries and intestines which tend to rupture (Figure 1) [10]. Neurovascular complications are seen in approximately 10% of patients and include intracerebral aneurysms of large and medium-sized arteries and (spontaneous) dissection of carotid and vertebral arteries, often without prior dilatation [12–17]. Aneurysms typically develop in the cavernous sinus or just as the carotid artery emerges from the sinus and bilateral carotid aneurysms have been reported [18]. These may be associated with other complications such as spontaneous carotid-cavernous fistulas [18–20]. Also, arterial tortuosity, ectasia and dilatation or stenosis have been described in EDS Type IV [21].

The diagnosis of EDS Type IV is based on clinical examination, biochemical analysis of the collagens on cultured skin fibroblasts and molecular analysis of the *COL3A1* gene [10, 16]. No current aetiological treatment is available and management focuses on counselling and symptomatic control. In this respect, management dilemmas may arise when confronted with a vascular EDS patient, as the extreme tissue fragility makes interventional or surgical procedures to medicate, for example, aneurysms less obvious, as they are associated with a tremendous risk for morbidity (especially haemorrhages) and mortality [18, 22, 23].

2.2. Type IV Collagen-Related Small Vessel Disease. Type IV collagen comprises a family of triple helical isoforms consisting of at least six genetically distinct chains with tissue-specific distribution. The heterotrimer isoform consisting of one alpha-1 and two alpha-2 chains, encoded by the *COL4A1* gene (chrom. 13q34) and *COL4A2* gene (chrom. 13q34), respectively, is located a.o. in the basement membrane of arteries throughout the body [24]. Mutations in *COL4A1* have already been established in autosomal dominant porencephaly and infantile hemiparesis [25, 26]. A *Col4a1* knock-out mouse model predisposes newborn and adult mice to intracerebral haemorrhage, with predominance in the basal ganglia. In addition, these knock-out mice showed retinal tortuosity together with glomerular basement membrane defects [27].

Recently, *COL4A1* gene mutations have been recognized as the cause of small vessel disease in adults presenting with either ischaemic stroke or intracerebral haemorrhage [28–30]. The mean age of onset was 36 years (range: 14–49 yrs.). In a majority of the young adults, small vessel disease was the presenting symptom. Other associated features may include previous history of infantile hemiparesis, seizures, cognitive impairment and a familial history of migraine [27, 31]. As in mice, these patients often have retinal arteriolar tortuosity *in fundo* [27, 31]. Also renal and muscular involvement has been documented. The association of a hereditary angiopathy, nephropathy, aneurysm and muscle cramps has been defined as the HANAC syndrome [32, 33]. These patients were shown to have microvascular brain disease and single or multiple intracranial aneurysms (primarily on the carotid siphon), together with retinal arteriolar tortuosity, cystic renal disease with thickened renal basement membrane featuring hematuria and muscle cramps with elevated creatinine kinase, possibly due to transient ischaemia or microhaemorrhages [32, 33].

The diagnosis of collagen Type IV -associated stroke can be made on brain imaging, featuring frequent leukoaraiosis, subcortical microbleeds, lacunar infarction and dilated perivascular spaces in conjunction with systemic features or positive familial history [27]. Additional investigations should include a funduscopic examination and renal evaluation. A skin biopsy has been suggested a useful examination in HANAC syndrome, with significant ultrastructural anomalies including replication of the lamina densa, altered dermal arteriolar wall morphology and dissociation of vascular smooth muscle cells [33]. No data are available on ultrastructural changes of the skin in nonHANAC *COL4A1* patients. Molecular confirmation can be obtained by *COL4A1* sequencing. So far, only missense mutations have been reported involving highly conserved glycine residues in

Table 1: Villefranche classification of Ehlers-Danlos syndrome (1998).

Type	Inheritance	Gene(s)	Phenotype
Classic EDS (Types I/II)	AD	COL5A1, COL5A2	Hyperelastic, soft skin, atrophic scars, easy bruising, joint hyperlaxity
Hypermobility EDS (Type III)	AD	Unknown	Gross joint hyperlaxity, mild atrophic scarring and easy bruising
Vascular EDS (Type IV)	AD	COL3A1	Typical facial gestalt, skin fragility, extreme vascular fragility, rupture of uterus and colon
Kyphoscoliosis EDS (Type VI)	AR	PLOD	Marfanoid habitus, hypotonia, kyphoscoliosis, ocular complications + features of Type I EDS
Arthrochalasis EDS (Types VIIA and B)	AD	COl1A1, COL1A2	Severe joint hyperlaxity, congenital bilateral hip dyslocation, easy bruising, scoliosis, hypotonia
Dermatosparaxis EDS (Type VII C)	AR	Procollagen, N-peptidase	Severe skin fragility, sagging redundant skin, excessive bruising

AD: autosomal dominant; AR: autosomal recessive.

a triple helical domain of the gene. It is currently unclear whether a solid genotype-phenotype correlation is present, though it has been suggested that the mutation site may relate to the phenotype, as the HANAC-associated mutations are closely related [28].

Management of individuals with a *COL4A1* mutation is symptomatic. As cerebral haemorrhage often occurred following trauma or anticoagulant therapy, both in mice and humans, the prevention of trauma and avoidance of risk factors for bleeding may decrease the risk for (repetitive) haemorrhaging in these patients [27].

2.3. Osteogenesis Imperfecta. Osteogenesis imperfecta (OI) is a heterogeneous group of heritable connective tissue disorders characterised by fragile and brittle bones, blue sclerae, dental malformations, deafness and hyperextensible ligaments (Figure 2) [34, 35]. Different subtypes can be recognized with a broad range in severity, from mild to lethal (Sillence classification, Table 2) [36]. The inheritance modus of OI includes both autosomal dominant and recessive forms, caused by mutations in different genes (*COL1A1*, *COL1A2*, *LEPRE1*, *CRTAP*, *FKBP10*, *PPIB*) [34, 35, 37–39]. Most patients have a mutation in one of the genes encoding Type I collagen, *COL1A1* (chrom. 17q21.31-q22) and *COL1A2* (chrom. 7q22.1). Type I collagen, a heterotrimer similar to Type IV collagen, has a broad tissue distribution, including bone and vessel wall [34, 35].

COL1A1 and *COL1A2* mutations will induce a diminished or aberrant production of osseous and vascular Type I collagen which in return will lead to diminished resistance of bone against repetitive stress as well as to the reported aortic dissection or ulnar artery aneurysms [37, 40, 41]. In the fully developed brain, Type I collagen can be found predominantly in and around large arteries [42]. Details on neurovascular involvement in OI are however scarce. The complications which have been reported, although infrequent, include ruptured cerebral aneurysm associated with fenestrated vertebral arteries, moyamoya-like disease, carotid-cavernous fistula, cervical and vertebral artery dissection [43–45].

The diagnosis of OI is based on familial history and a history of fractures, clinical and radiological examination, biochemical analysis of the collagens and molecular sequencing of the OI-associated genes [34, 35].

The objective of treatment in OI is maximal mobility and functionality via physiotherapy and revalidation. Intravenous bisphosphonates have also been generally accepted as part of the treatment with positive effect on bone density and cortical thickness [34, 35, 46].

2.4. Autosomal Dominant Polycystic Kidney Disease. Autosomal dominant polycystic kidney disease (ADPKD, OMIM# 613095, 173900) is an adult onset multisystem disorder characterised by bilateral renal cysts, cystic changes in other organs such as liver or pancreas, and vascular abnormalities, including dilatation and dissection of the aorta and intracranial aneurysms [47]. Its prevalence at birth is between 1 : 400 and 1 : 1000. There is evidence that ADPKD is a collagen matrix disease, as histological evaluation of resected kidney specimens showed dilated and tortuous parenchymous blood vessels as well as excessive and oedematous collagenous tissue. The weak and excessive collagen is suggested to play a central role in the pathogenesis of different manifestations of ADPKD [48]. ADPKD is caused by mutations in the *PKD1* (chrom. 16p13.3–p13.12) or *PKD2* gene (chrom. 4q21-q23), encoding polycystin 1 and 2, respectively, [47]. Though clinical manifestations of both types overlap, *PKD1* is associated with more severe disease than *PKD2*, with larger kidneys and earlier onset of renal failure [49]. Polycystin 1 is thought to be a membrane protein, involved in cell-to-cell or cell-matrix interactions, whereas polycystin 2 is thought to be a channel protein. The mechanisms contributing to cystogenesis are complex and are beyond the purpose of this paper [50].

The most frequent neurovascular complication of ADPKD is intracranial aneurysms, occurring in approximately 10% of patients, with a higher prevalence (22%) in those individuals with a positive familial history of intracranial haemorrhage [51, 52]. Most of these aneurysms are asymptomatic. However, the mean age of rupture is considerably lower, being 39 years in ADPKD patients versus 51 years in the general population. At the time of rupture, most patients still have normal renal function, though hypertension is often noted [53].

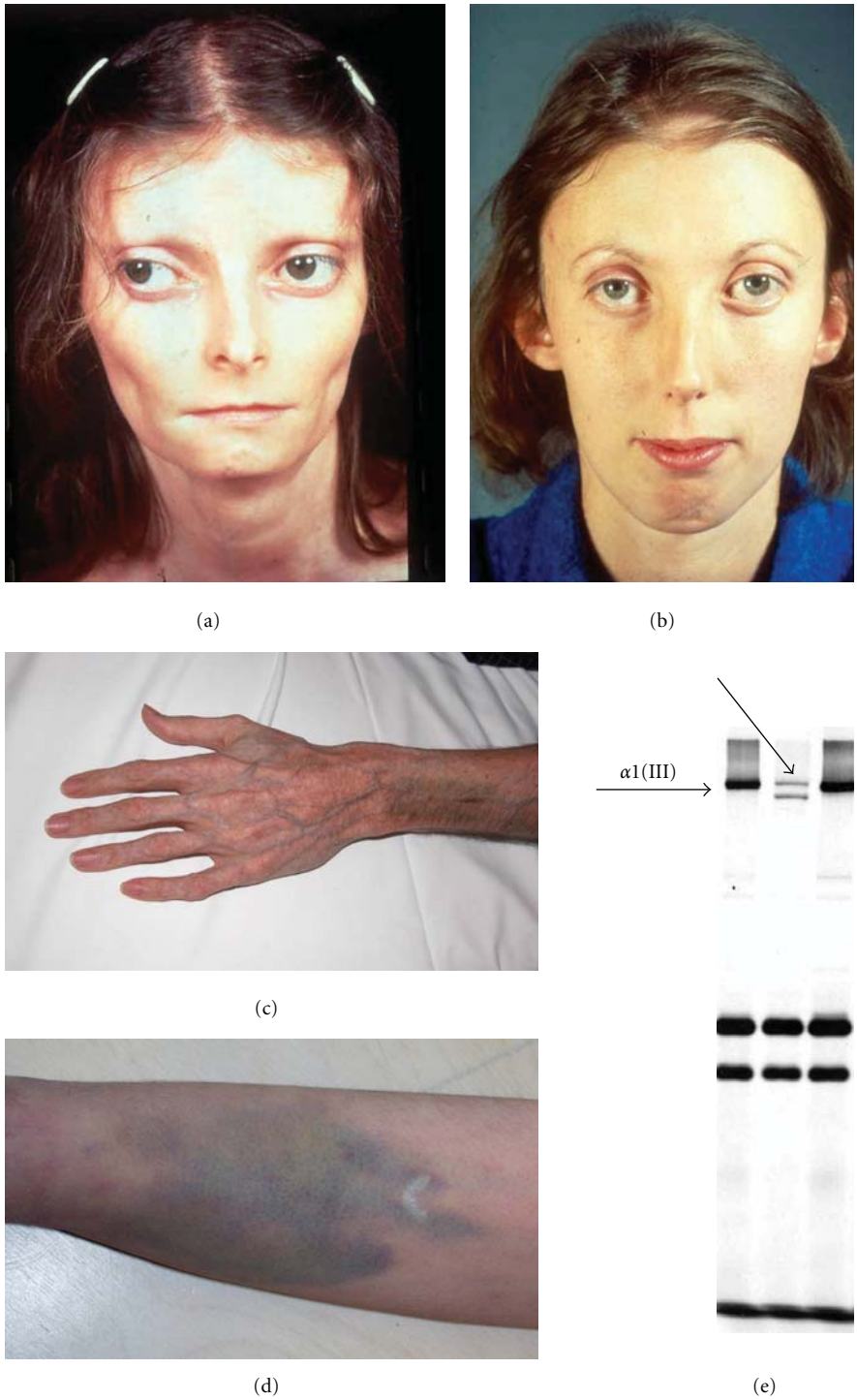
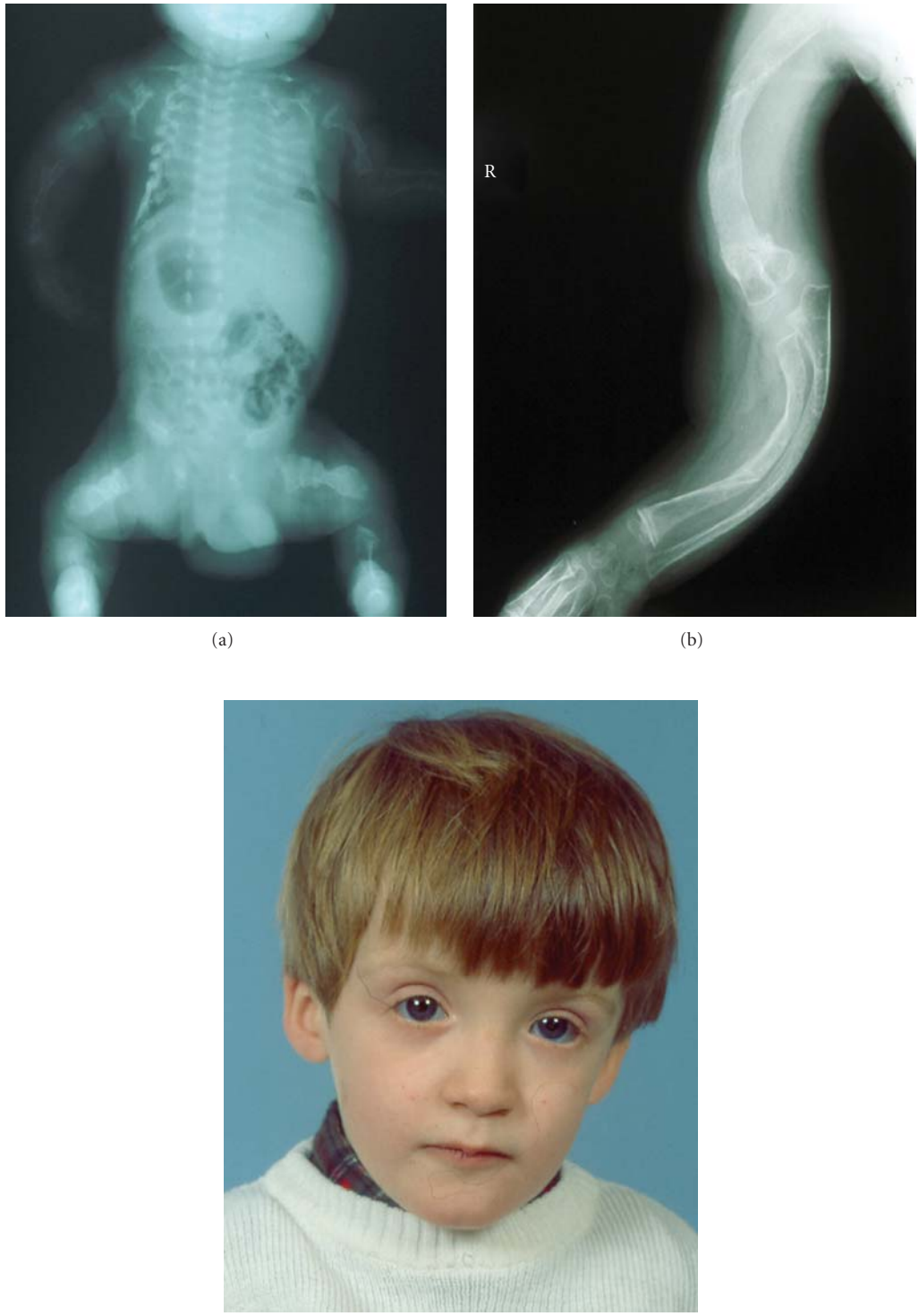


Figure 1: Clinical and biochemical characteristics of the vascular Ehlers-Danlos syndrome. Typical facial features with diminished subcutaneous fat, thin nose and lips (a, b), acrogeria (c) and easy bruising (d). Biochemical analysis of the collagens reveals a diminished amoun of collagen Type III (e).

For the diagnosis of ADPKD, renal ultrasonography is commonly used with highly predictive ultrasound diagnostic criteria being available. Molecular confirmation can be done using DNA linkage or gene-based direct sequencing. Screening should be performed in affected patients for extrarenal manifestations of the disease. Particularly in those patients with a positive family history of intracranial aneurysms, an MRI angiography should be included [54].

Management is directed toward reducing morbidity and mortality from the renal and extrarenal complications of



(a) (b)

(c)

Figure 2: Clinical features of osteogenesis imperfecta. Osteopenia and multiple fractures (a), bone deformities (b) and blue sclerae (c).

the disease and includes antihypertensive medication, cyst decompression, control of hyperlipidemia and dietary protein restriction [51, 55, 56]. Symptomatic cerebral aneurysms are usually treated by surgical clipping. Asymptomatic aneurysms are closely followed at yearly interval; controversy exists whether surgery is required at a diameter of more than 5 mm or 10 mm [57]. The main-stay therapy for ruptured or symptomatic intracranial aneurysm is surgical clipping. In some cases, endovascular treatment (coiling) may be indicated [51].

Table 2: Silence classification of osteogenesis imperfecta.

Type	Inheritance	Gene(s)	Phenotype
OI Type I	AD	COL1A1	Fractures, osteopenia, blue sclerae, *severe hearing loss*, dentinogenesis imperfecta in some
OI Type II	AD	COl1A1, COL1A2	*Multiple fractures, severe osteopenia and bone deformation*, short stature, blue sclerae
OI Type III	AD/AR	COl1A1, COL1A2	*Triangular face, severe scoliosis*, fractures, osteopenia and bone deformities, short stature, bleu sclerae, hearing loss, dentinogenesis imperfecta in some
OI Type IV	AD	COl1A1, COL1A2	Fractures, osteopenia and bone deformities, hearing impairment, dentinogenesis imperfecta, short stature in some
OI Type V	AD	Unknown	Fractures, osteopenia and bone deformities, hearing impairment, dentinogenesis imperfecta, short stature in some, often *luxation of head of radial bone*
OI Type VI	?	FKBP10	Multiple fractures, osteopenia and bone deformities, hearing impairment, short stature in some, *accumulation of osteoid in bone*
OI Type VII	AR	CRTAP	Multiple fractures, osteopenia and bone deformation, blue sclerae, *rhizomelia, coxa vara*
OI Type VIII	AR	LEPRE1	Multiple fractures, severe osteopenia and bone deformation, short stature, blue sclerae in some

AD: autosomal dominant; AR: autosomal recessive. Characteristics which may be of value in discriminating the subtypes are marked in italics.

3. Disorders Affecting Elastic Fibres

The elastic fibre system forms a network responsible for the resilience and elasticity of various tissues. It consists of interconnecting fibres of varying diameter, containing two distinct components: elastin, a well-characterised connective tissue protein and elastin-associated microfibrils, the components of which include fibrillin, a microfibril-associated glycoprotein. The biology of elastic fibres is complex because of its multiple associated molecules, tightly regulated developmental pattern of deposition, multi-step assembly, unique elastomeric properties and influence on cell phenotype. Several hallmark connective tissue disorders, such as Marfan syndrome or pseudoxanthoma elasticum, are caused by abnormalities of the elastic fibres, and can be related to stroke.

3.1. Pseudoxanthoma Elasticum and the PXE-Like Syndrome. Pseudoxanthoma elasticum (PXE, OMIM# 264800) is an autosomal recessive disorder characterised by skin, ocular and cardiovascular symptoms resulting from ectopic mineralization and fragmentation of elastic fibres [58, 59]. It is caused by mutations in the *ABCC6* gene (chrom. 16p13.1), encoding an ATP-binding transporter protein, the substrate and (patho)physiological role of which remain currently unknown [60]. Recent insights have revealed deficient vitamin K-dependent calcification inhibitors—due to low serum vitamin K in PXE patients—to induce the ectopic mineralization of elastic fibres [61]. The skin phenotype exists of yellowish papules of degraded elastic fibres in the flexural areas of the body, coalescing into larger plaques, sometimes associated with the presence of additional skin folds (Figure 3) [58, 59]. The PXE retinopathy, based on elastic fibre abnormalities in the Bruch's membrane, involves angioid streaks and subretinal neovascularisation, resulting in retinal haemorrhages and vision loss (Figure 3) [58, 59]. Cardiovascular complications exist of coronary and peripheral artery disease (hypertension, myocardial infarction, claudication), gastrointestinal haemorrhage as well as predominantly ischaemic stroke. The latter was found in 15% of PXE patients, with a mean age of onset of 49 years [58, 59]. Intracerebral haemorrhage has been described in rare cases of PXE [62].

Heterozygous carriers of 1 *ABCC6* mutation do not tend to develop symptomatic skin or ocular manifestations of PXE, but do have an increased cardiovascular risk [59, 63–65]. In addition, it has been shown that a significantly higher proportion of heterozygous *ABCC6* carriers can be found in an ischaemic stroke population compared to normal controls, suggesting it to be a molecular risk factor for ischaemic stroke (Vanakker et al., unpublished data).

In 2007, we described a novel autosomal recessive PXE-like syndrome (OMIM# 610842), characterised by a severe cutaneous phenotype with thick and redundant skin folds beyond the flexural areas, a mild retinopathy and a deficiency of the vitamin K-dependent coagulation factors (Figure 4) [66]. This disease was shown to be caused by mutations in the GGCX gene, encoding a gamma-carboxylase which performs an essential posttranslational modification step of several vitamin K-dependent proteins, such as clotting factors and mineralization inhibitors. In two of the originally described patients, cerebral aneurysms were present, one of which had recurrent cerebral aneurysms [66]. It is however at present unclear whether these are actually part of the phenotype or a coincidental finding.

The diagnosis of PXE should be thought of in the presence of skin or ocular symptoms and can be confirmed by skin biopsy and molecular sequencing of the *ABCC6* gene [59]. Depending on the phenotype, including cutis laxa and a clotting deficiency, *GGCX* sequencing may be appropriate

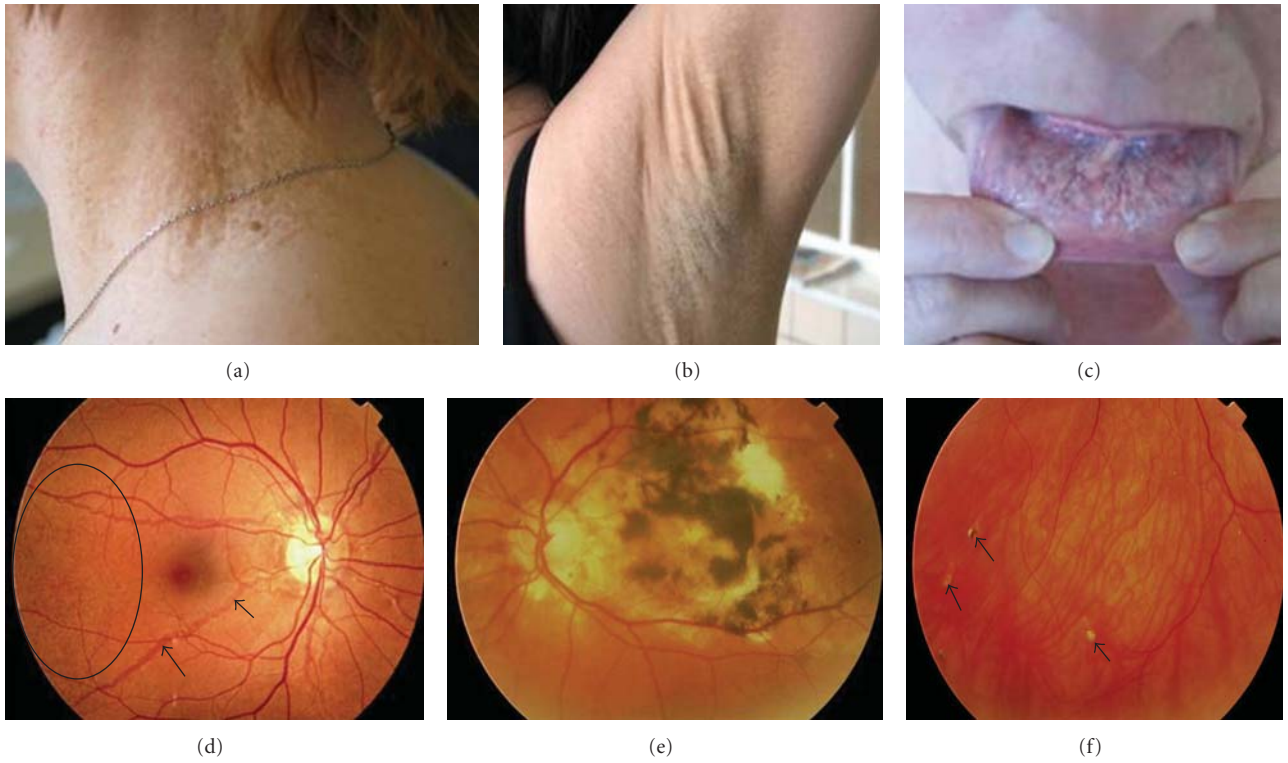


Figure 3: Cutaneous and ophthalmological symptoms of PXE. Plaques of papules in the neck region (a), increased skin laxity (b) and mucosal involvement with yeloowish pattern on the inner lip (c). The retinopathy consists of peau d'orange (d, oval), angioid streaks (d, arrowed), retinal hemorrhaging (e). In some cases calcifications of Bruch's membrane can be seen as comets or comet tails (f, arrowed).

[66]. In view of the number of heterozygotes in a general ischaemic stroke population, *ABCC6* analysis is suggested as a diagnostic option in young individuals suffering ischaemic stroke, with no significant conventional risk factors.

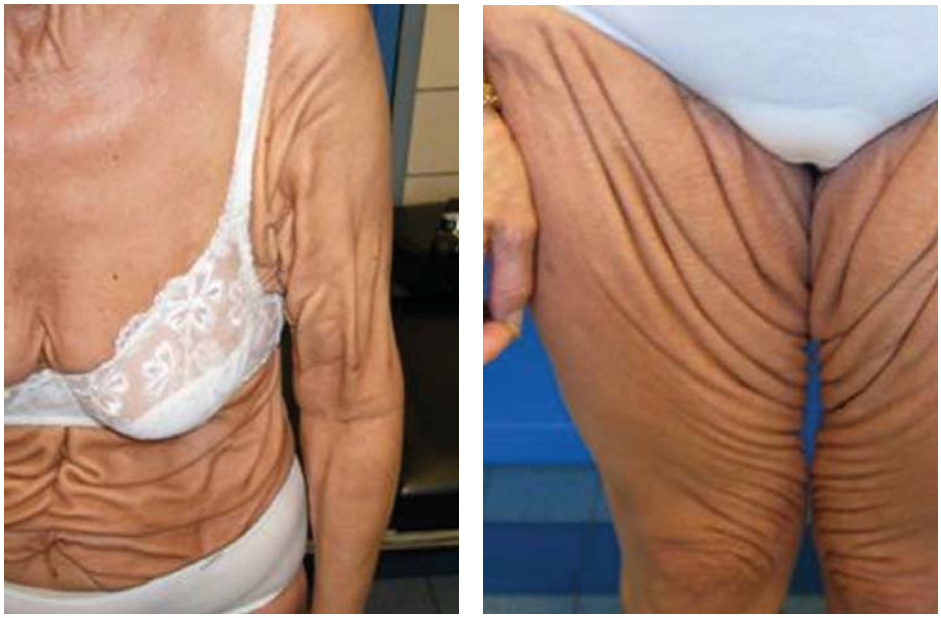
In the absence of an aetiological therapy, management of PXE is focussed on the prevention and treatment of complications [59]. Anti-VEGF antibodies, such as bevacuzimab or ranibizumab, are used to treat ocular complications such as neovascularisation, with significant success [67]. Other aspects of management include cardiovascular prevention measures and avoidance of anticoagulants, nonsteroidal antiinflammatory drugs and head trauma [59]. Particularly the relative contra-indication for anticoagulant therapy in PXE patients, because of the ocular and gastrointestinal bleeding diathesis, can create a therapeutic dilemma for which no ideal solution exists. An individual assessment should be made in each patient of the benefits and risks of starting such therapy, taking into account the specifics of the patients' phenotype.

3.2. Marfan Syndrome. The Marfan syndrome (MFS, OMIM# 154700) is an autosomal dominant multisystemic disorder characterised by skeletal (marfanoid habitus with tall stature, arachnodactyly, pectus deformity and joint hypermobility), ophthalmological (ectopia lentis, myopia) and cardiovascular symptoms (aortic root dilatation) (Figure 5) [68]. It is caused by mutations in the FBN1 gene (chrom. 15q21.1), encoding the ECM protein fibrillin 1, expressed in the heart and elastic arteries [69]. In about 25% of probands, this mutation occurs de novo [69].

The most frequent neurovascular complication in MFS is an extension of an aortic dissection into the common carotid artery [70]. Spontaneous dissections limited to the common or internal carotid artery have also been reported [71]. In a large retrospective study, Wityk et al. described a neurovascular event in approximately 3.5 percent of Marfan patients, most of which were TIAs (65%), cerebral infarctions (most often cardioembolic, 10%), spinal cord infarctions (10%), subdural haematomas (10%) or spinal subarachnoid haemorrhage (5%) [72]. A conclusive relationship between MFS and intracranial aneurysms has not been established [73, 74].

The clinical diagnosis of Marfan syndrome can be made based on the revised Ghent nosology criteria and confirmed molecularly by analysis of the FBN1 gene [75]. Treatment of the MFS involves the use of beta-blockade and angiotensin-converting enzyme inhibition therapy to achieve reduction of hemodynamic stress and delay the progression of arterial dilatation. When critical dilatation of the aorta occurs, with significant risk for aortic dissection or rupture, aortic root replacement surgery is performed [76, 77].

3.3. Loeys-Dietz Syndrome. Loeys-Dietz syndrome (LDS, OMIM# 608967, 609192, 610168, 610380) is an autosomal dominant disease caused by mutations in the transforming growth factor beta receptor 1 or 2 (TGFBR1 and TGFBR2,



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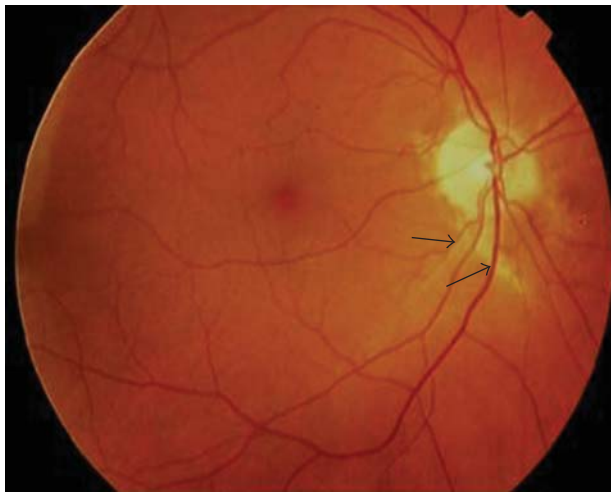
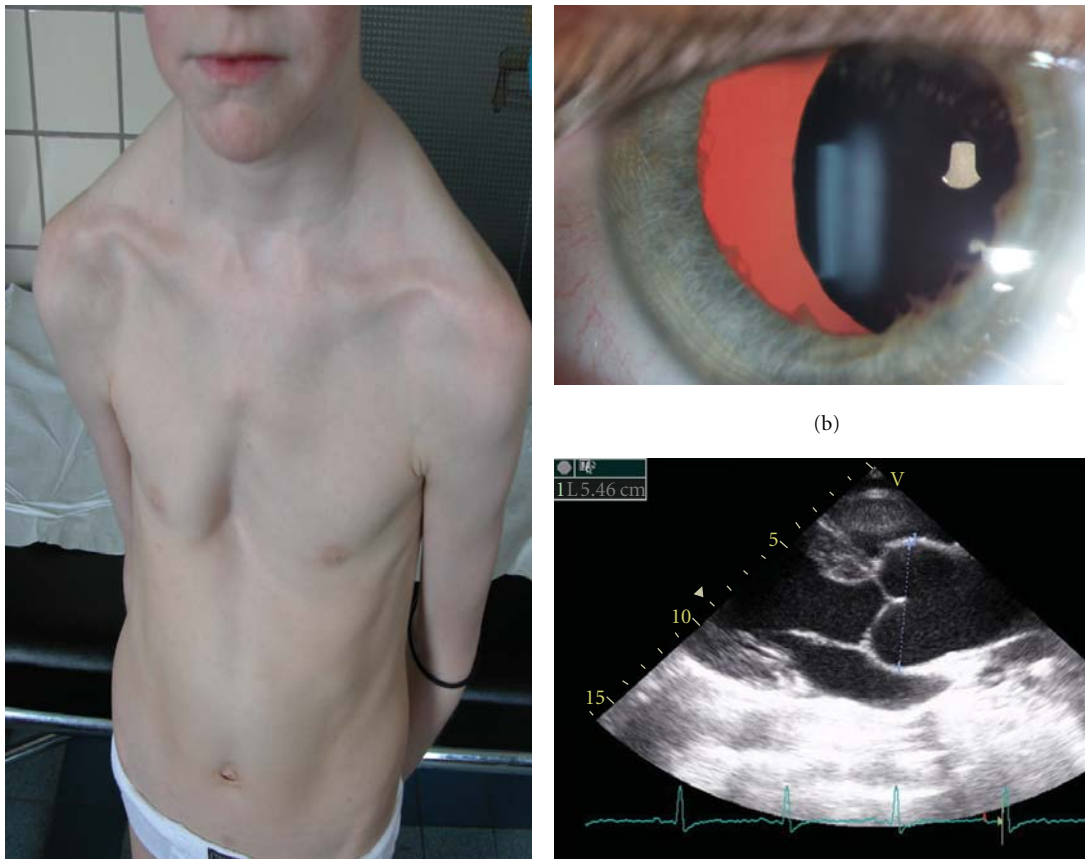


(b)

Figure 4: Clinical symptoms of the PXE-like syndrome. Severe cutis laxa-like skin folds beyond the flexural areas (a). A mild retinopathy with minimal angioid streaks (b, arrowed).

chrom. 9q22 and 3p22, resp.), altering the transmission of subcellular TGF-β signal, mediated by increased activation of Smad2 [78]. Common clinical features include aortic and arterial aneurysms or dissections and skeletal manifestations resembling Marfan syndrome (pectus deformity, arachnodactyly, joint laxity). Seventy-five percent of patients have LDS Type I with craniofacial features including hypertelorism and cleft palate or bifid uvula (Figure 6) [78, 79]. LDS Type II resembles vascular EDS, with cutaneous manifestations such as easy bruising and atrophic scars. In contrast with Marfan syndrome, generalised arterial tortuosity and aneurysms of other arteries besides the aorta have been noted. Tortuosity was most frequently seen in head and neck vessels [78, 79]. In LDS Type I and II, aneurysmal changes of the vertebral and head arteries were reported [80, 81]. In LDS Type I, 11% of patients had aneurysms of arteries in the head and neck, compared to 7% in LDS Type II [79]. Importantly, these vascular abnormalities tend to manifest at a younger age, with a more aggressive evolution which can be observed by dissection or rupture at a vessel diameter which is not predictive of such an event. This aggressive nature is also reflected in a mean age of death of LDS patients of 37 years, with cerebral bleeding as the third leading cause of demise after thoracic and abdominal aortic dissection [78, 79].

The diagnosis of LDS is based on the clinical characteristics and can be confirmed by mutation analysis of the TGFBR1 and TGFBR2 gene [78, 79]. As the natural history



(a) (b) (c)

Figure 5: The Marfan syndrome. Patients present with skeletal findings such as pectus excavatum (a), lens luxation (b) and aortic root dilatation (c).

of LDS differs from that of other CTD, management is individualised and involves measures as described for the Marfan syndrome but with an even more rigorous followup and option of surgical repair of aortic dilatation at a smaller diameter and at an earlier age compared to Marfan patients [78, 79, 82].

3.4. Bicommisural Aortic Valve with Ascending Aortic Aneurysm. Bicommisural (bicuspid) aortic valve with ascending aortic aneurysm (BAV, OMIM# 109730) is considered a separate entity characterised by an aortic valve with 2 rather than 3 leaflets, which can be associated with life-threatening aneurysm or dissection of the aorta (Figure 7) [83, 84]. It is inherited in an autosomal dominant fashion with reduced penetrance, especially in females [85]. BAV is thought to be genetically heterogeneous, with at present only one gene identified, the *NOTCH1* gene, on chrom. 9q34.3 [86]. NOTCH1 is a signalling and transcription regulator which causes a spectrum of developmental nonsyndromic aortic valve anomalies and severe valve calcification [87]. BAV is a common congenital heart defect, affecting 1 to 2% of the population. Though it was a long-standing belief that the aortic changes were due to postvalvular hemodynamic changes, it has now become clear that they are primarily related to the underlying arteriopathy, thus making BAV a generalised CTD [83, 84].

The BAV arteriopathy does not seem to be confined to the thoracic aorta, as spontaneous dissections of the cervical and intracranial arteries have been reported [88–90]. Recently, Schievink et al. reported an increased frequency of aneurysms of the intracranial carotid and cerebral arteries among patients with BAV, levelling up to 10% compared to 1% in controls [91].

The diagnosis of BAV is made via heart auscultation and confirmed by cross-sectional and doppler echocardiography [83, 84]. Molecular analysis of the *NOTCH1* gene may be helpful in familial screening, though BAV is undoubtedly genetic heterogeneous [85]. Management includes regular clinical followup, endocarditis prophylaxis and surgical intervention if necessary. No formal screening protocol has been established for BAV patients to evaluate the presence of intracranial aneurysms. Further studies are needed to evaluate the usefulness of sequential MRI-angiography in this patient population [92]. First degree relatives of a patient should be offered screening for BAV.

3.5. Arterial Tortuosity Syndrome. Arterial tortuosity syndrome (ATS, OMIM# 208050) is an autosomal recessive

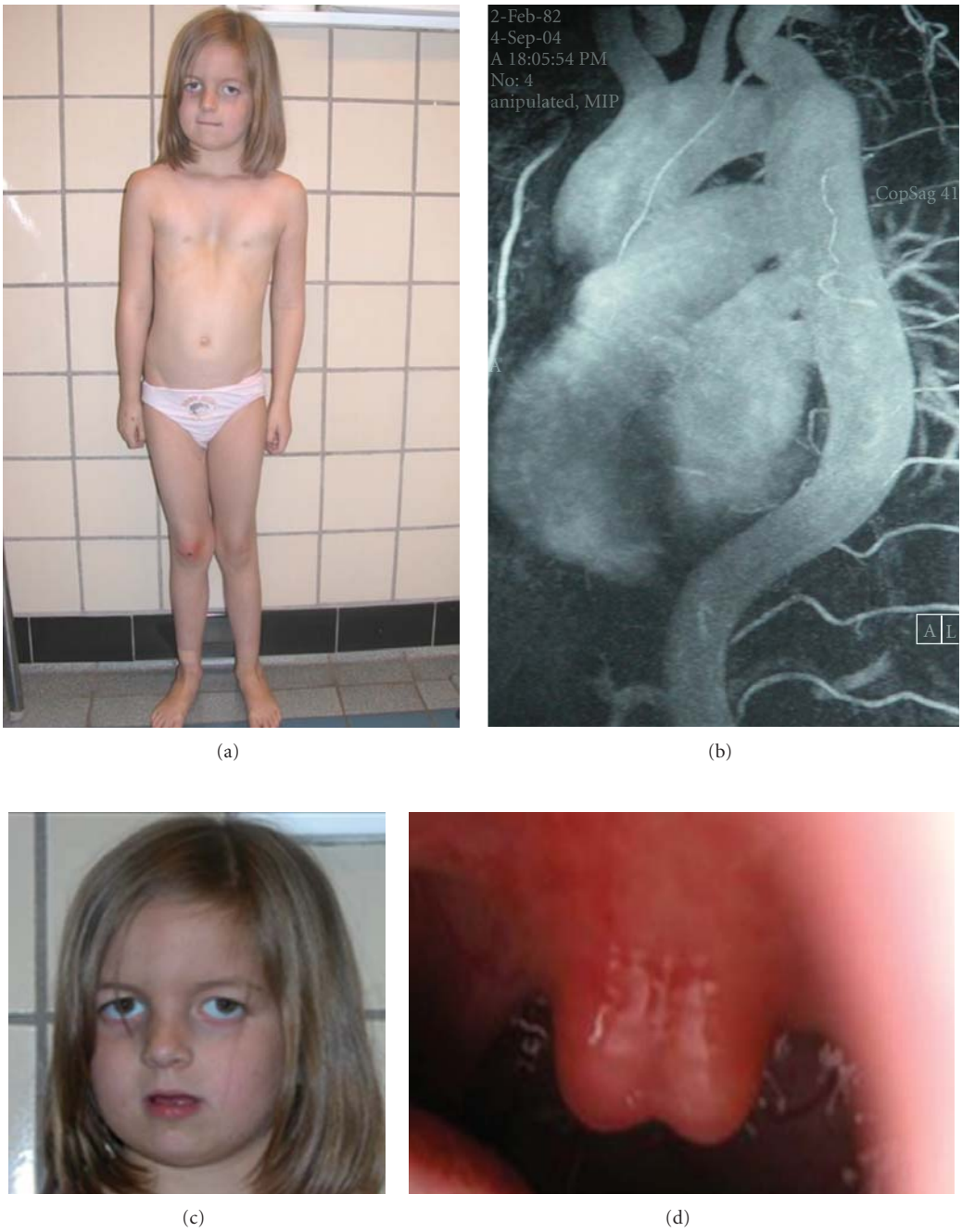


Figure 6: Features of the Loeys-Dietz syndrome Type I. Patients present a marfanoid habitus and hypertelorism (a, c), aortic dilatation (c) and a bifid uvula (d).

connective tissue disorder, characterised by arachnodactyly, joint and skin laxity and widespread arterial involvement with elongation, tortuosity and aneurysm of the medium-sized and large arteries [93]. Facial characteristics include a long slender face with sagging cheeks, beaked nose, thin skin, large ears and high-arched palate (Figure 8) [93, 94]. It is caused by mutations in the SLC2A10 gene, encoding the facilitative glucose transporter GLUT10 [95]. Deficiency of GLUT10 is associated with upregulation of the TGF-β pathway in the arterial wall, similar to LDS, resulting in disruption of elastic fibres and fragmentation of the internal elastic membrane [95, 96].

Ischaemic stroke has been described in four cases of ATS, all of which were in young adults. The mechanism by which ATS leads to stroke has not been established but may involve alterations of the endothelial surface leading to arterial thrombosis, arterial stenosis evolving to occlusion and infarction or dissection of an affected vessel [94, 97].

The diagnosis of ATS is made based on clinical examination and bloodvessel imaging by means of ultrasound and

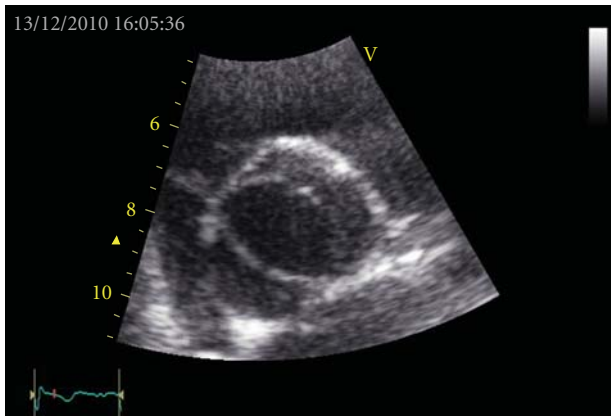


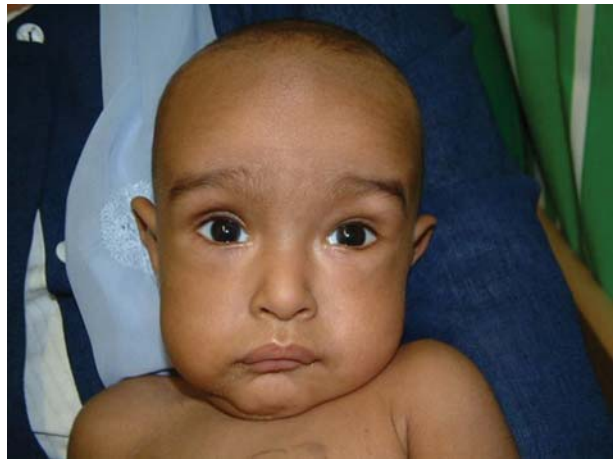
Figure 7: Echocardiographic image of a bicuspid aortic valve.

MRI-angiography to demonstrate arterial tortuosity. The diagnosis can then by confirmed by analysis of the SLC2A10 gene. Currently, no aetiological treatment exists for ATS and management is focussed on prevention, detection and treatment of the complications [93, 94].

3.6. Supravalvular Aortic Stenosis. Supravalvular aortic stenosis (SVAS, OMIM# 185500) may occur as an autosomal dominant isolated disease or as part of a complex developmental disorder, the Williams-Beuren syndrome (WBS) [98, 99]. Clinical and structural characteristics of SVAS are however identical in both groups. Isolated SVAS is caused by mutations in the elastin gene (*ELN*, chrom. 7q11.2), leading to disorganization of the lamellar architecture of the tunica media, irregular elastic fibres and smooth muscle cell hypertrophy [100]. Patients may present with dyspnoea, angina and syncope due to a variable degree of left ventricular outflow tract obstruction [98]. In addition to the aorta, other major arteries, including carotid and cerebral vessels, may also be affected by narrowing in patients with SVAS, leading to susceptibility to stroke from childhood on [101].

As part of the WBS, an autosomal dominant syndrome featuring besides the cardiovascular and connective tissue problems also neurobehavioural, facial, metabolic and growth abnormalities, it is associated with a 1.5–2 MB microdeletion on chrom. 7q11.2 [99]. SVAS can be observed in 70% of patients. Arterial narrowing may be isolated or can occur simultaneously at different locations, including the intracranial vessels. WBS patients can suffer ischaemic stroke in the presence or absence of stenosis of the cerebral vasculature [102]. Prognosis may be compromised if intracerebral haemorrhage occurs simultaneously [103]. Besides SVAS, also hypertension due to renal artery involvement may be a contributory factor to stroke in WBS.

Diagnosis of SVAS is made on echocardiography. Treatment consists of surgical patch grafting of the stenotic region of the aorta. Less invasive procedures, such as balloon angioplasty or stenting, have been successful but carry a higher risk for rupture, aneurysm or restenosis [99].



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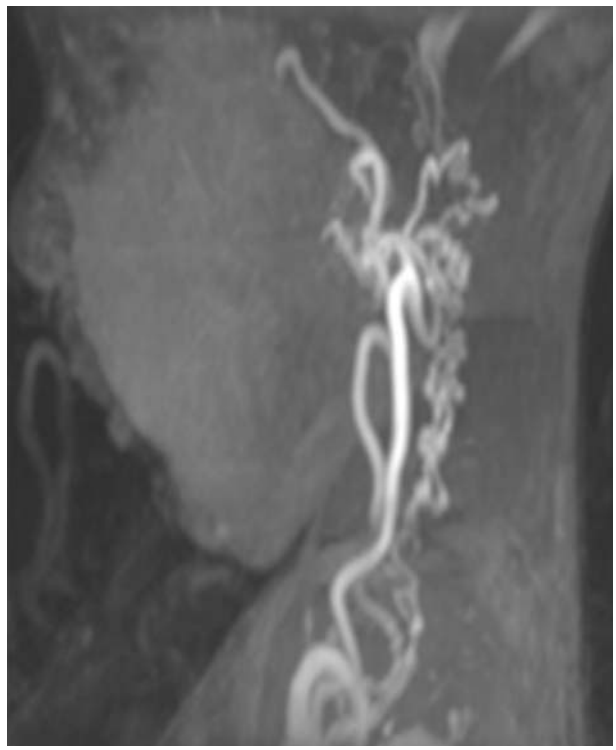

(b)

Figure 8: Patient characteristics of the Arterial Tortuosity Syndrome. Longslender face with sagging cheeks and large ears (a). Marked arterial tortuosity (b).

4. Disorders with Generalised Connective Tissue Involvement

4.1. Spontaneous Cervical Artery Dissection. Spontaneous cervical artery dissection (SCAD, OMIM# 147820) is an important cause of ischaemic stroke in young patients [104]. Though some CTD, such as osteogenesis imperfecta or the classical and vascular form of EDS, predispose for SCAD, most patients do not feature other symptoms of CTD [105–107]. Still, ultrastructural analysis revealed mild but

reproducible disruption of connective tissue morphology, with involvement of either collagen or elastic fibres or both [108]. Its pathogenesis being unclear, several candidate genes and loci have been proposed, many of which are involved in the biosynthesis of the ECM. However, several genes involved in important CTD, such as *COL3A1*, *COL5A1*, *COL5A2* and *ABCC6* have been excluded in sporadic SCAD patients [109–112]. Large studies, such as the European CADISP (Cervical Artery Dissection and Ischaemic Stroke Patients) study, are currently ongoing to unravel the genetic background of SCAD [113].

In a minority of patients, a positive familial history is present, suggesting an autosomal dominant inheritance pattern [114, 115]. As most patients do not have such a family history, it is proposed that the penetrance of the genetic predisposition of SCAD is low, meaning that the connective tissue aberration is not a sufficient cause for SCAD. Other constitutional and environmental factors which have been identified in SCAD patients and may influence the phenotype include infection and mild hyperhomocysteinemia [116].

The diagnosis of SCAD being a clinical one, the probable heterogeneous genetic aetiology of the disorder does not allow specific diagnostic molecular analysis in patients at this time if classic CTD such as EDS, OI or Marfan syndrome have been clinically excluded [117]. It must be noted though that associated CTD symptoms can be very mild, emphasizing the importance of a thorough clinical history and examination.

4.2. Hereditary Haemorrhagic Telangiectasia. Hereditary haemorrhagic telangiectasia (HHT, Rendu-Osler-Weber syndrome, OMIM# 187300) is an autosomal dominant vascular dysplasia described as the triad of mucocutaneous telangiectases, recurrent epistaxis or gastrointestinal haemorrhage and a family history of the disorder (Figure 9) [118]. Visceral involvement, the fourth clinical criterion, includes that of the lung, liver and brain [118]. Most patients exhibit symptoms by the age of 40. The pathogenesis of the arteriovenous malformations in HHT includes dilatation of postcapillary venules which enlarge and connect through capillaries with dilated arterioles. With increase in size, the capillary segments disappear and an AV communication is formed [118].

HHT is caused by mutations in the *ENG* and *ALK1* gene (chrom. 9q34.1 and 12q11-q14), encoding endoglin and Activin A receptor Type II-like 1, respectively, [119, 120]. Other genetic loci for HHT have been reported, indicating genetic heterogeneity [121]. Endoglin is a TGF-β binding protein and causes HHT1, which is associated with an earlier onset of epistaxis and telangiectasias. *ALK1*-associated HHT (HHT2), caused by disruption of the Type I cell-surface receptor for the TGF-β superfamily of ligands, features later onset and more hepatic involvement compared to HHT1 [120, 121].

Cerebral and spinal complications of HHT include telangiectases, arteriovenous malformations and carotid-cavernous fistulas [122]. Moreover, HHT patients are prone to pulmonary arteriovenous fistulae, responsible for paradoxical embolism resulting in stroke or transient ischaemic attack [123]. Cerebral haemorrhage in HHT patients usually has a devastating effect [122].

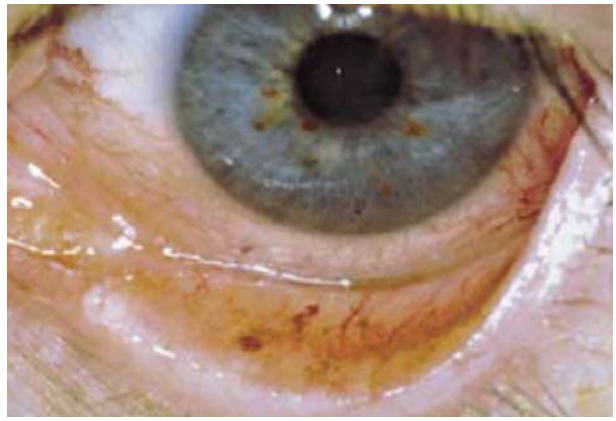

Figure 9: Telangiectasias on the inner side of the lower eyelid in a HHT patient.

The diagnosis of HHT is based on the presence of the above mentioned criteria and can be made if at least 3 criteria are present [118]. Molecular analysis of the *ENG* and *ALK1* genes can confirm the diagnosis and allows familial screening and counselling. In this respect, it is important to recognize that children of a patient cannot be reassured of not having HHT without negative molecular analysis as symptoms most often only occur in the second or third decade of life. Molecular testing in such young individuals, who are not able to give consent, remains however controversial. A similar controversy exists about the screening of asymptomatic individuals for cerebral arteriovenous malformations, though it is recommended in some countries due to the devastating effects of a cerebral bleeding.

Management of HHT can consist of therapy with bevacizumab, an antiVEGF antibody of which several successful reports were published [124]. Other treatments, including estrogen or antifibrinolytic therapy, have inconsistent results. Importantly, all patients should be screened for pulmonary arteriovenous fistulae. No optimal screening protocol has been established but should include chest radiography and contrast echocardiogram. Depending on the results, this can be complemented with CT scan of the chest or pulmonary angiography [125, 126].

4.3. Fibromuscular Dysplasia. Fibromuscular dysplasia (FMD, OMIM# 135580) is an autosomal dominant noninflammatory, nonatherosclerotic segmental disease of the arteries, occurring in young to middle-aged individuals [127]. While renal arteries are most commonly affected, resulting in hypertension, other large vessels including carotid and vertebral arteries may be involved [128, 129]. The origin of FMD remains currently largely unknown, with speculation of a collagen disorder, congenital aetiology and inflammatory origin. Thus far, no unequivocally associated genes have been discovered [127].

Table 3: Summary of the most important connective tissue diseases related to stroke in young adults.

Disease	Inherit.	Diagnosis	Phenotype
Vascular Ehlers-Danlos syndrome	AD	Biochemical analysis (skin biopsy) COL3A1 analysis (fibroblasts)	Facial gestalt (thin nose and lips, sunken cheeks), skin fragility, extreme vascular fragility, rupture of uterus and colon *Intracerebral aneurysm*, *carotid/vertebral dissection*
Type 4 collagen-related small vessel disease	AD	COL4A1 analysis (blood sample)	Infantile hemiparesis, seizures, migraine, retinal artery tortuosity, renal and muscular involvement *Small vessel ischaemic stroke or haemorrhage*
HANAC syndrome	AD	Skin biopsy COL4A1 analysis (blood sample)	Hereditary angiopathy with retinal artery tortuosity, cystic renal disease, *cerebral aneurysm*, muscle cramps
Osteogenesis imperfecta	AD AR	Radiological examination Biochemical analysis (skin biopsy) Molecular analysis of OI genes (fibroblasts and blood sample)	Fractures, osteopenia, bone deformities, hearing loss, blue sclerae, dentinogenesis imperfecta *Intracerebral aneurysm, moyamoya-like disease, carotid/vertebral dissection*
AD polycystic kidneys	AD	Renal ultrasonography PKD1/2 linkage analysis (blood) PKD1/2 molecular analysis (blood)	Bilateral renal cysts, liver and pancreas cysts, aortic dilatation/dissection *Intracranial aneurysm*
Pseudoxanthoma elasticum	AR	Skin biopsy ABCC6 analysis (blood sample)	Yellowish skin papules in flexural areas, retinopathy, coronary and peripheral artery disease *Ischaemic stroke in patients and heterozygous carriers*
PXE-like syndrome	AR	Coagulation testing Skin biopsy GGCX analysis (blood sample)	Generalized cutis laxa, mild retinopathy, coagulation disorder *Cerebral aneurysm?*
Marfan syndrome	AD	Revised Ghent Nosology Fibrillin 1 analysis (blood sample)	Tall stature, arachnodactyly, pectus deformity, ectopia lentis, aortic root dilatation *Carotid artery dissection, cerebral and spinal cord infarction*
Loeys-Dietz syndrome Type I	AD	TGFBR1 and 2 analysis (blood sample)	Marfanoid habitus, hypertelorism, cleft palate, bifid uvula, generalized arterial tortuosity and aneurysms *intracranial aneurysm, carotid and vertebral aneurysm*
Loeys-Dietz syndrome Type II	AD	TGFBR1 and 2 analysis (blood sample)	Vascular EDS-like phenotype, generalized arterial tortuosity and aneurysms *intracranial aneurysm, carotid and vertebral aneurysm*
Bicuspid aortic valve	AD	Echocardiography NOTCH1 gene in familial cases (blood sample)	Bicuspid aortic valve on ultrasound *Dissection of carotid and cerebral arteries, intracranial aneurysm*
Arterial tortuosity syndrome	AR	*SLC2A10* analysis (blood sample)	Facial dysmorphism, arachnodactyly, joint and skin laxity, arterial elongation, tortuosity and aneurysms *Ischaemic stroke?*
Supravalvular aortic stenosis	AD	ELN analysis (blood sample)	Left ventricular outflow obstruction *Ischaemic stroke*
Williams-Beuren syndrome	AD	FISH or microarray	SVAS, facial dysmorphism, short stature *Ischaemic stroke, intracerebral haemorrhage*
Spontaneous cervical artery dissection	AD	Clinical examination	Exclude vascular EDS, Marfan syndrome and osteogenesis imperfecta
Hereditary haemorrhagic telangiectasia	AD	Clinical evaluation ENG and ALK1 analysis (blood sample)	Mucocutaneous telangiectases, epistaxis, gastrointestinal haemorrhage *Cerebral/spinal telangiectases, carotid-carvernous fistulas, ischaemic stroke or TIA, cerebral haemorrhage*
Fibromuscular dysplasia	AD	Doppler ultrasound and angiography	String of beads in affected vascular beds *TIA and ischaemic stroke, cervicocranial dissection, intracerebral aneurysm*

Cerebrovascular phenotypes are indicated in italics. AD: autosomal dominant; AR: autosomal recessive.

Neurological implications of FMD include TIA and stroke, resulting from occlusion, arterial dissection of cervicocranial vessels or subarachnoid haemorrhage due to ruptured aneurysm [129–135]. The latter may be more likely when there is also renal involvement, due to the hypertension. Particularly the association of haemorrhage due to aneurysm rupture and ischaemic stroke due to stenosis in a given patient is characteristic of cerebral FMD.

Diagnosis of FMD is made based on clinical history, doppler ultrasound and angiography, via which the typical

image of "string of beads" can be seen [127]. Treatment may imply either surgical correction with resection of the diseased vessel portion or stenting by a vascular radiologist. The success of these treatments depends largely on the early detection of the disease [127, 136].

5. Candidate Extracellular Matrix Genes

Besides the distinct connective tissue disorders described above, some ECM proteins playing an essential role in connective tissue homeostasis have been suggested to be implicated in haemorrhagic or ischaemic stroke. As the ECM contains over 2500 proteins, the summary below is not limitative and several other ECM constituents are likely to be involved in stroke, either leading to a well-defined phenotype or as a more general risk factor.

5.1. Stromelysin. Stromelysin-1 or MMP3 is a member of the matrix metalloproteinase (MMP) family, regulating the accumulation of ECM. Recently, an association was found in Italian ischaemic stroke patients who were homozygous for a common promotor variant (genotype 5A/5A), in which both alleles have a run of 5 adenosines [137]. This finding was inconsistent with in vitro studies which showed a promotor variant with a run of 6 adenosines to be associated with a higher IMT and warrants further study [138].

5.2. Versican. Versican is a proteoglycan playing an important role in ECM assembly. The gene encoding versican, CSPG2 (chrom. 5q) is located in a genomic region reported to be associated with intracranial aneurysms. Ruigrok et al. suggested that SNPs around and in the versican gene play a role in the susceptibility of intracranial aneurysms, which was confirmed in a second, larger study [139, 140]. It is currently unclear though to what extent these basepair changes are causal for the aneurysms.

5.3. Perlecan. Perlecan (heparansulfateproteoglycan) is a major component of basement membranes, encoded by the HSPG gene (chrom. 1p36.1). Like versican, it is also located in a region reported to be associated with intracranial aneurysms. HSPG SNPs were recently shown to be mildly associated with intracranial aneurysms; the exact nature of this pathogenetic link needs to be further clarified [139].

5.4. 92 kDA Type IV Collagenase. 92 kDA Type IV collagenase or MMP9 is an enzyme, encoded by the MMP9 gene (chrom. 20q11.2–q13.1) that degrades Type IV and V collagens. It has been shown that collagenolysis plays an important role in aneurysmal rupture, whereas elastinolysis is pertinent to vessel dilatation [141]. An MMP9 polymorphism associated with higher promotor activity has been shown to occur at a higher frequency in patients with intracranial haemorrhage, though a second independent study was not able to confirm this relation [142, 143]. MMP9 has also been implicated in haemorrhages following intravenous thrombolysis and haemorrhagic transformation of ischaemic stroke [144]. Further studies are needed to test these associations.

6. Conclusion

The objective of this paper was to bring to attention several connective tissue disorders which can be related to ischaemic and/or haemorrhagic stroke in young adults (Table 3). While some are more prevalent than others, it should be emphasized that the severity of the clinical spectrum of many of these disorders is highly variable. This probably leads to underdiagnosis, a phenomenon which has been clearly established for some CTD, such as PXE. In this respect, the importance of a well-oriented clinical history and examination as well as a good familial history should be emphasized, as often only the combination of all these data will raise suspicion of an underlying connective tissue cause. As many of these disorders have important implications, in first instance for the patient but also for his relatives, recognition of CTD as a cause for stroke is no longer an academic issue but an essential part of the stroke aetiological evaluation in children and young adults. Though molecular testing is already available for several of these disorders, it can be foreseen that many more ECM constituents and other proteins involved directly or indirectly in connective tissue homeostasis will be identified as a cause of or risk factor for stroke in the young.

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Review Article

The Migraine-Ischemic Stroke Relation in Young Adults

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In spite of the strong epidemiologic evidence linking migraine and ischemic stroke in young adults, the mechanisms explaining this association remain poorly understood. The observation that stroke occurs more frequently during the interictal phase of migraine prompts to speculation that an *indirect* relation between the two diseases might exist. In this regard, four major issues might be considered which may be summarized as follows: (1) the migraine-ischemic stroke relation is influenced by specific risk factors such as patent foramen ovale or endothelial dysfunction and more frequent in particular conditions like spontaneous cervical artery dissection; (2) migraine is associated with an increased prevalence of cardiovascular risk factors; (3) the link is caused by migraine-specific drugs; (4) migraine and ischemic vascular events are linked *via* a genetic component. In the present paper, we will review epidemiological studies, discuss potential mechanisms of migraine-induced stroke and comorbid ischemic stroke, and pose new research questions.

1. Introduction

Migraine affects about 15% of people in developed countries [1] and is three times more common in women than in men. Patients have a median of one attack per month, and 25% have at least two attacks per month [2]. Patients with more than one attack per month are at increased risk of brain lesions [3]. In the last decades, several studies have emphasized the high prevalence of migraine among young individuals with stroke as well as a dysfunction of cerebral arteries during migraine attacks and the finding of silent infarct-like brain lesions in migraineurs, thus leading to the hypothesis that a comorbidity between migraine and cerebral ischemia exists [4].

2. Evidence of Association

The first epidemiological suggestion that migraine may be an independent risk factor for stroke came from the Collaborative Group for the Study of Stroke in Young Women, published in 1975, which showed an increased relative risk of stroke with migraine compared with neighbor controls [5]. Since then, the association of migraine with the risk of stroke has been investigated in several observational studies, most of which have been summarized in a recent meta-analysis [6].

According to this meta-analysis, the pooled relative risk of ischemic stroke among patients with any type of migraine is 1.73 (95% CI, 1.31 to 2.29). The relative risk for women is increased (RR 2.08, 95% CI 1.13 to 3.84) but not for men (RR 1.37, 95% CI 0.89 to 2.11). Stratifying analysis by age, people with migraine aged less than 45 have an higher risk than the overall group (RR 2.65, 95% CI 1.41 to 4.97), which was further increased among young women (RR 3.95, 95% CI 2.21 to 6.04).

The risk is apparently more than tripled by smoking (RR 9.09, 95% CI 4.22 to 19.34) and more pronounced by oral contraceptives (OCs) use (RR 7.02, 95% CI 1.51 to 32.68). In line with this analysis, data from the Stroke Prevention in Young Women study (SPYW) showed a higher risk of stroke in women with probable migraine with visual aura who were cigarette smokers and oral contraceptive users

[7]. Overall, these observations reinforced the hypothesis that specific subgroups of patients in which the migraine-stroke pathogenic link is more expressed might be identified. Moreover, the meta-analysis found an increased risk of ischemic stroke among people who had migraine with aura (MA) (RR 2.16, 95% CI, 1.53 to 3.03) but not among those who had migraine without aura (MO) (RR 1.23, 95% CI 0.90 to 1.69), challenging whether MO should be considered a stroke risk factor. Is this enough to conclude that migraine is a risk factor for stroke? Some limitations of the included studies should be considered. First, migraine is biologically heterogeneous [8], and latent class analysis of migraine symptoms indicated the existence of a continuum of severity, with MA being more severe but not etiologically distinct from MO, thus reinforcing the view that the two migraine subtypes are not separate entities [9, 10]. The use of the categories of the International Headache Society classification [11] as phenotypes (MO and MA) might present an oversimplified picture of migraine phenotype, which in reality has a complex genetic and environmental background, and using this phenotype might result in too heterogeneous a set of patients for association analyses. As in other complex diseases, the use of single traits or other new phenotyping strategies for migraine might help in stratifying study samples into less heterogeneous groups. Second, potential bias in the selection of patients should be taken into account. At least theoretically, a *referral bias* may exist if stroke patients with migraine would be referred to the recruiting centres more frequently than stroke cases without migraine, or if the investigators were more prone to include stroke cases with migraine than without migraine. A further selection bias could be the consequence of a stroke-migraine misdiagnosis. As TIA are sometimes difficult to distinguish from an attack of MA, especially when the aura occurs without headache, and migraine with prolonged neurological aura (lasting longer than 24 hours) may mimic stroke, the end results of such misclassifications would be an overestimation of the prevalence of migraine in cases and, therefore, an overestimation of the risk. Third, in most of the considered studies, a consistent definitions for migraine is lacking. Accurate diagnosis of migraine is important to avoid nondifferential misclassification of exposure, which will bias the risk estimate towards showing no association. If this is the case, however, we cannot but assume that the increased risk of stroke emerging from the pooled analysis of data from observational studies is rather an underestimation of the effect. As such, it should be retained as an argument in favour of the reported association between migraine and stroke. Furthermore, in case-control studies, an *interviewer bias* and a *recall bias* can arise as possible consequences of the retrospective design. Fourth, in some of the studies, the influence of several confounders on the final results was not considered, while others were not controlled for. These include, for example, the use of medications with a potential effect on stroke risk (i.e., antihypertensive agents), or risk factors for both migraine and stroke, such as antiphospholipids antibodies. Finally, most studies are limited to younger individuals (aged 45 years or younger) leaving the association between migraine and stroke among the elderly unclear and ignoring the fact that migraine may start later in life.

Overall, there is strong epidemiological evidence that migraine, particularly MA, is associated with increased risk of cerebral ischemic events, which appears to be stronger among the young but may persist in the elderly. In this regard, data from 39,876 US female health professionals aged 45 or older included in the Women's Health study after a mean of 9 years of followup showed that MA increased 1.5-fold the risk of total stroke after adjusting for potential confounders of age, hypertension, menopausal status, contraceptive use, and alcohol consumption (HR 1.53; 95% CI 1.02 to 2.31) and a 1.7-fold the risk of ischemic stroke (HR 1.71; 95% CI 1.11 to 2.66) when compared to participants without migraine [12]. In contrast, there was no association between MO and total stroke or ischemic stroke. This association between MA and cerebrovascular disease as well as with ischemic stroke was confirmed in a large cohort of individuals ≥55 years of age at the time of migraine assessment, who participated to the Atherosclerosis Risk in Communities (ARICs) study [13]. A recent population-based cohort study during up to four decades of followup found that at midlife people with MA were at increased risk of all-cause mortality (HR 1.21, 95% CI 1.12 to 1.30) and mortality from cardiovascular disease (HR 1.27, 95% CI 1.13 to 1.43) compared with people with no headache, while those with MO and nonmigraine headache were not. In particular, people with MA were at increased risk of mortality from coronary heart disease (HR 1.28, 95% CI 1.11 to 1.49) and stroke (HR 1.40, 95% CI 1.10 to 1.78) [14]. Thus, these findings provide arguments to the assumption that migraine may have some influence on stroke risk even in older subgroups. However, effect modification by age is evident from prospective data, the risk of stroke being higher in younger age groups and decreasing over time, with no increased risk among the elderly (age 60 or older) according to case-control analyses [15].

3. What Is the Pathogenic Mechanism Linking Migraine and Stroke?

Although the relationship between migraine and stroke remains one of the most perplexing problems for neurologists, there are also valid arguments to assume that the hypothesis of a pathogenic relation between these two entities is biologically plausible. The observation that stroke may occur during migraine attacks prompts to speculation that migraine may *directly* cause an ischemic event (i.e., migrainous infarct). Alternatively, as stroke occurs more frequently during the interictal phase of migraine, an *indirect* relation between the two diseases might exist. In this regard, four major issues might be considered which may be summarized as follows: (1) migraine-ischemic stroke pathway is modulated by the intervention of common risk factors; (2) migraine is associated with an increased prevalence of cardiovascular risk factors; (3) the link is caused by migraine-specific drugs; (4) migraine and ischemic vascular events are linked *via* a genetic component [16].

4. Is Migraine a *Direct* Cause of Cerebral Ischemia?

"Migrainous infarction" is defined as a stroke occurring during a typical attack of MA in the IHS migraine classification. This condition suggests a causal relationship between stroke and migraine. Diagnostic criteria include a history of MA and the neurological deficits occurring in the same vascular distribution as the aura, persisting for more than 60 minutes, and being associated with an ischemic brain lesion in a suitable territory demonstrated by neuroimaging. Other possible causes of ischemic stroke have to be excluded by appropriate investigations [11]. However, which investigations should be done and when is not clear. The absence of causes other than migraine does not necessarily imply that migraine is the cause, given that about half of the ischemic strokes in young adults have no detectable cause. According to large series, the incidence of migrainous infarction [17–21] varies between 0.5 and 1.5% of all ischemic strokes and 10 and 14% of ischemic strokes in young patients. The clinical features typifying migrainous stroke included female sex, mean age in the low-to-mid-30 s, a history of cigarette smoking, and ischemic involvement of the PCA territory [19]. Although the limitations inherent in the diagnostic criteria which might be too strict for a correct diagnosis of migrainous infarction, and in the consequent weakness of the epidemiological studies, it seems reasonable to assume that migrainous infarction does not account for all strokes occurring during migraine attacks, and, overall, it is responsible for only a minority of migraine-related infarcts. Notwithstanding, it represents a useful model to understand the potential mechanisms underlying the relation between migraine and stroke. Migraine is considered to be a neurovascular disorder, in which arterial constriction and decreased blood flow to the posterior circulation are consequences of a spreading wave of neuronal depression in the cerebral cortex (cortical spreading depression, CSD). The first vascular phenomenon associated to CSD is a short-lived increases in cerebral blood flow (CBF) and tissue hyperoxia [22] followed by a more profound oligemia and consequent increased intraparenchymal vascular resistance [23]. Thus, low flow in major intracerebral vessels may be due to increased downstream resistance, not major intracranial arterial vasospasm. Essentially, a prolonged decreased in CBF and neuronally mediated vasodilatation could cause sluggish flow in large intracerebral vessels during the aura of migraine. The combined effect of conditions predisposing to coagulopathy, such as dehydration hyperviscosity or intravascular thrombosis, could induce migraine-induced cerebral infarction, although rarely. Neurogenically mediated inflammatory responses accompanying vasodilation of extra-parenchymal vessels caused by release of vasoactive peptides, nitric oxide (NO), activation of cytokines, and upregulation of adhesion molecules also predispose to intravascular thrombosis [24]. This could explain why migraine-induced stroke usually respects intracranial arterial territories while aura involves more widespread brain regions. In addition, frequent aura, if due to CSD, could induce cytotoxic cell damage and gliosis based on glutamate release or excess intracellular calcium accumulation [25]. Thus, a persistent neurological deficit could be due to selective neuronal necrosis. Finally, the occurrence of arterial vasospasm, as a consequence of the release of vasoconstrictive substances such as endothelin and serotonin, once thought to be the mechanism of migraine aura, has been implicated in migrainous infarction, although documented cases are rare.

5. Is Migraine an *Indirect* Cause of Cerebral Ischemia?

5.1. Potential Common Biologic Mechanisms

5.1.1. Patent Foramen Ovale. Several investigators have reported an increased prevalence of patent foramen ovale (PFO), an interatrial septal cardiac abnormality associated with increased risk of ischemic stroke in young adults in patients who suffered MA than in patients without migraine [26, 27]. Similarly, in patients with ischemic stroke, MA is twice as prevalent in patients with PFO than in those without [28, 29]. Multiple observational studies, from both single and multicentre experiences, suggest PFO closure to reduce the frequency of migraine attacks. In particular, among migraineurs, this might be proposed for those patients in the MA subgroup and might indirectly reduce the risk of stroke, in spite of the small stroke predisposing effect of PFO and some recent findings indicating no stronger association between MA and ischemic stroke among women with PFO compared with women without [7]. However, the following limitations in these reports need to be considered including absence of control group, retrospective design which implicates recall bias, placebo effect that can result in up to 70% reduction of attacks frequencies [30, 31], administration of aspirin after PFO closure, and its potential prophylactic effect [32]. Paradoxical embolism is suggested to be the causal link between migraine and PFO, but insufficient data are available to substantiate the hypothesis that migraine frequency (and, indirectly, ischemic stroke risk) is reduced by PFO closure. The only way to address this issue is by randomization. At present, only one prospective, randomised, double-blind trial on the therapeutic effect of PFO device closure on MA patients compared to sham has been conducted (Migraine Intervention with STARFlex Technology, MIST) without reaching a positive end point and being associated with substantial controversy [33, 34]. A more comprehensive analysis of current data is desirable to provide information about how to identify patients who may have an improvement of their migraine, and a large number of patients with longer followup seems necessary. Other studies examining the efficacy of PFO closure for prevention of migraine are under way. Based on all these findings, the possibility of a PFO-migraine-ischemic stroke triangular association remains actually a matter of speculation.

5.1.2. Endothelial Dysfunction. Another topic of recent attention is that migraine may be a risk factor for endothelial dysfunction, representing a challenging link to ischemic stroke and heart disease. Endothelial dysfunction is characterized

by reduction in bioavailability of vasodilator (such as NO), increase in endothelial-derived contracting factors, and consequent impairment of the reactivity of the microvasculature. It also comprises endothelial activation, characterized by a procoagulant, proinflammatory, and proliferative milieu, which, in turns, predisposes to an increased rate of cerebro- and cardiovascular ischemic events. Traditional vascular risk factors are known to have an unfavorable effect on endothelial function. Therefore, given its biological properties, vascular endothelium (and, thus, endothelial dysfunction) can be considered as the "missing link" between any risk factor and its detrimental vascular effect. In this context, endothelial dysfunction can be regarded as "the ultimate risk of the risk factors" [35]. Endothelial dysfunction is mediated by increased oxidative stress, an important promotor of the inflammatory process [35], which has been proposed in the pathogenesis of migraine. In fact, compared to migraine-free controls, oxidative stress markers have been found to be higher in migraineurs, even during the interictal period, thus yielding support to the association. These findings, as well as the known efficacy of anti-inflammatory agents in migraine attacks, indirectly support this assumption and further strengthen the hypothesis of a pathogenic relation migraine-endothelial dysfunction-cerebral ischemia.

5.1.3. Cervical Artery Dissection. In the last years, migraine has been suggested to be a predisposing condition for spontaneous cervical artery dissections (sCADs), one of the most common causes of stroke in young patients leading to speculation that migraine might be a predisposing condition for specific pathogenic subtypes of ischemic stroke particularly in young patients. In two French case-control studies, migraine resulted twice as common in patients with sCAD than in patients whose ischemic stroke was not related to an sCAD [36, 37], and this association was stronger and more significant in patients with dissections involving multiple vessels. A large Italian case-control study confirmed these findings [38]. The association between sCAD and a specific migraine subtype is controversial since it has been suggested to be stronger for MO than for MA, but recently a hospital-based case-control study found a higher prevalence of migraine with aura among sCAD patients as compared to a control group [39].

The mechanism by which migraine may affect the risk of sCAD is unknown. A common generalized vascular disorder is hypothesized to be a predisposing condition for both diseases. Increased activity of serum elastase, a metallopeptidase which degrades specific elastin-type aminoacid sequences, reported in migraineurs suggests a possible extracellular matrix degradation [40] which might facilitate sCAD occurrence. Furthermore, in line with previous observations of altered common carotid artery distensibility in patients with sCAD [41], Lucas and coworkers recently reported that the endothelium-dependent vasodilatation assessed in the brachial artery is significantly impaired in these subjects [42]. Similar vascular changes have been observed in migraine patients during interictal periods [43] and replicated in a recent cross-sectional study in migraineurs of recent onset, thus excluding possibility of bias due to longstanding history of migraine and repeated exposure to vasoconstrictor drugs [44]. Finally, the analysis of small families has shown that the structural abnormalities related to sCAD might be familial and follow an autosomal dominant pattern of inheritance [45, 46]. This implicates that genetically determined alterations of the extracellular matrix may play a crucial pathogenic role and that candidate genes involved in the regulation of the endothelial and the vessel wall functions, might increase susceptibility to both conditions [47–49].

6. Migraine and Cardiovascular Risk Factors

Several reports have associated migraine with a more unfavourable cardiovascular risk profile. According to the results of the Genetic Epidemiology of Migraine (GEM) study, migraineurs are more likely to smoke and to have a parental history of myocardial infarction. MA was also found to be associated with an unfavourable cholesterol profile, elevated blood pressure, early onset coronary heart disease, or stroke [50]. Data from the population-based American Migraine Prevalence and Prevention (AMPP) study recently provided further support to the perception that migraineurs have a higher probability of having an unfavorable risk factors profile [51]. However, a number of large-scale epidemiologic analyses conducted over the last years have questioned these findings and suggested that the migraine-stroke association is particularly present in the absence of traditional cardiovascular risk factors [16, 52]. Therefore, the possibility that the relation between migraine and ischemic stroke may be due to the known pathogenic effect of traditional vascular risk factors seems unlikely.

7. Effects of Migraine-Specific Drugs

Since the potential of triptans and ergotamine for adverse vascular effects, in the last years large-scaled studies have investigated the risk of ischemic events and death in migraineurs patients treated with these agents. Data from General Practice Research Database in the United Kingdom showed that in general practice triptan treatment did not increase the risk of ischemic events [53]. Similarly, this finding was confirmed by a wide retrospective cohort study from a health care provider in USA [54]. This study also investigated the rates of vascular events in relation to ergotamine use finding no association. Recently, a retrospective nested case-control study using data from the PHARMO Record Linkage System conducted in Netherlands investigated whether overuse of triptans and ergotamina is associated with an increased risk of ischemic events [55]. Results showed that while ergotamine overuse increases significantly the risk of ischemic complications (OR 2.55; 95% CI, 1.22–5.36) especially in patients concomitantly using cardiovascular drugs (OR 8.52; 95% CI, 2.57–28.2), overuse of triptan, neither in the general populations nor in those using cardiovascular drugs increases the risk of cerebral, cardiovascular, or peripheral ischemic events. However, therapeutic doses of either triptans or ergotamines were not associated with an increased risk of ischemic vascular events.

Taken together, these findings suggest that triptan use and even triptan overuse are generally safe although heighten the risk of ischemic complications due to ergotamine overuse, likely in relation to its greater vasoconstrictive properties.

8. Genetic Influence

Based on twin and family history studies, genetic predisposition has been suggested to play a major role in the occurrence of both migraine and ischemic stroke. Interestingly, several candidate genes for migraine are also good candidate for cerebral ischemia. Among them, in spite of the inconsistent in migraine [56], the C677T polymorphism of the MTHFR gene seems particularly promising, because of its probable independent effect on ischemic stroke risk [57]. In this regard, recently the results of a genotype-migraine-stroke interaction study have been reported in which the TT-genotype of the C677T MTHFR polymorphism was found to be associated to both diseases and influence their relation [58]. Applying a mediation modelling strategy on a group of patients with sCAD, a group of young patients whose ischemic stroke was unrelated to an sCAD (non-CAD) and a group of control subjects, both migraine and the TT-genotype were found significantly associated to the group of patients with ischemic stroke as compared to controls, with a stronger stroke subtype specific effect for sCAD. These findings suggest that migraine may act as mediator in the MTHFR-ischemic stroke pathway with a more prominent effect in the subgroup of patients with sCAD and prompt speculating that the C677T MTHFR polymorphism may be one of the hitherto unknown factors linking migraine to cerebral ischemia. These findings have been replicated in a separate analysis of the Women's Health study data [59]. Overall, these findings may be viewed considering the prevailing hypothesis that migraine and ischemic stroke are the end phenotype of polygenic disorders reflecting the effect of several genetic loci modulating different pathophysiological processes and the combination of many hundreds of genetic variants; as a consequence, it is reasonable to hypothesize that certain genes might have an effect on both diseases and influence their relation. At what levels in the migraine-stroke pathway these genetic influences might be operating to increase the propensity to cerebral ischemia and whether such effects might vary according to different stroke subtypes are important and still poorly investigated aspects of stroke pathogenesis.

Ischemic stroke and migraine further coexist in the context of some syndrome characterized by peculiar phenotype, proven inherited background, and chronic alterations of the wall of cerebral small vessel arteries suggesting a common pathogenic mechanism shared by these two conditions.

CADASIL is an autosomal dominant disease of vascular and smooth muscle cells due to Notch-3 mutations [60], characterized by leucoencephalopathy, small deep infarcts, and subcortical dementia. MA is usually the first manifestation, presenting about 15 years before stroke and before the appearance of MRI signal abnormalities. MA is present in one-third of symptomatic subjects, and its frequency can vary greatly among the affected pedigrees. In 40% of families, more than 60% of symptomatic subjects had a history of MA [61, 62] and within some families, MA is the most important clinical aspect of the phenotype. The mechanism underlying MA in CADASIL is not clear. Presenting 10–20 years before ischemic manifestations, MA is not the consequence of subcortical infarcts. In CADASIL, absence of difference in the frequency and distribution of white-matter abnormalities between patients with and without MA suggests that chronic subcortical hypoperfusion is also unlikely. Another hypothesis is that MA directly relates to dysfunction of smooth muscle cells of meningeal and cortical vessels, triggering CSD [63]. Furthermore, if the cells signalling abnormalities (resulting from the mutation) extend and reach neurons, the resulting hyperexcitable membrane instability could predispose to CSD.

Cerebroretinal vasculopathy (CRV) and hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) are two rare inherited conditions characterized by a primary microangiopathy of the brain in combination with vascular retinopathy.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is associated to several mutations in mitochondrial DNA (mtDNA). The phenotypic expression is highly variable ranging from asymptomatic state to severe childhood multisystem disease with lactic acidosis. Recurrent episodes of headache (mostly migraine) are part of the clinical spectrum.

Migraine is also part of the clinical spectrum of hereditary haemorragic teleangiectasia (HHT; Osler-Weber-Rendu disease), an autosomal dominant vascular dysplasia characterized by a high prevalence of vascular malformations in various organs, including lung, liver, kidney, and brain, as well as by mucocutaneous teleangiectasias [64].

9. Conclusion

Given all the epidemiological evidence suggesting that migraine, in particular MA, increases the risk of cerebral ischemic events, some questions related to the pathogenic link between migraine and ischemic stroke still remain. Strong arguments support the assumption that MA is associated with a systemic vascular disorder, especially in young stroke patients. The use of new phenotyping strategies for migraine and ischemic stroke should be taken into account in order to provide a more direct insight into the underlying biology of the two diseases and how to identify migraineurs at highest risk of ischemic stroke. Whether stroke can be prevented by migraine prophylaxis, endothelial repair, anti-inflammatory treatment, platelet inhibition, or a combination of these strategies is a further goal of future research.

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Review Article

Role of Investigating Thrombophilic Disorders in Young Stroke

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Our knowledge about various inherited and acquired causes of thrombophilic disorders has increased significantly during the past decade. Technology for various diagnostic tests for these rare disorders has matched the rapid advances in our understanding about the thrombophilic disorders. Inherited thrombophilic disorders predispose young patients for various venous or arterial thrombotic and thromboembolic episodes. Our understanding has also improved about various gene-gene and gene-environment interactions and their impact on the resultant heterogenous clinical manifestations. We describe various thrombophilic disorders, their diagnostic tests, pathogenic potential in isolation or with other concurrent inherited/acquired defects and possible therapeutic and prophylactic strategies. Better understanding, optimal diagnostic and screening protocols are expected to improve the diagnostic yield and help to reduce morbidity, disability, and mortality in relatively younger patients harbouring these inherited and acquired thrombophilic disorders.

1. Introduction

Ischemic stroke (IS) is a common cause of morbidity and mortality with significant socioeconomic impact especially when it affects young patients. The incidence of ischemic stroke varies from 3 to 23 per 100,000 among the young IS sufferers [1]. Although the cutoff age for defining young IS remains debatable, it is generally believed that the risk factors and underlying etiologies tend to become similar to the older patients at around 44 years of age. Therefore, most of the studies define "stroke in young" as occurring in patients at age 44 years or less [2]. Young strokes generate immense interest among the stroke neurologists even when a larger proportion of patients continue to be classified as "stroke of undetermined etiology" [2].

Compared to the older adults, the incidence, risk factors, and etiology are distinctly different in younger IS. Accordingly, cardioembolism (20%–35%), dissection of extracranial arteries (6%–25%), drugs (10%), and hypercoagulable states (5%–10%) are relatively more commonly detected in younger IS patients [3–5]. Furthermore, additional factors such as migraine, pregnancy and oral contraceptive use are observed with higher frequency [4, 5].

Young IS attracts a barrage of diagnostic tests, mainly searching for an underlying thrombophilic state. We discuss various thrombophilic disorders, their available diagnostic tests and significance of testing for these uncommon causes.

2. Thrombophilic Disorders and Ischemic Stroke

Thrombophilic states are disorders of hemostatic mechanisms that result in a predisposition to thrombosis [6]. Thrombophilia is an established cause of venous thrombosis. Therefore, it is tempting to assume that these disorders might have a similar relationship with arterial thrombosis. However, thrombophilia, alone, rarely causes arterial occlusions. Even in individuals with a positive thrombophilia screen and arterial thrombosis, the former might not be the primary etiological factor [7]. Although thrombophilic disorders and their contribution to the stroke risk are uncommon, their detection often helps in management decisions, long-term prognostication, screening family members "at-risk", and possible primary prophylaxis.

Thrombophilic disorders can be broadly divided into inherited or acquired conditions. Inherited thrombophilic disorders are far less commonly observed in young IS. These include deficiencies of natural anticoagulants such as protein C, protein S, and antithrombin III (AT III) deficiency,

polymorphisms causing resistance to activated protein C (Factor V Leiden mutation), and disturbance in the clotting balance (prothrombin gene 20210G/A variant). Of all the inherited thrombophilic disorders, Factor V Leiden mutation is perhaps the commonest cause, accounting for about half of the cases. Prothrombin gene mutation, protein C, protein S deficiency, and antithrombin deficiency account for most of the remaining cases. On the contrary, acquired thrombophilic disorders are more common and include conditions such as the antiphospholipid syndrome, associated with lupus anticoagulant and anticardiolipin antibodies.

In general, primary thrombophilic disorders contribute to about 1%–4% of ischemic strokes. However, the prevalence varies widely between different ethnic groups, age, and geographic distributions. An exhaustive 15-years follow-up study of 150 families with different inherited thrombophilic disorders failed to demonstrate any association between these coagulation defects and arterial thrombosis [8]. However, these inherited thrombophilias were associated with a high incidence of venous thrombosis, conferring almost 100% risk of deep vein thrombosis (DVT) in protein S deficiency. DVT with or without pulmonary embolism was the most frequent type of thrombosis. Similar observations were reported in a case-control study that looked at the association between inherited thrombophilic disorders and acute IS [7]. It found that 1 in 7 patients with first-ever acute IS had a positive test for at least one of the thrombophilias. However, this relationship was considered coincidental instead of an actual cause of stroke for all the IS subtypes, even when adjusted for age [6].

3. Thrombophilic Disorders

3.1. Factor V Leiden. Although factor V Leiden mutation accounts for almost half of the thrombophilic states, its prevalence varies among different ethnic groups. It is more commonly seen in Caucasians (prevalence 1% to 8.5%). However, Factor V Leiden mutation has been reported rarely among patients of Chinese, Japanese, and African descent [8, 9]. Although this mutation predisposes to a higher risk of venous thrombosis, its association with arterial disease remains unestablished for myocardial infarction as well as IS [9]. In a study of 203 young IS patients, Nedeltchev et al. reported 0.9% incidence of Factor V Leiden mutation [10].

3.2. Prothrombin G20210A Mutation. Wide variations are observed in the geographic and ethnic prevalence of prothrombin (factor II) G20210A gene mutation. Similar to the Factor V Leiden, this mutation is also rare in patients of Asian and African descent, but occurs in about 0.7% to 4.0% of the Caucasians [11]. Although Prothrombin gene mutation is not considered a risk factor for IS in the older populations, an association has been suggested in the younger population [12, 13]. In a study of younger IS patients (below ages 50 and 60 years, respectively), without other established vascular risk factors, were more likely to have this gene mutation as compared to the controls (6–7.6 versus 1–1.2%) [12]. However, another study of 131 patients with IS contradicted these results and found that the prevalence of Prothrombin gene mutation was similar to the control population [13].

3.3. Deficiencies in Coagulation Factors (Inherited Coagulopathies). Inherited coagulopathies are generally more common in Black Africans and Black Caribbeans, with or without IS. In a prospective study of multiethnic population, black African patients were found to have significantly lower protein S ($P < .001$) protein C ($P = .049$), and antithrombin III ($P = .056$) levels when compared to the whites [14]. Similar trends were noted for protein S deficiency in a smaller study that reported its higher incidence in blacks than non-blacks (34% versus 13%, $P = .001$) [15].

Protein C is one of the three key proteins that regulate coagulation besides protein S and antithrombin III. It is a vitamin K-dependent glycoprotein and its deficiency presents in 2 forms. Type I deficiency has plasma protein C concentration below 70% of the overall mean value. Type II deficiency states are relatively less common and have normal blood levels. However, the functional activity of protein C is impaired. In general, the incidence of protein C deficiency is 1 in 200 to 500 [16]. Nedeltchev et al. reported 0.5% incidence rate of protein C deficiency in young IS patients [10]. An association between young IS and inherited protein C deficiency has been reported in individual case reports [17]. However, larger studies failed to demonstrate this relationship [18]. Protein C deficiency alone does not appear to increase the risk or arterial thrombosis, slightly higher incidence of myocardial infarction is noted when it is coupled with other vascular risk factors [19, 20]. Uncommonly, some physiological and disease states like pregnancy, drugs, severe infection, and liver disease can produce an acquired protein C deficiency.

Protein S acts as a cofactor for protein C. Isolated protein S deficiency may be seen in up to 10% patients with young IS. However, except for a few case reports, [21] significant relationship between this disorder and arterial thrombosis has never been established [18]. Instead, most of the patients with isolated protein S deficiency develop DVT, and they usually do so before the age of 25 years.

Antithrombin deficiency occurs in 1 of 5000 healthy blood donors [22]. Among patients with a first thrombotic event, the prevalence of this inherited disorder is approximately 0.5% to 1% [23, 24]. This protein may contribute to thrombotic events either by being deficient or dysfunctional. Again, direct association of antithrombin deficiency with arterial thrombosis remains controversial [22, 24].

3.4. Disorders That Are Polygenic and Interact with Dietary or Environmental Factors. Cross-sectional and observational epidemiological studies have suggested that elevated plasma homocysteine concentrations might constitute a higher risk for major thrombotic events [25–27]. Some randomized trials demonstrated that homocysteine levels in the blood can be lowered by treatment with B vitamins and folic acid [28]. Homocysteine metabolism may be impaired due to genetic (abnormal enzymes in its metabolic pathway) as well as nutritional factors (vitamin B6, folate, and B12 deficiencies).

The most common genetic mutation of hyperhomocysteinemia is a C-to-T substitution of nucleotide 677 (C677T) of the gene 5,10-methylenetetrahydrofolate reductase (MTHFR). The VITATOPS, a randomized, double-blind, placebo-controlled trial involving 8164 patients, recently tested the homocysteine-lowering multivitamin therapy in patients with transient ischemic attacks or strokes [29]. The study concluded that the daily administration of folic acid, vitamin B6, and vitamin B12 in patients with recent stroke or transient ischemic attack was safe but did not reduce the incidence of major vascular events as compared to the placebo.

4. Acquired Thrombophilic Disorders

4.1. Antiphospholipid Antibody Syndrome. The most common acquired thrombophilic disorder is antiphospholipid syndrome (APS). APS is a multisystem autoimmune disorder which can be either primary or secondary to other autoimmune diseases. It occurs more commonly in females and is characterized by arterial and venous thrombosis. It is associated with antiphospholipid antibodies such as lupus anticoagulant and anticardiolipin antibodies. A case control study suggested that lupus anticoagulant is a major risk factor for arterial thrombotic events in young women and found 17% of patients with IS as tested positive for the antibody [30]. Lupus anticoagulants are considered to carry a 5 to 16 times higher risk for thrombotic events than anticardiolipin antibodies [31].

4.2. Diagnosis of APS. APS can be diagnosed based on an international consensus criteria which was designed mainly for application to clinical studies of APS, and its diagnosis is based on clinical criteria of one or more occurrence of pregnancy morbidity or vascular thrombosis, and laboratory criteria of the presence of antiphospholipid antibodies on two or more occasions at least 12 weeks apart [32].

4.3. Laboratory Measurement of Antiphospholipid Antibodies. Consensus guidelines recommend screening for lupus anticoagulants (LA) with 2 or more phospholipid-dependent coagulation tests, which is best done when the patient is not receiving oral anticoagulants or unfractionated heparin, which can result in prolonged clotting times and subsequent false-positive results [33]. Both anticardiolipin antibodies and anti-β_2-glycoprotein I antibodies can be detected using enzyme-linked immunosorbent assay (ELISA) techniques, but many of these assays are not standardized. Consensus guidelines recommend semiquantitative reporting of anticardiolipin antibody results (low, medium, or high titer) [34].

4.4. Antithrombotic Treatment of APS for Patients with Arterial Thromboembolism. The choice of antithrombotic treatment is still controversial due to the lack of randomized treatment trials. Treatment choices should be individualized by balancing the risk of thrombosis and hemorrhage of each patient. Generally, the most common presentation of arterial thromboembolism in APS is ischemic stroke (13%), and transient ischemic attack (7%) of patients meeting consensus diagnostic criteria [35]. The presence of lupus anticoagulants or anticardiolipin antibodies have also been found to be associated with a 2-fold increase in first ischemic stroke [36].

The APASS study (APL and Stroke Study), [37] was a prospective cohort study within the Warfarin Aspirin Recurrent Stroke Study (WARSS), which was a randomized double-blind study comparing warfarin and aspirin for preventing recurrent stroke or death [38]. They found that patients treated with warfarin had a similar relative risk of recurrent ischemic stroke or death as patients treated with aspirin, and there was no difference whether patients were tested positive or negative for antiphosphospholipid antibodies [37]. Based on this, antithrombotic recommendations have been that both warfarin and aspirin are reasonable first choice antithrombotic treatments for patients presenting with a first ischemic stroke, with aspirin having the benefit of a lower bleeding risk and not requiring regular INR monitoring [39]. However, it should be noted that the median INR achieved in this study by the patients on warfarin was 1.9. There are currently no studies evaluating the optimal duration of treatment, and so patients are often treated indefinitely, similar to those patients with venous thromboembolism [39].

4.5. Heparin-Induced Thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is another cause of transient acquired thrombophilia. It is due to heparin-dependent platelet activating immunoglobulin which further causes a temporary hypercoagulable state through several mechanisms. The risk of HIT-associated thrombosis ranges from 50% to 90%, with higher risk of thrombosis in the lower platelet group [40]. Generally, venous thrombosis like deep vein thrombosis and pulmonary embolism are most common, but arterial thrombosis including lower limb ischemia, stroke, and myocardial infarction are also relatively common [40].

4.6. Lipoprotein (a) and Stroke. Another important cause of acquired thrombophilia is lipoprotein (a). It is a glycoprotein attached to the LDL. In a prospective study, lipoprotein (a) concentration was associated with chronic heart disease (risk ratio of 1.16, 95%CI, 1.11–1.22) and ischemic stroke (risk ratio of 1.10, 95%CI, 1.02–1.18) [41]. The mechanism is still unclear but increasing thrombosis and impaired fibrinolysis at the sites of plaque rupture are the possible causes [42].

4.7. Other Related Disorders That Increase the Risk of IS. Presence of thrombophilic state typically predisposes a patient predominantly to venous thrombosis and carries only a small risk for arterial thrombosis or IS. More typically, the thrombophilic disorders contribute to DVT in lower extremities and pelvic veins travels and an embolus from them may traverse through an atrial septal defect or patent foramen ovale (PFO) to cause paradoxical cerebral arterial embolization [43]. In a series with 125 young IS patients (age 34 ± 7.3 years), the PT G20210A variant and FV G1691A mutation were more frequent in the PFO positive group compared to the controls (PFO negative) [44]. However, the phenomenon of paradoxical embolization through a PFO remains largely

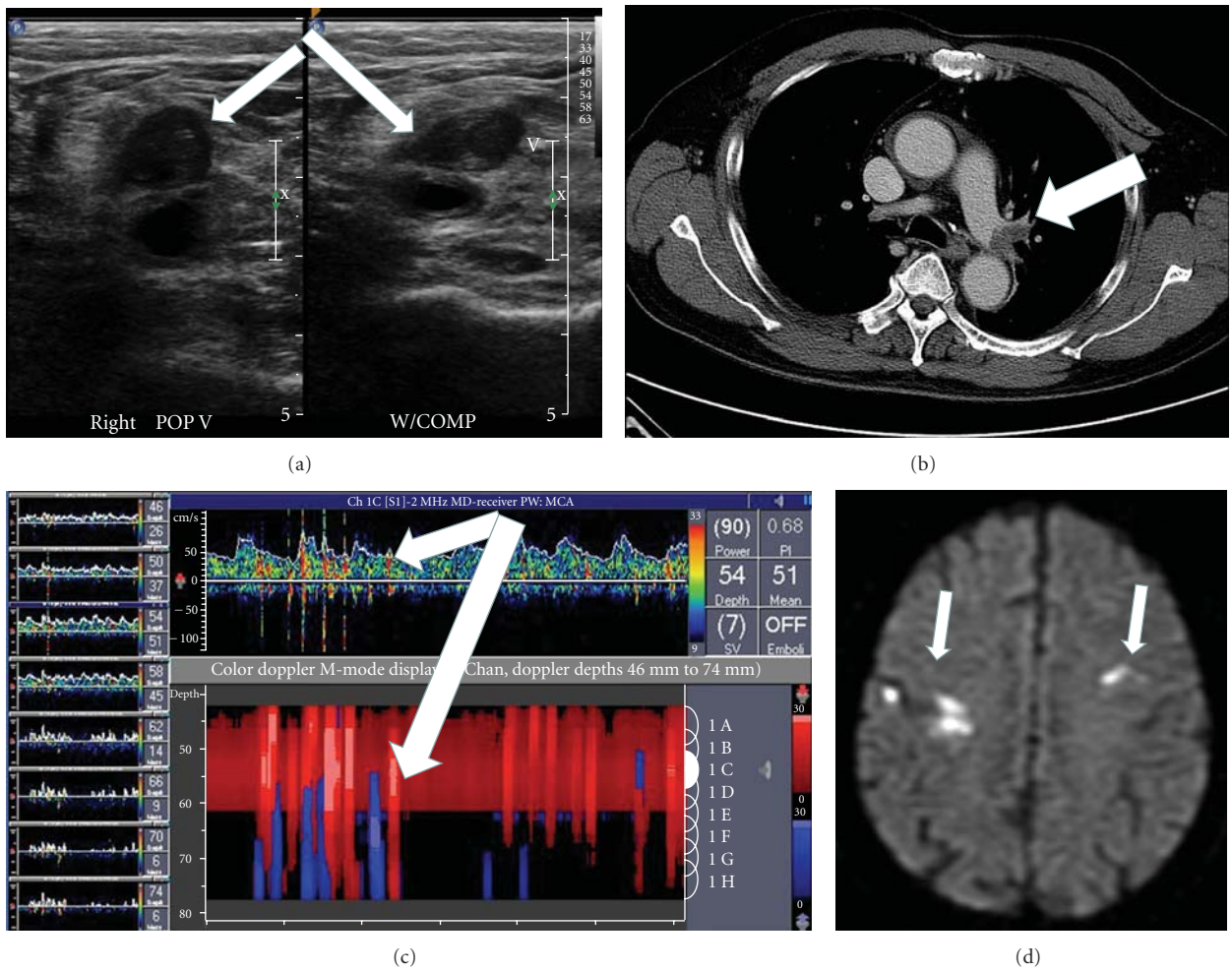

Figure 1: A 27-year-old woman, without any vascular risk factors, presented with mild right-sided weakness of suddenonset. She was noted to have swelling and pain in the right leg. Duplex sonography revealed extensive deep vein thrombosis involving the popliteal as well as superficial femoral vein, as characteristic noncompressibility and echogenic mass in the venous lumen. (a) Computerized tomographic angiography of thorax revealed filling defect in the left pulmonary artery. (b) Transcranial Doppler ultrasonographic monitoring of left middle cerebral artery during the "bubble test" (injection of agitated 9 mL normal saline and 1 mL air) revealed numerous microembolic signals, (c) suggestive of a right-to-left shunt (patent foramen ovale). Multiple acute ischemic infarcts involving many arterial territories were evident on the diffusion-weighted magnetic resonance imaging of the brain. (d) Blood tests were positive for lupus anticoagulant and anticardiolipin antibodies.

hypothetical. Various epidemiological studies have reported an increased incidence of PFO in cryptogenic stroke patients as compared to the general population. Since cerebral embolization through a PFO is considered to be the possible etiological mechanism, identification of the presence of a venous thrombus and its migration via the PFO are essential to confirm this pathogenic mechanism. However, both of these essential components are often difficult to establish due to various methodological and temporal issues [45]. Imaging findings in a patient with thrombophilia, extensive deep vein thrombosis, pulmonary embolism as well as multiple cerebral ischemic infarctions due to paradoxical embolization through a PFO are shown in Figure 1.

4.8. Synergisms. We believe that acute IS in young thrombophilic patients is the result of interaction between the underlying genetic disorder and environmental factors. This interaction might influence the stroke severity also. Common environmental factors that are believed to increase the risk of thrombotic events in patients with relevant genetic disorders include smoking, hypertension, dyslipidemia, and diabetes mellitus. In a study that looked at the cumulative effect of some of the inherited thrombophilias and their interactions with modifiable predisposing factors (smoking, hypertension), the odds for IS were 1.73 in subjects with one polymorphism. The risk increased to 3.00 if the subjects had two or more polymorphisms [46].

Oral contraceptive pills are believed to increase the risk of venous thrombotic events and, at times even IS, especially in patients with thrombophilia [47]. In a case-control study on women less than 45 years old with a first IS, oral contraceptives doubled the risk of IS in the first 6–18 months of use.

The risk increased dramatically to 13 times higher in patients who were also carriers of Factor V Leiden mutation and 9 times higher with coexistent hyperhomocysteinemia [48].

5. The Controversy of Testing for Thrombophilia

Young IS patients, especially those without the common vascular risk factors and classified as "strokes of undetermined etiology" [2], are usually investigated for uncommon causes, with special emphasis on thrombophilic disorders. As a result, up to a third of all IS patients may undergo a barrage of tests for various thrombophilic states [49]. However, indiscriminate ordering of these tests is often debatable. The cost of this gamut of tests can run up to more than $1000 US dollars in the United States [49], US $500 in the United Kingdom, and US $200 in Australia [50]. Apart from the high cost, these tests generate some psychological impact on the patients and their families, especially due to the possible genetic component [51]. Potential psychological and social consequences include fear, depression and worry [51], and difficulty of getting life or disability insurance in the future if the tests show an abnormal result [52].

The actual benefit of routine testing for thrombophilic disorders in IS remains uncertain [49, 50, 53]. The primary aims of testing for these uncommon disorders are to ascertain the definite diagnosis, possible prognostication, and to provide an appropriate treatment as well as secondary prophylaxis. Furthermore, primary prophylaxis may also be offered to family members of the proband who are carriers of a particular genetic defect but have not yet had a symptomatic thrombotic event [54]. However, the yield of performing extensive diagnostic tests is often poor and, in the majority of cases, no established curative measures exist.

6. Who Should be Screened?

The prevalence of thrombophilic disorders among the general population is low [7–10]. Furthermore, even when they occur with a higher prevalence (Factor V Leiden and prothrombin gene mutations in Caucasians), the thrombophilic states may not carry an alarmingly increased risk of thromboembolism [54]. The acquired thrombophilic disorders (lupus anticoagulant and anticardiolipin antibodies) confer a relatively higher risk for arterial thrombosis and IS [31]. However, the inherited thrombophilic disorders account for a very low thrombotic risk [6, 54, 55]. Furthermore, the prevalence of various thrombophilic disorders is very low in some ethnic groups of African or African-Caribbean descent [6, 54, 55]. Therefore, it has generally been believed that the routine screening of the general population is not justified.

Morris et al., in their analysis of the case-control studies of the 5 most commonly inherited thrombophilias with ischemic stroke: protein C and S deficiencies, antithrombin deficiency, factor V Leiden and prothrombin gene mutations, found no convincing associations with stroke, even in young patients and patients with patent foramen ovale [56]. In light of this, they have recommended that patients without a white ancestor should not be tested for Factor V Leiden or Prothrombin and that levels of protein C and protein S should be interpreted cautiously in those of African descent. They also recommended that cryptogenic stroke patients with patent foramen ovale should be investigated for deep venous thrombosis in the legs and pelvic veins. As part of their recommendations, investigating for inherited thrombophilias should be done in patients having any of the other clinical features necessitating a thrombophilic workup as set out by WHO recommendations: history of venous thromboembolism—either unprovoked or in unusual location, family history of venous thromboembolism, thrombosis at a young age (less than 45 years old), and frequent thrombotic recurrences [57].

Walker et al. [6] observed a nonsignificant trend towards a higher prevalence of thrombophilia, especially in 20.5% of IS classified as "cardioembolic stroke" according to the TOAST classification [2]. The study postulated that the hypercoagulable state promoted the development of "red" fibrin thrombi in areas of stasis such as veins and heart chambers. These "red" clots were considered rich in fibrin and differed from the usual "white" clots, rich in platelet content, that develop in arteries [6]. Similarly, Carod-Artal et al. [58] found that prothrombotic conditions were more frequent among the young IS patients classified as "strokes of undetermined cause" [2]. However, they did not observe any association between inherited thrombophilic disorders and any of the pathogenic subtypes of IS among the older patients. Interestingly, isolated protein S deficiency was associated with "stroke of undetermined cause" in the young patients.

Selection of patients for performing various diagnostic tests for the thrombophilc disorders should not be influenced by IS involving a specific vascular territory. For example, anterior cerebral artery (ACA) territory infarctions, comprising less than 3% of IS, are usually considered cardioembolic in origin [59]. Stroke in ACA territory are, therefore, often investigated for an underlying cardioembolic or thrombophilic cause. However, in some ethnic populations, especially Chinese, ACA may be involved in the generalized atherosclerotic process [60]. IS resulting from the thrombophilic disorders might involve any arterial territory and often affects multiple arterial territories together [61]. The more useful and practical approach of ordering various diagnostic tests for the uncommon thrombophilic states tests should be determined by a detailed clinical history, physical examination, imaging studies and evaluating whether an underlying hypercoagulable state appears more likely. History of a prior thromboembolic event, especially that occurred after minimal stimuli or at unusual sites is an important clue for thrombophilic disorders [62]. Similarly, venous thrombosis is the most common manifestation of coagulopathy [63] while a history of unexplained miscarriage may signify the presence of antiphospholipid syndrome [64]. Some other clues that might suggest the presence of a thrombophilic disorder include thrombocytopenia, livedo reticularis, or Sneddon syndrome (skin necrosis during initiation of oral anticoagulant therapy), family history of clotting events at a young age, absence of conventional

vascular risk factors, presence of malignancy or sepsis, and recurrent thrombotic events despite appropriate treatment [65]. History of previous venous thrombosis and miscarriage is the most important fact that is often missing in patients' medical records which leads to a delay in diagnosis [49].

An important factor that should be used in selecting patient for testing the thrombophilic disorders is age. While thrombophilia is rarely associated with arterial occlusive disease in adults, it constitutes an important cause in childhood and young IS. Accordingly, Duran et al. found that 57% of pediatric IS patients tested positive for at least one thrombophilic marker as compared to 15% of age-matched controls [66]. Furthermore, 10% of the pediatric population had 2 or more positive markers. Similarly, a high prevalence of antiphospholipid syndrome is observed in children with idiopathic cerebral ischemia [67], with 76% of children aged 5 to 16 years tested positive for lupus anticoagulant or anticardiolipin antibodies. However, it should always be kept in mind that atherosclerosis and cardioembolism still constitute more likely causes [68] as compared to the thrombophilic disorders that account for only 10% to 15% of the cases of IS in the young [3]. In another study of subjects less than 18 years of age, half to two thirds of IS demonstrated thrombophilic states [69]. Considering the rarity of childhood IS, congenital heart disease would have complemented multiple coexisting thrombophilic states in causing the high prevalence of IS [69]. Finally, screening for prothrombotic states should also be considered in symptomatic siblings and first-degree family members to identify patients at relatively highrisk [70].

7. What Should be Screened?

Some young patients suffer from multiple thrombophilic disorders that confer an additive or multiplicative risk of thromboembolism. For example, the combined defects of protein C or protein S deficiencies plus Factor V Leiden, or the acquirement of hyperhomocysteinemia with Factor V Leiden, increase the risk of thromboembolism compared to either defect in isolation. Similarly, a combined antithrombin III deficiency with Factor V Leiden mutation poses a very high risk of thromboembolism when compared to either defect alone. Therefore, the laboratory screening should be comprehensive and avoid missing the coexisting defect [54]. Accordingly, functional assays for proteins C, protein S, and antithrombin III should be performed if activated protein C (APC) resistance is observed; prothrombin 20210A, fibrinogen, homocysteine, D-dimers, and factor VIII should be tested carefully if there is coexisting ulcerative colitis [71]. It is important that a diagnostic search protocol should include tests for both inherited and acquired thrombophilic disorders. Finally, assessment of plasma homocysteine has been advised in all IS patients since it is considered easily reversible with vitamin supplementation [71]. However, the recently published VITATOPS trial failed to demonstrate any significant beneficial effects of this approach [29].

8. What Is the Appropriate Timing for Screening?

Since the therapeutic approach (anticoagulation and thrombolytic therapy) determines the clinical outcomes, early diagnosis of the thrombophilic disorders plays an important role. Furthermore, the timing of test performance of some of the thrombophilic defects (like protein C, protein S, antithrombin III and fibrinogen levels) is often critical since these proteins can behave as acute phase reactants and erroneously elevated levels of these factors may be observed in patients with acute thrombotic events [54, 71]. On the other hand, the plasma levels of vitamin K-dependent proteins (protein C, protein S and APC resitance) may not be reliable in patients taking vitamin K antagonists [72]. Similarly, antithrombin III measurements are unreliable in patients receiving heparin. Therefore, it is suggested that plasma-based assays for these disorders should be repeated 3 to 6 months after the initial thrombotic episode to avoid false-positive results and avoid unnecessary prolonged anticoagulation therapy. The assays for these disorders are recommended after discontinuation of oral anticoagulant treatment or heparin for at least 2 weeks [54, 71].

DNA-based assays are not affected by acute thrombotic events or use of anticoagulation and thrombolytic therapy. Therefore, screening for these genetic mutations can be performed reliably at any time following a thrombotic event [54, 71].

Finally, natural history for some of the thrombophilic disorders should be considered during the interpretation of their diagnostic assays. Accordingly, lipoprotein (a) levels increase during the first year of birth. Hence, it is necessary to repeat testing 8 to 12 months after the acute thrombotic onset in neonates suffering from thromboembolism [71].

9. Factors to be Considered during the Interpretation of Diagnostic Tests

As mentioned above, the interpretation of the tests for some of the thrombophilia markers depends on its timing in relation to the acute thrombotic event as well as concurrent medications, especially vitamin K antagonists and heparin. In addition, patients' age also might affect the results of some these markers. For example, antithrombin III levels decline with increasing age, and the reference range may therefore need some adjustments accordingly [6]. Another important factor that may alter the results is patients' ethnicity. The conventionally employed reference ranges for some biomarkers of thrombophilia may lead to false positive diagnoses in black Africans or black Caribbeans due to their inherent lower concentrations when compared to the Caucasian population [14].

The presence of concomitant medical conditions and drug therapies should also be taken into consideration during the interpretation of results. For example, antithrombin III levels can be relatively lower in liver disease, nephritic syndrome, inflammatory bowel diseases and pregnancy; liver disease can be associated with lowered protein C and S levels; pregnancy can result in lowered protein S levels and acquired

APC-resistance. Furthermore, protein S levels and the acquired APC resistance may be affected by sex-hormonal treatment in females [72]. Correct interpretation of anticardiolipin antibody titers can also be difficult in some patients, as the blood levels can be affected by other conditions such as viral, bacterial or parasitic infections, lymphoproliferative disorders, paraproteinemia, or drugs such as phenothiazine, procainamide, phenytoin, quinidine and hydralazine [73]. Therefore, other clinical or laboratory features of APS should be sought for an accurate diagnosis [43].

10. What Secondary Stroke Prevention Method Should be Instituted If the Screening Is Positive?

In the event that the screening was done indiscriminately for a stroke patient, it is reasonable to first interpret the results with caution. One must first evaluate whether a more obvious stroke mechanism is present, or whether a coexisting condition is already present which would already necessitates the use of anticoagulation, for example a cardioembolic source. The results should also be assessed if they are truly positive, for example if the protein C or S levels were drawn shortly after an acute thrombosis, or if the blood test were done with patient still on anticoagulant therapy. Lastly, one should interpret the significance of the positive result in light of the patient's cardiovascular risk profile and age, for example, it would have greater implications in a young patient without cardiovascular risk factors [74].

Treatment of an ischemic stroke is not as clearly defined as that for venous thromboembolism in all of the inherited thrombophilias. Acute venous thromboembolism is treated with heparin or low-molecular-weight heparin and then warfarin to achieve a target INR of 2.0 to 3.0 for at least 6 months to an indefinite period of time [57]. For ischemic stroke, however, there is only 1 prospective observational study comparing cryptogenic stroke patients with and without thrombophilia, and the use of anticoagulation did not affect outcomes [75].

Oral anticoagulation is therefore not recommended for asymptomatic carriers of these defects, though symptomatic patients may possibly be treated in the same way as that of venous thromboembolism, though anticoagulation may be avoided in the acute phase due to the concerns for hemorrhagic transformation of the infarction [56].

11. Conclusion

Our understanding of various mechanisms for thromboembolism has improved considerably in the past decade. Furthermore, the diagnostic tests have become simpler, cheaper, faster, more reliable, and widely available. Low prevalence and diagnostic yield of various thrombophilic disorders does not support strongly the routine screening of the general population. However, a careful selection of high-risk patients, the timing of testing, and the type of tests often contribute towards appropriate therapeutic decision making [76]. Future research in this field would improve our understanding about various thrombophilic disorders and aid in developing optimal therapeutic and preventive strategies for younger ischemic stroke patients.

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Review Article

Fabry Disease and Early Stroke

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Fabry disease, an X-linked lysosomal storage disorder, results from deficient activity of the enzyme α-galactosidase A. Affected males with the classic phoenotype have acroparaesthesias, hypohidrosis, and corneal opacities in childhood and develop renal failure, cardiac hypertrophy or strokes in the third to fifth decade of life. Some female heterozygotes are asymptomatic, some as severely affected as males. The natural history of Fabry patients includes transitory cerebral ischaemia and strokes, even in very young persons of both genders. The mechanism is partly due to vascular endothelial accumulation of GL-3. White matter lesions on MRI occur. Both males and females can be safely treated with enzyme replacement; and thus screening for Fabry disease of young stroke populations should be considered. There are, however, no hard data of treatment effect on mortality and morbidity. The analyses of results from ongoing studirs will add to the decision on whether or not to screen young stroke patients for Fabry disease. Finally, stroke prophylactic therapy should be used liberally in patients of both genders with verified Fabry disease. This includes primary prevention such as lifestyle counseling, targeting blood pressure, managing atrial fibrillation, diabetes mellitus, hyperlipidaemia, and ASA.

1. Introduction

Fabry disease is a rare X-linked inborn error of glycosphingolipid metabolism resulting from reduced production of lysosomal (α-galactosidase A (α-Gal A)) [1]. The enzymatic deficiency leads to lysosomal accumulation of glycosphingolipids, primarily globotriaosylceramide (GL-3), particularly in vascular endothelial cells throughout the body. Affected males and symptomatic heterozygous females with the classical phenotype have manifestations in childhood or adolescence including angiokeratoma, acroparesthesia, gastrointestinal manifestations, and corneal opacities. With advancing age, the progressive vascular involvement results in renal insufficiency, cardiac disease, and strokes [1]. Patients with Fabry disease have a shortened life expectancy due to the development of a specific vasculopathy. Male patients typically develop renal impairment in their third or fourth decade of life, as well as cardiac hypertrophy and conduction abnormalities. Life expectancy is reduced with a median life expectancy between 50 and 57 years for the male population [2–4]. In females, the disease is more variable, with less involvement of the kidneys, but life span is shortened as well [2, 3, 5]. In female patients, cardiac disease and cerebral white matter lesions dominate and contribute to morbidity and mortality.

Stroke is a common and serious clinical manifestation of Fabry disease. Recent evidence, from papers on natural history of Fabry and postmarketing surveillance databases of Fabry patients treated with enzyme replacement therapy, has indicated that stroke may appear even in young patients [6, 7], and stroke has been seen in some patients as the first disease event [7]. Although patients with Fabry disease are known to experience transient ischaemic attacks (TIAs) and strokes at an early age [8, 9], there are few quantitative markers of disease burden in the central nervous system. Fabry patients frequently exhibit white matter lesions, which can be detected by conventional neuroimaging methods (reviewed in [10]). Recently, magnetic resonance diffusion tensor imaging has been used to quantify these abnormalities [11]. However, the risk of clinical cerebrovascular manifestations, such as stroke and TIAs, is difficult to predict. Thus, because of the various ways by which different studies defined cerebrovascular complications, the stroke incidence and median age at first stroke cannot be readily compared across studies.

The approval of r-hα-GAL-A treatment has subsequently put a pressure on both clinicians and authorities to begin therapy in affected individuals, and therefore a number of questions may never be answered by randomized placebo-controlled trials. Consequently, the only realistic possible sources to obtain future long-term data is to rely on the postmarketing surveillance databases run by the pharmaceutical companies who market the enzyme products, that is, Fabry Outcomes Survey (Shire Inc) and Fabry Registry (Genzyme Inc). The Fabry Registry provides information on the worldwide largest cohort of patients with Fabry disease. Both databases are ongoing, observational databases that track the natural history and outcomes of patients with Fabry disease. Patient and physician participation is voluntary. All patients provide informed consent and may decline to participate or withdraw consent at any time. The treating physicians determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine followup. However, there is a recommended schedule of assessments for the enrolled patients. This schedule encompasses assessments of cerebrovascular and neurological manifestations of the included patients with Fabry disease.

Although these databases provide only surrogate sources of information on the clinical outcome of therapy, the level of evidence is more conclusive than clinical experience with singular cases, and the two databases have already provided useful information on the baseline phenotype in women, information that has not been possible to obtain by other means in this rare disease [8, 12].

2. Mechanisms for Stroke in Patients with Fabry Disease

The understanding of the pathophysiology of the vasculopathy in Fabry disease is limited, as recently reviewed by Rombach et al. [13]. the removal of glycosphingolipid from various cell types has been reported in studies investigating the efficacy of enzyme replacement therapy [14–17]. However, it has become apparent that the removal of stored glycosphingolipid from the endothelial cells, as identified by conventional histological examination, does not prevent the progression of vascular disease in many patients [18, 19]. Thus, the traditional concept that prominent storage in endothelial cells is primarily responsible for the vascular dysfunction cannot be held. Several investigators have attempted to unravel the components that contribute to the general vascular damage. Most studies have been performed in limited patient populations, usually focusing on one aspect of the vascular dysfunction rather than on the complex interplay of all the different factors involved.

The mechanisms underlying the stroke pathogenesis in Fabry disease have thus not been clearly delineated. Progressive accumulation of GL-3 within the endothelium of intracranial blood vessels is thought to play a primary role in the vasculopathy and risk of ischaemic stroke [20]. However, other factors such as the presence of a prothrombotic state, abnormalities in cerebral blood flow velocity, autonomic dysfunction [21], and increased production of reactive oxygen species were also identified as being contributing to the development of stroke in patients with Fabry disease [13, 21–24]. Another different mechanisms contributing to the strokes could be emboli or other consequences of cardiac arrhythmias [7], that are some of the most important and common cardiac manifestations in Fabry patients of both genders [25].

The role of vascular or autonomic dysfunction as a pathogenic mechanism for stroke in Fabry patients by compromising cerebral blood flow velocities and cerebral autoregulation has been elegantly studied by Hilz et al. [21]. They used transcranial Doppler sonography in 22 Fabry patients and 24 controls and assessed the resistance index, pulsatility index, cerebrovascular resistance, spectral powers of oscillations in RR intervals, mean blood pressure, and mean cerebral blood flow velocities. They hypothesized that the decreased cerebral blood flow velocities might result from downstream stenoses of resistance vessels and dilatation of the insonated segment of the middle cerebral artery due to reduced sympathetic tone and vessel wall pathology with decreased elasticity. Furthermore, the augmented gain between blood pressure and cerebral blood flow velocities oscillations indicates an inability to dampen blood pressure fluctuations by cerebral autoregulation. Thus, both reduced cerebral blood flow velocities and impaired cerebral autoregulation are likely to be involved in the increased risk of stroke in patients with Fabry disease.

The normal function of GL-3 is still a mystery, and the potential contribution of secondary metabolic phenomena to the evolution of Fabry disease is unknown [2]. Enzyme replacement therapy with intravenous infusion of r-hα GAL-A has been found to consistently decrease GL-3 levels in plasma and clear lysosomal inclusions from vascular endothelial cells. Whether this occurs to the same extent in brain vasculature is unknown. The effects of enzyme therapy on other tissues are not obvious, and therefore recommendations for the treatment include commencement early in the course of the disease in order to be optimally effective in preventing initial or progressive organ failure and to establish which complications of the disease that do not respond to intravenously delivered enzyme [20].

The conclusion from the review by Rombach et al. [13] was that the smooth muscle cell is the primary cell involved in the vasculopathy of Fabry disease and that in an early stage of Fabry vasculopathy, angiotensin II production becomes upregulated. The proliferation of smooth muscle cells and GL-3 storage results in a higher intima-media thickness. Increased reactive oxygen species production as well as enhanced nitric oxide production may result in different findings with respect to endothelial activation markers, which can be severely enhanced in the context of other vascular risk factors. Selective angiotensin I receptor blockade may be an interesting option for optimal nitric-oxide-mediated vasodilatation and should be explored as adjunctive therapy [13]. Therefore, further studies not only on both the uptake of α-GAL A in brain vasculature and tissue, but also on the vasculopathy are needed in order to

optimise the management of the stroke risk and consequent treatment in patients with Fabry disease.

3. Cerebral Imaging in Fabry Disease Patients

The cerebral involvement in Fabry disease can be visualized on conventional magnetic resonance imaging (MRI) as multiple lesions located in the deep white matter and in the subcortical grey matter of both hemispheres. The cerebral lesion burden visible on these imaging methods increases with age and can precede the onset of neurological symptoms [26]. Females who are carriers of the disease might show MRI abnormalities similar to those of affected males [27, 28]. More recent studies, using proton emission tomography [29] and proton MRI spectroscopy [30], have suggested that metabolic abnormalities can be found even in the absence of cerebral lesions in patients with Fabry disease. This was substantiated [31] in 8 patients (4 males) with Fabry disease by the use of brain proton MRI/MR spectroscopic imaging examinations to obtain measures of total brain volumes, total brain lesion volumes, and magnetization transfer ratios in white matter and central brain levels of N-acetylaspartate (NAA) to creatine (Cr). The authors concluded that subtle structural and metabolic tissue damage could extend beyond white matter in subjects with Fabry disease. A diffuse decrease in brain NAA/Cr could occur in Fabry subjects in relation to the degree of their CNS involvement and its evolution over time.

Moore et al. [32] studied neuroradiologic records of 104 hemizygous patients with Fabry disease for the presence of hyperintensity on the T1-weighted images. Additional CT, gradient-echo (T2*-weighted), and fat-suppression MR studies were reviewed to characterize further the T1 abnormality in selected patients. Overall, 22 patients (23%) demonstrated pulvinar hyperintensity on T1-weighted images; the frequency increased with age to over 30% by age 50 years. They concluded that hyperintensity in the pulvinar on T1-weighted images is a common finding in Fabry disease, likely reflecting the presence of calcification, and exclusive involvement of the pulvinar may be distinctively characteristic to Fabry disease. Increased cerebral blood flow in the posterior circulation, particularly the thalamus, suggested that the dystrophic calcification was secondary to cerebral hyperperfusion and selective vulnerability of the pulvinar and adjacent thalamic nuclei. Thus, according to the authors, the finding of isolated pulvinar hyperintensity on T1-weighted images should suggest Fabry disease, particularly when seen in conjunction with other nonspecific neuroradiologic manifestations of the disease.

This finding was later supported by Burlina et al. [33] who investigated the pulvinar sign and its relationship with other clinical findings in a total of 36 patients (16 males, 20 females) from 14 families. The pulvinar sign was found in 5 male patients but not in any of the investigated female patients. Seven patients had had at least one stroke (territorial or lacunar), but there was no correlation between the occurrence of stroke and the pulvinar sign. All patients with the pulvinar sign had hypertrophic cardiomyopathy. Four patients out of five with the pulvinar sign were on dialysis or had had a kidney transplantation. They suggested that the pulvinar sign is a highly specific sign of Fabry disease, found in male patients with cardiac signs and severe kidney involvement, and very recently, they also demonstrated the pulvinar sign in a female Fabry patient (Burlina, personal communication).

The importance of the pulvinar sign was recently challenged by Fellgiebel et al. [34], who could not find similar results in a comprehensive study on the diagnostic utility of different MRI and MR angiography measures in Fabry disease. They investigated 25 clinically affected patients with Fabry disease (age 36.5 ± 11.0 years) and 20 age-matched controls by structural MRI, MR angiography, and diffusion tensor imaging. They determined individual white matter lesion volumes, global mean diffusivity, and mean cerebral artery diameters. Using receiver-operating characteristic analyses, they were able to demonstrate that enlarged diameters of the middle cerebral artery, posterior cerebral artery, carotid artery, and basilar artery significantly separated patients with Fabry disease from controls. A total of 87% of the individuals were correctly classified by basilar artery diameters (sensitivity 95%, specificity 83%), while neither white matter lesion volumes nor global mean diffusivity values could significantly separate patients from controls. In their study, basilar artery diameters were superior to all other MR measures for separating patients with Fabry disease from controls with an accuracy of 87%, and they therefore recommended that future studies should adopt basilar artery measurements for early detection and monitoring of brain involvement in Fabry disease. All in all, the latter could speak in favour of performing further investigations to reveal if the dilated vasculopathy in Fabry disease could be a screening marker to detect Fabry disease in a cohort of other cerebrovascular diseases, especially in cryptogenic stroke in young individuals.

4. Prevalence of Stroke in Fabry Patients

Several studies have estimated the incidence of stroke in various small cohorts of patients with Fabry disease. Vedder et al. [2] reported that 12 of 25 males (48%) and 13 of 41 females (32%) had experienced a cerebrovascular accident or lacunar stroke, at a median age of 46 and 52 years, respectively. Gupta et al. [35] reported that 4 of 54 female Fabry patients (7%) had experienced strokes, at a median age of 51 years, and Mehta et al. [26] found that 24 of 216 males (11%) and 27 of 172 females (16%) had experienced either a TIA or a stroke. Grewal et al. reviewed various types of imaging data and reported that 8 of 33 Fabry patients (24%) had experienced strokes at a median age as low as 26.5 years [36].

From the FOS Registry, the overall prevalence of ischaemic stroke or TIAs was 13% [37], events tending to occur at an earlier age with 12 times higher number of ischaemic strokes in the male 25–44 years age group compared to what could be expected in the general population. A significantly higher proportion of patients with Fabry disease, who had

a history of cerebrovascular complications, had valvular heart disease, left ventricular hypertrophy, arrhythmias, or hypertension compared to those with no history of such complications. Not surprisingly, Sims et al. [7] found in the Fabry Registry that patients who had strokes were much more likely to have reported a medical history of various risk factors for strokes, as compared to other patients. Compared to nonstroke patients, those who had strokes were more likely to report TIAs (36.2% versus 5.4%), arrhythmias (32.6% versus 12.7%), or hypertension (52.9% versus 20.5%). Furthermore, similar percentages of male and female stroke patients reported a history of TIAs. Male stroke patients were more likely than females to have reported a history of arrhythmias. A greater percentage of females who had strokes reported a history of hypertension (32 of 52, 61.5%), as compared to males (41 of 86, 47.7%). Among the two subpopulations of patients with strokes at <30 years (all of whom had ischaemic strokes) and those with haemorrhagic strokes, respectively, the proportion of patients with a history of TIAs or arrhythmias was generally similar to that observed in the overall population of Fabry stroke patients. Finally, patients with hemorrhagic strokes were more likely to have reported a history of hypertension (11 of 16, 68.9%) than patients with a stroke below 30 years of age (8 of 30, 26.7%), and overall, 73 of 138 Fabry stroke patients (52.9%) had a history of hypertension.

Thus, the presence of hypertension should be a warning sign for future strokes in young Fabry patients and be treated vigorously with antihypertensive drugs, antiplatelet drugs, and statins if appropriate, in order to prevent strokes. Another warning sign is cardiac affection, in particular arrhythmia as mentioned above.

5. Prevalence of Fabry Disease among Young Patients with Stroke

A screening study of 721 young German patients (age 18 to 55) who had strokes of unknown aetiology reported that 4.9% of males and 2.4% of females had Fabry disease [38]. Based on these findings, it was estimated that 1% to 2% of all stroke patients within this age range could have Fabry disease [28]. Others have suggested that this percentage may be higher [39] or lower [40]. A very recent study [41] was published from Portugal, where during one year, all patients aged 18 to 55 years with first-ever stroke, who were admitted into any of 12 neurology hospital departments, were prospectively enrolled (n = 625) and assessed for presence of a *GLA* mutation. Alpha-galactosidase activity was further assayed in all patients with *GLA* mutations. Four hundred ninety-three patients (mean age, 45.4 years; 61% male) underwent genetic analyses: 364 with ischaemic stroke, 89 with intracerebral hemorrhage, 26 with subarachnoid hemorrhage, and 14 with cerebral venous thrombosis. Twelve patients had missense *GLA* mutations: 9 with ischaemic stroke, including 5 patients with an identified cause of stroke (2 with cardiac embolism, 2 with small vessel disease, and one with other cause), 2 with intracerebral haemorrhage, and one with cerebral venous thrombosis. Leukocyte α-galactosidase activity was subnormal in the hemizygous males and subnormal or lownormal in the heterozygous females. The estimated prevalence of missense *GLA* mutations was thus 2.4% (95% CI, 1.3% to 4.1%).

The Stroke Prevention in Young Men Study enrolled men (15 to 49 years) with first ischaemic stroke in the Baltimore-Washington area in 2004 to 2007 [42]. Frozen plasma samples were assayed for α-Gal A activity, and DNA from patients with consistently low plasma α-Gal A activities was sequenced. In the study sample of 558 men (42% African-American; median age 44 years), stroke was cryptogenic in 154 (40% African-American). Ten patients had low plasma α-Gal A activities, but DNA sequencing identified alterations in the α-Gal A gene in only 2 of these patients. Their study suggested a low yield of screening for Fabry disease in young men with an initial ischaemic stroke regardless of aetiology. The yield of screening in recurrent cryptogenic ischaemic stroke in young adults still remains unclear. There is therefore a need for a large sample size replication of the findings of the German study [28], which suggested a prevalence of 24.3% for unrecognized Fabry disease among men with recurrent cryptogenic stroke. Because Fabry disease is a treatable condition and the diagnosis has implications for other family members, the decision to screen for Fabry disease should be made on an individual basis. A better understanding of the natural history of cerebrovascular manifestations of Fabry disease may provide valuable information about which patients may be at greatest risk for stroke. Such information can also raise the awareness of Fabry disease within the broader medical community and highlight the importance of improved monitoring and management options. Despite a low diagnostic yield, screening for *GLA* mutations should probably be considered in different types of stroke. Restricting investigation to patients with cryptogenic stroke may underestimate the true prevalence of Fabry disease in young patients with stroke.

6. The Special Case of Females with Fabry

In recent years, the involvement in heterozygous females has been more extensively documented [1, 5, 8, 9, 12, 43]. Heterozygotes for the classic phenotype of Fabry disease can be asymptomatic throughout life or have as severe manifestations as affected males [1, 5, 8, 9, 12, 42–44]. Most mutation-confirmed heterozygotes have the corneal opacities, which are observed by slit-lamp microscopy and are a useful diagnostic finding. About 53 to 70% of heterozygous females will have episodic neuropathic pain as reported in several studies [5, 8, 12, 42–44]. So the findings of pain in the extremities, which is exacerbated by fever, exercise, and stress, together with the typical eye changes are significant diagnostic findings. Other findings in Fabry heterozygotes include sparse angiokeratoma, hypohidrosis, gastrointestinal pain and cramping, and diarrhea. Interestingly, female Fabry patients were shown to have a higher prevalence of strokes or TIAs of 16% compared to 11% in males in the FOS registry

natural history paper [3], perhaps because fewer of them die from renal failure.

7. Diagnosing Fabry Disease

The diagnosis of Fabry disease in males is reliably made by demonstrating the α-Gal A enzymatic deficiency [45]. However, in heterozygous females, the α-Gal A enzymatic activity can range from very low to high normal values due to random X-inactivation [45–47]. To accurately identify heterozygote, the family's mutation must be identified. Suspect heterozygotes with no family history of Fabry disease require α-Gal A gene sequencing for diagnostic confirmation. In a few cases, this is also difficult if the patient does not display a mutation on sequencing, as in case of large deletions (Feldt-Rasmussen et al., unpublished observation). In such cases, eye examination, neurological assessment, and kidney biopsy can be of importance.

8. Screening for Fabry Disease?

The frequency of the classic phenotype has been estimated at ~1 in 40,000 males [1], and recent newborn screening studies have found the incidence of classically affected males to be ~1 in 24,620 by screening over 147,700 consecutive newborn males in Taiwan [48, 49] and ~1 in 37,000 newborn males screened in Italy [50]. In the latter study, 12 male neonates had deficient α-Gal A activities and specific mutations, revealing a surprisingly high Fabry disease incidence of one in 100 males. Of the 12 neonates with α-Gal A deficiency, 11 had mutations predicting the later-onset phenotype for an 11:1 ratio of later-onset/classic phenotypes [50]. No similar studies have been done in females. These figures have given rise to a discussion as to whether or not newborn screening for Fabry males should be done due to availability of a safe treatment option and probably an efficient one if started early in life to prevent progressive irreversible tissue and organ damage.

While waiting for such decision, it may rather be worthwhile for clinicians to consider screening of specific patient populations for Fabry disease [51]. These considerations should include young people with stroke or TIAs at least those without other known aetiology. It seems that approximately 1-2% of young stroke patients are demonstrated with Fabry disease. The recruitment to the sifap1 (stroke in young Fabry patients) study provides the largest prospective case series of young stroke patients reported so far. Results are expected to provide novel information on the prevalence of Fabry in the population as well as characteristics of the patients. The further analyses of results of this study will therefore possibly add to the decision on whether or not to screen young stroke patients for Fabry disease [52].

However, screening for Fabry disease among young stroke patients would only be meaningful if it can be verified that subsequent enzyme replacement or other therapy can prevent further stroke episodes. Currently, such information is not available from any of the published studies on treatment efficacy [53–55].

9. Treatment Options

As mentioned previously, ERT replacement in Fabry disease is now a treatment option in most countries [18, 53, 54], although a production limitation in Fabrazyme has been known for a while, an issue which is not yet solved. One of the drawbacks of the treatment is the fact that it needs intravenous infusion, another one is the price. Whether or not to start treatment early, particularly in males, to prevent progression of organ manifestations or in some cases to wait and see is still not agreed upon internationally. One of the difficulties in obtaining proper evidence is the rarity of the disease and the relatively short treatment and follow-up period in the existing trials.

Apart from that, trials are going on concerning the use of chaperone therapy, which is oral, but only effective in certain genotypes. It may, however, also prove efficient in patients with other genotypes as adjunctive therapy to ERT, and gene therapy is another imminent therapy ready for clinical testing [52]. In addition, it is becoming increasingly important to use also other treatments, for example, primary stroke prevention including lifestyle counseling and blood pressure and lipid lowering drugs, but additionally ACE inhibitors, angiotensin I and II receptor antagonists [13], and finally anti-inflammatory agents [24] and vitamin D receptor agents [56] may prove effective in slowing down the progression of the vasculopathy and not only be used for renal protection.

The evidence for providing firm algorithms for initiation of therapy in males and females, respectively, is not available, and they are therefore currently arbitrary and diverging between countries and treatment centers.

10. Conclusion

Fewer patients than previously with Fabry disease die from renal failure mainly due not only to a better general renal care but also to ERT, and therefore more of them live to experience other complications such as cardiac arrhythmias, left ventricular hypertrophy, hypertrophic cardiomyopathy, and stroke occurring with advancing age in both genders [1, 5, 9, 12, 44, 57]. Thus, pediatricians, neurologists, cardiologists, and internists should be aware of the disease manifestations in children, adolescents, and young adults, particularly because the earlier the diagnosis is suspected and confirmed and the earlier treatment, including ERT is initiated, the more effective is the therapy [18, 53, 56, 58]. Thus, it is important to add primary stroke prevention including lifestyle counseling, blood pressure and lipid-lowering drugs, and additionally ACE inhibitors, angiotensin I and II receptor antagonists [13], in order to slow down the progression of the vasculopathy and not only be used for renal protection. Targeted screening for Fabry disease among young individuals with stroke seems to disclose unrecognized cases and may therefore very well be recommended as routine in the future. For this to be verified, the results of the sifap study is much awaited [52].

Disclosures

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Review Article

Stroke in Young in India

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Stroke in young has special significance in developing countries. This is so because some etiologies like cardioembolic infections are more common than in developed countries, and the affection of economically productive group adds further to the overall disease burden. The paper discusses the burden of stroke in young and its implications in a developing country like India along with an approach to identifying different causes that are known to occur in this age group.

1. Introduction

Stroke in young poses a major health problem. WHO defines stroke as an event caused by the interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue [1]. The most common symptom of a stroke is sudden weakness or numbness of the face, arm, or leg, most often on one side of the body, occurring in 90% of the strokes [2]. Other symptoms include confusion; difficulty speaking or understanding speech; difficulty seeing with one or both eyes; difficulty walking, dizziness, and loss of balance or coordination; severe headache with no known cause; fainting or unconsciousness. The effects of a stroke depend on which part of the brain is injured and how severely it is affected. A very severe stroke can cause sudden death.

Globally, stroke is the third commonest cause of mortality [3] and the fourth leading cause of disease burden [4]. It makes an important contribution to morbidity, mortality, and disability in developed as well as developing countries. In recent years, there has been increasing economic and demographic development in developing countries resulting in a shift from diseases caused by poverty toward chronic, noncommunicable, lifestyle-related diseases [5]. This happening in the younger age group adds to the social burden, and as such these patients merit special attention in diagnostic, therapeutic, and preventive care. It leaves the patients with residual disabilities like physical dependence, cognitive decline, depression, and seizures. The review discusses the burden of stroke in young and its implications in a developing country like India along with approach to identifying different causes that are known to occur in this age group.

2. What Is So Special about Stroke Occurring in Young?

Age wise segregation of cases in stroke is important due to several reasons. Age has been shown to have a strong association with the incidence of stroke. While the peak age of stroke occurrence is 55–65 years [6], events occurring at a younger age assume importance in being occurring in a productive age group and having a different set of causes which have to be looked into apart from the conventional ones (Tables 1, 2, and 3). They are also different from childhood strokes which have been classified as those occurring in less than fifteen years of age.

Cerebral venous thrombosis and rheumatic heart disease are the leading causes of stroke in the young in India [18]. Tubercular meningitis leading to arteritis or autoimmune angiitis are also important stroke risk factors in young [19, 20]. Other Indian studies that have reported risk factors

Table 1: Causes of stroke in young-Ischemic.

Cardioembolic		Vasculitis		Others	
Common	Less common	Common	Less common	Common	Less common
Rheumatic heart disease	Patent foramen ovale	Infections	Polyarteritis nodosa	Atheroscler otic vascular disease	MELAS
Prosthetic valve	Myxoma and other tumors	Antiphospholipid antibody syndrome [7, 8]	Takayasu's arteritis	Arterial dissection	Prothrombotic states
Atrial fibrillation	Acute myocardial infarction	Systemic lupus erythematosus	Wegener's granulomatosis		Sickle cell disorder
Bacterial endocarditis	Mitral valve prolapsed				Protein C/S deficiency [9]
	Atrial and ventricular septal defects				Fibromuscular dysplasia [10]
					Polycythemia vera
					Antithrombin III deficiency [11]
					Paroxysmal
					Nocturnal Hemoglobinuria
					CADASIL and CARASIL [12]
					Fabry's disease
					Familial hypercholesterolemia [13]
					Thrombophilia [14]
					Hyperhomocytienemia [15]
					Migraine [16]
					Hyperthyroidism [17]

Table 2: Causes of stroke in young-Hemorrhagic.

Common	Less common
Arterio venous malformations	Moya moya syndrome
Saccular aneurysms	Arteritis (septic or mycotic)
Bleeding disorders	Intracerebral tumors
Anticoagulants	Substance abuse like cocaine

Table 3: Causes of stroke in young-Venous.

Common	Less common
Pregnancy	Prothrombotic states
Postpartum	Red blood cell disorders
Dehydration	Bechet's disease
Oral contraceptive	Connective tissue disease
Other prothrombotic states	

among the young include coagulopathy, elevated lipoprotein (a), homocysteine, and elevated anticardiolipin antibodies [21–25]. Some Indian studies have reported interesting causes of stroke, like viper envenomation, and also suggested mechanisms like squatting whilst on the toilet as an important triggering factor for stroke in Indians, by raising the blood pressure [26, 27]. A recent study from Pakistan [28] in 50 young stroke patients also found infective meningitis including tuberculosis meningitis and bacterial meningitis as the leading cause of stroke (34%). The second most common cause was cardioembolism (20%) comprising Valvular heart diseases (14%), Cardiomyopathies (4%), and atrial myxoma (2%). Hypertension was found in 14% cases. Pregnancy-related causes (including Pregnancy-induced hypertension and puerperal sepsis) were 12%. Systemic lupus erythematous and nephritic syndrome was 4% each. Various causes which constitute 4% or less were grouped together as miscellaneous and they include hyperhomocysteinaemia and hyperlipidaemias.

While the data from several studies worldwide in young stroke population have realized that conventional risk factors for all strokes still are most prevailing in young strokes as well and while more than a decade-old Baltimore Washington [29] study found cardiac embolism (31.1%), hematologic and other (19.8%) small vessel (lacunar) disease (19.8%), nonatherosclerotic vasculopathy (11.3%), illicit drug use (9.4%), oral contraceptive use (5.2%), large artery atherosclerotic disease (3.8%), and migraine (1.4%) in their 428 young ischemic stroke patients, a later case series from Rome [30] confirmed smoking in 56% of patients, hypertension in 23%, dyslipidemia in 15%, migraine in 26%, and diabetes mellitus in 2% in 394 young ischemic stroke patients. Diabetes, hypertension, heart disease, current smoking, and long-term heavy alcohol consumption are major risk factors for stroke in young adults as in elder population [31].

Data on primary intracerebral hemorrhage (ICH) in young is scarce in India. Mehndiratta et al. [32] found

Table 4: Studies on stroke conducted in India.

Study	Setting	Results	Comments
Abraham et al. [48], 1970, Vellore	Rural and urban, community-based, all stroke prevalence	Prevalence: 56.9/100,000	25% of the stroke patients were below the age of 40 years.
Bansal et al. [49], 1975, Rohtak	Urban, community-based study, all stroke prevalence	Population: 79,046 Prevalence: 44/100,000	
GourieDevi et al. [50], 1987, Karnataka	Rural, community based study, all stroke prevalence	Population: 57,660 Prevalence: 52/100,000	
Razdan et al. [37], 1989, Kashmir	Rural, community based study, all stroke prevalence	Population: 63,645 Prevalence: 143/100,000	10.9% of age group 15–39 years (prevalence rate 41/100,000)
Dalal et al. [51], 1989, Mumbai	Urban, hospital based study, 1963–1968 and 1978–1982	Case fatality rate changed from 32 to 12% over this period	Studied only young stroke
Nayak et al. [52], 1997, Kerela	Hospital based, retrospective, 15–45 years of age	177 patients from 1988 to 1994.	Studied clinical features and risk factors in young
Mumbai stroke registry [53]	Population based, urban, Jan to Dec 2005, all age groups	Population: 1, 86,000 Crude incidence rate: 148/100, 000	77% ischemic, hypertension in 25.3%
JIPMER stroke registry [53]	Hospital based, 2005, all age groups	105 in six months	36.2% patients <40 years of age
Trivendrum stroke registry [53]	Population-based, urban and rural, 2005, all age groups	Population: 925,867 Crude incidence rate: 97.9/100,000 urban, 81.3/100,000 rural	Stroke in young 4.3%
Das et al. [36], 2007, Kolkata	Population based, urban, 2003–2005, all age groups	Population: 52 377 Annual incidence rate (AIR)123/100,000/year	AIR in <40 years 4.22/100,000/year
Lipska et al. [41], 2007, Kerala	Case control study, 15–45 years, ischemic stroke	214 cases, 195 controls,	Metabolic syndrome and smoking-associated ischemic stroke in young
Dalal et al. [54], 2008, Mumbai	Population based study, all stroke types, Jan 2005–Dec 2006	Population: 156,861 Annual incidence 145/100,000 in >25 years of age	
Nagaraja et al. [55], 2009, Bangalore	Hospital based, all stroke types	1174 patients	18% less than 40 years of age
S. Kaul et al. [56], 2009, Hyderabad	Hospital based, 2001–2005, all stroke types	Annual incidence of stroke 145/100,000	10–15% of stroke in young

ICH in their 18 (14.2%) of 127 young stroke patients. Most common etiology was ruptured aneurysm (44.4%) followed by ruptured Arteriovenous Malformations (AVM) and hypertension (22.2% each) and eclampsia in 11.1%. Causes of ICH in young in other parts of the world have yielded variable results. The Hemorrhagic Stroke Project (HSP) [33] had 217 out of 1714 patients with primary ICH. The independent risk factors found were hypertension, diabetes, menopause, current cigarette smoking, alcoholic drinks > or =2/day, caffeinated drinks > or =5/day, and caffeine in drugs.

3. Why Its Identification Is Important in Developing Countries Like India?

By 2050, it is anticipated that 80% of stroke events will occur in people living in developing regions of the world [34, 35]. Interestingly, the Kolkata study sample consisted of mainly younger people (>80% were aged <60 years) who are active in the workforce. When stroke occurs in the main income earner in the household, there may be enormous consequences for the welfare of the family [36]. Indian studies have shown that about 10% to 15% of strokes occur in people below the age of 40 years [37]. It is believed that the average age of patients with stroke in developing countries is 15 years younger than that in developed countries [38, 39]. In India, nearly one-fifth of patients with first ever strokes admitted to hospitals are aged <40 years [40]. However, in the Trivandrum Stroke Registry [41], only 3.8% of incident strokes occurred in people aged <40 years, 9.5% aged <50 years, and 18.1% aged <55 years; these data are very similar to that in another community-based study from northeastern India [36] and those from developed countries [42]. The reported occurrence of stroke in the young, therefore, appears to be largely an artifact related to hospital-based case ascertainment [43].

4. What Information Do We Have So Far about Stroke in Young in India?

Literature is available suggesting that risk of coronary artery disease (CAD) is higher in Indians especially in the young population [44, 45]. While we know that the risk factors for stroke and coronary artery disease are same, recent studies show that the risk of stroke may be comparable to other populations [46, 47]. A number of well-designed prevalence studies of stroke were carried out in hospital and community in various parts of the country in the past and recently, which have not only looked at risk factors but also focused upon the young stroke population [41]. Table 4 shows the studies conducted in various parts of India.

While these studies do reflect the enthusiasm of neurologists and stroke specialists in India to acquire knowledge about stroke in young and stroke at large, the wider community-based study is still wanting. The conventional risk factors still play an important role in causation of stroke in young [41], and genetic causation studies have evaluated MTHFR polymorphisms [57, 58], alpha1 antichymotrypsin [59], −344C/T aldosterone synthase (CYP11B2) [60], Phosphodiesterase 4D (PDE4D) [61], Prothrombin G20210A [62], eNOS [63], and Angiotensin-converting enzyme [64] gene mutation in Indian stroke patients. These might assume a greater importance in patients with family history of stroke and young patients.

5. What Information Is Still Needed from Studies?

More robust evidence is still required to dispel the myth that young Indians are more susceptible to stroke [65]. The areas which require more information and insights are intracerebral hemorrhage, cerebral venous sinus thrombosis in young apart from ischemic stroke which forms the majority and also the focus of stroke studies. Not only this, the less conventional risk factors like migraine [16] and patent foramen ovale [66], emerging factors like arterial dissection [67], and established but less studied causes like peripartum [68, 69] and infection [70, 71] need greater evidence from India as well.

6. Limitations of the Review

As mentioned, definite answers are still required to answer whether young Indians have increased susceptibility to stroke. Most of the studies have a heterogeneous population are hospital-based data with admission and selection bias. Future studies should aim for a multicentric well-defined prospective evaluation on representative population samples to acquire robust answers.

7. Conclusion

While it might turn out through more evidence that stroke in young Indians might not be very different from that in other countries, the implications in a developing country are many. Preventive measures could aid immensely in bringing down costs and emotional burden on the family. But this would need prior and correct identification of burden and risk factors prevailing in the community. Of added interest would be risk factors, both acquired and genetic, which are unique to this geographic area.

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Clinical Study

Comparison between Ischemic Stroke Patients <50 Years and ≥50 Years Admitted to a Single Centre: The Bergen Stroke Study

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Introduction. Young adults are likely to differ from old patients concerning cerebral infarction. *Methods*. We compared characteristics of patients aged under and above 50 years, admitted to the Department of Neurology with cerebral infarction between 2006 and 2009, based on prospective registration. Investigation followed one common protocol for both groups. *Results and Discussion*. One hundred patients (8.2%) were <50 years old, and the proportion of males was higher in this group (72% versus 55.8%, $P = .002$). Young stroke patients are more often current smokers (44.1% versus 23.6%, $P < .001$). Common causes for stroke in the young were cervical artery dissection (18% versus 0.6%, $P < .001$) and cardiac embolism due to disorders other than atrial arrhythmias (18% versus 5.5%, $P < .001$). Among the old, atrial fibrillation and flutter dominated (29.1% versus 5%, $P < .001$). Stroke severity and location did not differ. Old patients more often suffered from pneumonia (10.6% versus 2%, $P < .003$) and urinary tract infection (14.6% versus 2%, $P = .001$). *Conclusions*. Males dominate, and current smoking is more common in the young. Cervical artery dissection and nonarrhythmic heart disorders are frequent causes among young patients, while traditional risk factors dominate the old. Stroke severity is similar, but old patients seem more exposed for infectious complications.

1. Introduction

Cerebral infarction may have serious consequences for patients in their prime of life and influence on choice of education, vocation, and family planning. More knowledge regarding pathophysiological mechanisms and prognosis is urgently needed. Several studies have shown that risk factors and etiology differ between young and old patients. Migraine is frequently reported among young adults [1–5] whereas traditional risk factors such as hypertension and dyslipidemia are usually less frequent. Large-artery atherosclerosis is rare [3, 6] whereas cervical artery dissection is a common cause of cerebral infarction among young adults [2, 4, 6, 7]. Cardioembolic stroke is in the majority of cases caused by cardiac conditions with low to uncertain embolic risk, such as patent foramen ovale and atrial septal aneurysm [4, 8]. Methodological differences may obscure comparison between different centres. There has not been many comparisons between young and old patients treated and investigated in a single centre.

The aim of this study was to compare characteristics of cerebral infarction between young and old patients undergoing treatment and investigations according to one common protocol in a single centre.

2. Methods

2.1. Patients. All consecutive patients with acute cerebral infarction (the index stroke) admitted to the Stroke Unit, Department of Neurology, Haukeland University Hospital, Bergen, Norway, between February 2006 and March 2009, were prospectively registered in a database (The Bergen Stroke Registry). Cerebral infarction was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient

Table 1: Demography of young and old patients with cerebral infarction, based on patient history recorded on admission.

	Young patients ($n = 100$)	Old patients ($n = 1117$)	P
Age (mean)	40.8 (SD 7.6)	73.4 (SD 11.8)	
Females	28 (28.0)	494 (44.2)	.002
Males	72 (72.0)	623 (55.8)	
Married	62 (62.6)	631 (57.8)	.40
Employed	81 (85.3)	236 (22.0)	<.001
Prior cerebral infarction	4 (4.0)	179 (16.2)	<.001
Myocardial infarction	4 (4.0)	155 (13.9)	.003
Angina pectoris	4 (4.0)	160 (14.4)	.002
Mechanic aortic valve	5 (5.0)	21 (1.9)	.05
Peripheral artery disease	3 (3.0)	89 (8.1)	.08
Hypertension	27 (27.0)	598 (53.8)	<.001
Paroxysmal atrial fibrillation	2 (2.0)	104 (9.4)	.009
Chronic atrial fibrillation	0 (0.0)	105 (9.46)	<.001
Diabetes mellitus	10 (10.0)	163 (14.8)	.23
Migraine	14 (17.7)	149 (19.4)	.88
Prior depression	15 (18.3)	185 (22.8)	.41
Current smoking	41 (44.1)	249 (23.6)	<.001
Never smoking	38 (40.9)	439 (41.6)	
Quitted smoking	14 (15.1)	368 (34.9)	

Data are expressed as mean or n (%). SD: standard deviation.

ischemic attacks where CT or MRI showed infarctions related to the clinical findings [9]. The patients were dichotomized into two groups: <50 years (young patients) and ≥50 years (old patients).

All patients had CT or MRI. Isolated acute ischemic lesions on CT or MRI were defined as lacunar infarctions (LI) if <1.5 cm and located as subcortical or in the brainstem. All other acute ischemic lesions were defined as nonlacunar infarction (NLI). NLI comprised subcortical and brainstem infarction ≥1.5 cm, cortical infarction, mixed cortical and subcortical infarction, and cerebellar infarction. Leukoaraiosis was defined as the presence of hypodense periventricular abnormalities on MRI (T2).

The National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity. NIHSS measurements were performed on admittance and 7 days after stroke onset or earlier if the patient was discharged earlier (NIHSS7). Likewise, modified Rankin Scale (mRS) score and Barthel Index (BI) were obtained 7 days after stroke onset or earlier if the patient was discharged earlier. Blood pressure, body temperature, and serum glucose on admittance were registered. Diagnostic workup included ECG, Holter monitoring, echocardiography, and duplex sonography of neck vessels. Holter monitoring was performed among patients with embolic stroke and no known atrial fibrillation.

Risk factors including hypertension, smoking, diabetes mellitus, myocardial infarction, angina pectoris, peripheral artery disease, and atrial fibrillation were registered on admittance. Hypertension was defined as prior use of antihypertensive medication. Current smoking was defined as smoking at least one cigarette per day. Diabetes mellitus was considered present if the patient was on glucose-lowering diet or medication. Angina pectoris, myocardial infarction, and peripheral artery disease were considered present if diagnosed by a physician any time before stroke onset. Atrial fibrillation required ECG confirmation any time prior to stroke onset. A history of prior cerebral infarction was registered. Old infarctions on CT or MRI were registered, including both clinically silent and symptomatic infarctions. Etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment classification (TOAST) [10], performed by a neurologist (HN). Clinical classification was based on the Oxfordshire Community Stroke Project (OCSP) scale which includes lacunar syndrome (LACS), partial anterior circulation syndrome (PACS), total anterior circulation syndrome (TACS), and posterior circulation syndrome (POCS) [11].

ICA stenosis was defined as a percentage of area reduction in neurosonology, graded from 30–49%, 50–69%, 70–99%, to occlusion (Table 5). Calculation was performed by Phillips software, integrated in IU 22.

Complications including pneumonia, urinary tract infection, and seizures were registered.

2.2. Statistics. Chi-square test, Fisher's exact test, and student's t-test were performed when appropriate. Logistic regression was performed to analyse the effect of the two age groups (young or old patients) on outcome day 7 adjusting for sex

Table 2: Characteristics of cerebral infarction in young and old patients.

	Young patients ($n = 100$)	Old patients ($n = 1117$)	P
Classification			
LACS	20 (20.2)	281 (25.2)	.33
TACS	17 (17.2)	184 (16.5)	
PACS	38 (38.4)	458 (41.0)	
POCS	24 (24.2)	193 (17.3)	
Parameters on admission			
Systolic blood pressure (mmHg)	155	168	<.001
Body temperature (centigrade)	36.8	36.6	.47
Serum glucose (mmol/L)	6.5	6.8	.26
Scores			
On admission			
NIHSS	5.7	6.3	.45
At day 7			
NIHSS	4.4	4.9	.50
mRS 0–2	70 (70.0)	677 (60.6)	.11
mRS 3–5	26 (26.0)	408 (36.5)	
mRS 6	4 (4.0)	32 (2.9)	
Barthel Index (mean)	86.9	78.1	.01
Complications			
Nasogastric feeding	6 (6.0)	132 (11.8)	.10
Pneumonia	2 (2.0)	118 (10.6)	.003
Urinary tract infection	2 (2.0)	163 (14.6)	<.001
Seizures	4 (4.0)	40 (3.6)	.78
Etiology			
Large-artery atherosclerosis	3 (3.0)	139 (12.4)	.003
Cardiac embolism	21 (21.0)	328 (29.4)	.08
Small vessel disease	14 (14.0)	170 (15.2)	.88
Other causes	23 (23.0)	10 (0.9)	<.001
Unknown	39 (39.0)	468 (41.9)	.4

Data are expressed as mean or n (%).
NIHSS, The National Institute of Health Stroke Scale; LACS, lacunar stroke syndrome; TACS, total anterior circulation stroke syndrome; PACS, partial anterior circulation stroke syndrome; POCS, posterior circulation stroke syndrome; mRS, modified Rankin Scale.

and NIHSS score on admission. mRS score 0–2 versus 3–6 was used as dependent variable. STATA 11.0 was used for analysis.

3. Results

In total, 1217 patients were included. One hundred (8.2%) were <50 years (range: 18–49 years) and 1117 (91.2%) were ≥50 years (range: 50–98 years). The proportion of males was higher among young patients: 72% versus 55.8% (Table 1).

The following risk factors were more frequent among old patients: myocardial infarction, angina pectoris, hypertension, atrial fibrillation, and prior cerebral infarction. Mechanic aortic valves and current smoking were more frequent among young patients (Table 1).

There was no difference concerning NIHSS score on admittance or OCSP classification. Systolic blood pressure was lower among young patients on admittance: 155 mmHg versus 168 mmHg (Table 2).

Outcome on day 7 (or on discharge if discharged earlier) was similar regarding mRS score and NIHSS score, whereas mean Barthel Index was higher among young patients: 86.9 versus 78.1. Figure 1 shows mRS scores according to age. The mortality rates did not differ significantly on day 7, respectively, on discharge ($P = .5$). Logistic regression showed that mRS score 0–2 versus 3–6 was associated with NIHSS score on admittance (odds ratio (OR) 1.29 (95% confidence interval (CI) 1.25–1.34), $P < .001$), but not with sex (OR .76 (95%CI .57–1.01), $P = .064$) or young versus old patients (OR .69 (95%CI .40–1.20), $P = .19$). Subanalysis for patients >45 years and <45 years, traditionally regarded as "young" in stroke literature, did not change the results concerning stroke severity on admission (NIHSS): 6.9 in the young versus 6.2 in the old group, $P = .6$, neither was there a difference regarding short-term outcome at day 7: mRS 2.3 versus 2.3, $P = .81$.

Pneumonia and urinary tract infections were less frequent among young patients. Seizures were seen in about 4% in both groups (Table 2).

Cardiac embolism was found in 21% of the young patients versus 29.4% of the old patients and included most frequently in the young with patent foramen ovale (in 2 cases combined with atrial septal aneurysm), mechanical heart valve and paroxysmal atrial fibrillation, or combinations

Table 3: Heart disorders associated with cardiac embolism.

	Young patients ($n = 21$)	Old patients ($n = 328$)	P
Patent foramen ovale	4	9	—
Patent foramen ovale and atrial septal aneurysm	2	0	—
Patent foramen ovale and paroxysmal atrial fibrillation	1	0	—
Atrial fibrillation (paroxysmal and chronic)	3	261	<.01
Atrial flutter	0	6	.54
Atrial septal defect	1	0	—
Atrial septal defect and paroxysmal atrial fibrillation	1	0	—
Atrial septal aneurysm	0	2	—
Ventricular septal defect	1	0	—
Anterior myocardial infarction/akinesia	2	6	—
Heart valve dysfunction	0	15	—
Mechanical heart valve	4	10	—
Mechanical heart valve and prothrombotic disorder	1	0	—
Ventricular thrombus	0	2	—
Papillary fibroelastoma	1	0	—
Cardiomyopathy	0	2	—
Severe heart failure	0	3	.66
Other	0	12	—
Cardiac embolism due to atrial fibrillation/atrial flutter*	5 (5)	267 (29.1)	<.001
Cardiac embolism due to disorders other than atrial fibrillation/atrial flutter*	18 (18)	61 (5.5)	<.001

P value is given only for diagnoses where equal investigation methods were used for both groups.
*in relation to all 100 young and 1117 old patients included in the study.

of these conditions. Other causes were found in 23% of young patients versus 0.9% of the old patients, and cervical artery dissection was the most frequent one (18%). More rare conditions included pseudoaneurysm of the ICA, giant aneurysm of the MCA, prothrombotic disorders, and Moya moya. Large-artery atherosclerosis was less frequent among young patients: 3% versus 12.4% (Tables 2, 3, and 4).

Table 4: Other causes of cerebral infarction.

	Young patients ($n = 23$)	Old patients ($n = 10$)	P
Cervical artery dissection	18	7	<.001
Giant aneurysm MCA	1	0	.001
Pseudoaneurysm ICA	1	0	.001
Moya moya	1	0	.001
Prothrombotic disorder	1	1	.03
Pulmonary shunt	1	0	.001
Migraine	0	1	.76
CADASIL	0	1	.76

MCA, middle cerebral artery; ICA, internal carotid artery.

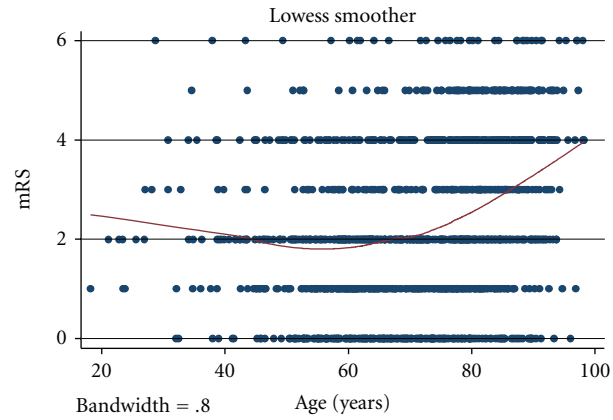

Figure 1: mRS scores, at day 7 or at discharge (if before 7 days), among patients with cerebral infarction according to age. Solid line shows mean mRS. mRS, modified Rankin Scale.

The frequency of atrial fibrillation on ECG on admittance was low among young patients compared to old patients: 2.4% versus 17.0%. Likewise the frequency of atrial fibrillation disclosed on Holter monitoring was low among young patients: 1.8% versus 17.7% (Table 5).

Based on MRI findings, there were no differences concerning location of cerebral infarction. Fewer young patients showed leukoaraiosis (7.8% versus 50.4%) or had sequels after old infarctions on MRI (10% versus 21.3%) (Table 6).

4. Discussion

The proportion of males was larger among the young patients than among the old patients. The proportion of males was also higher compared to other studies of cerebral infarction among young adults [7, 12]. Accumulation of traditional risk factors probably starts earlier in males than in females. Women have a longer life expectancy, which may play a role for the relatively larger proportion of female stroke patients in the older group. On the other hand, it is possible that a change in risk factors or life style has reduced the

Table 5: Investigations.

	Young patients ($n = 100$)	Old patients ($n = 1117$)	P
ECG on admission			
Total	82 (82)	1057 (94.6)	
Atrial fibrillation	2 (2.4)	181 (17.1)	<.001
Left bundle branch block	0 (0)	38 (3.6)	.11
Left ventricle hypertrophy	6 (7.3)	73 (6.9)	.82
Unspecific ST depression	7 (8.5)	232 (21.9)	.003
Acute anterior myocardial infarction	0 (0)	3 (.3)	1.00
Old anterior myocardial infarction	2 (2.4)	52 (4.9)	.42
Acute inferior myocardial infarction	0 (0)	2 (.2)	1.00
Old inferior myocardial infarction	2 (2.4)	59 (5.6)	.31
Echocardiography			
Total	63 (63)	357 (32.0)	
TTE	28 (44.4)	284 (79.6)	
TEE	35 (55.6)	73 (20.4)	
Left ventricle hypertrophy	7 (11.1)	119 (33.3)	<.001
Patent foramen ovale	10 (15.9)	14 (3.9)	.001
Sequelae anterior myocardial infarction	2 (3.2)	19 (5.3)	.75
Sequelae inferior myocardial infarction	0 (0)	16 (4.5)	.15
Holter monitoring			
Total	57 (57)	434 (38.9)	
Paroxysmal atrial fibrillation	1 (1.8)	78 (18.0)	.001
Duplex of cervical arteries			
Total	86 (86)	893 (79.9)	
ICA stenosis[1]	11 (12.8)	356 (39.9)	.000
Symptomatic ICA stenosis ≤49%[1]*	0 (0)	83 (13.9)	.002
Symptomatic ICA stenosis 50–69%[1]*	0 (0)	55 (9.2)	
Symptomatic ICA stenosis 70%–99%[1]*	2 (3.9)	34 (5.7)	
Symptomatic occlusion[1]*	5 (9.8)	29 (4.9)	
No ICA stenosis[1]*	44 (86.3)	397 (66.4)	

Data are expressed as mean or n (%).
ECG, electrocardiography; ICA, internal carotid artery.
[1] Area reduction measured by neurosonology.
* Among patients with ipsilateral infarction in the middle cerebral artery territory.

frequency of stroke among young females in recent years. Smoking has decreased among young women [13], and there has been a change regarding the use of oral contraceptives [14]. Another possible reason is better diagnostic methods of cerebral infarction because of high use of DWI. Psychogenic neurological symptoms are, for example, more frequent among females [15, 16] and may sometimes be mistaken for stroke but are easily distinguishable by DWI. Other studies showed migraine as a cause of stroke in up to 20% in the early 1990s [17], while newer studies find this in only few patients [4, 7, 18–21]. Complex migraine might have been misdiagnosed as cerebral infarction in the pre-DWI era. It is unlikely that this mistake was performed in this study because there was no difference regarding the frequency of migraine among young and old patients. The diagnosis of migraine was based on an interview by a neurologist during the hospital stay strengthening our findings. Thus, our result indicates that migraine is not particularly related to cerebral infarction among young patients compared to old patients.

Most traditional risk factors were less frequent among young patients. However, the fact of smoking made an exception. It has previously been shown that smoking is more frequent among young patients with cerebral infarction compared to matched controls [6]. In our study, the proportion of current smoking was clearly higher among the young compared to the old, and the proportion of

Table 6: MRI findings among young and old patients with cerebral infarction.

	Young patients	Old patients	*P*
MRI	89 (89)	848 (76.0)	.003
DWI positive	84 (93.3)	815 (96.7)	.13
Anterior circulation	68 (68)	812 (72.7)	.35
Posterior circulation	30 (30)	297 (26.6)	.48
Middle cerebral artery	66 (66)	790 (70.7)	.36
Anterior cerebral artery	3 (3)	37 (3.3)	1.00
Occipital	8 (8)	102 (9.1)	.86
Thalamus	3 (3)	79 (7.1)	.15
Mesencephalon	3 (3)	20 (1.8)	.43
Pons	2 (2)	64 (5.7)	.16
Medulla oblongata	5 (5)	24 (2.2)	.08
Cerebellum	11 (11)	87 (7.8)	.25
More than one artery domain	6 (6)	57 (5.1)	.54
Anterior and posterior circulation	2 (2)	35 (3.1)	.83
Bilateral middle cerebral arteries	4 (4)	22 (2)	.19
Leukoaraiosis (MRI)	7 (7.8)	424 (50.4)	<.001
Old infarctions (MRI)*	10 (10)	238 (21.3)	.006
Embolic infarction (MRI)	66 (79)	594 (73)	.30
Lacunar infarction (MRI)	18 (21)	223 (27)	.25

Data are expressed as mean or *n* (%).
MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.
*Including both silent and symptomatic infarctions.

past smoking was lower in the young patients group. The frequency of diabetes mellitus did not differ between young and old ischemic stroke patients.

Large-artery atherosclerosis was a rare cause of cerebral infarction among the young patients. Its frequency was also lower than among young patients with cerebral infarction in previous studies [6, 7]. This may indicate that symptomatic atherosclerosis has decreased among young people in recent years.

There was no difference concerning small vessel disease among young and old patients, and the frequency was similar to the findings in other studies of cerebral infarction among young adults [6, 7]. This is perhaps surprising because there is much uncertainty regarding the pathophysiological mechanisms of lacunar infarctions [22–24].

The frequency of cardiac embolism was similar between young and old patients (Table 2), and the proportion of cardiac embolism in the young is in line with other findings [3, 7, 19, 20, 25]. However, the specific cardiac sources differed between young and old patients. Atrial fibrillation was the dominating cardiac source among old patients but infrequent among young adults. In young adults the dominating heart disorders were patent foramen ovale with and without atrial septal aneurysm, followed by mechanical heart valves. This matches with the findings in other studies [7, 19], but mechanical heart valves were more frequently found as the cause of infarction in our study.

The proportion of other causes did not differ from most investigations [3, 4, 6, 7, 18, 21, 26]. Cervical artery dissection was with 18% the most common other cause among the young patients. Dissections were mostly located in unilateral ICA, less frequently in unilateral VA, and in a few cases in bilateral ICA.

Neither proportion of patients with unknown etiology was different from other studies, which is 31–62% in young patients [3, 6, 20, 27] and 35% in stroke patients overall in this category [26].

The distribution of infarctions in the anterior and posterior circulation was similar between young and old patients. The frequency of posterior circulation infarction was lower than in some other studies including young patients [7, 12]. We believe that this reflects better diagnostic precision in this study because most patients underwent DWI. Frequent MRI may also explain that we found a higher frequency of leukoaraiosis in old patients compared to recent studies [7, 12]. In our study, 7.8% among the young versus 50.4% among the old patients had leukoaraiosis. Old infarctions on MRI were found in 10% of the young patients versus 21.3% of the old ones. Multiple infarctions were common but less frequently seen in our study compared to recent publications [7, 12], and there was no difference between young and old patients.

There was no difference with respect to severity of neurological deficits on admittance between young and old patients. There was also small difference in the one-week outcome or mortality at day 7. Only Barthel Index was significantly higher among young patients whereas modified Rankin score or NIHSS score did not differ, neither was

there any difference concerning the one-week improvement among young and old patients on multivariate analyses. This may indicate that young adults in our investigation do not tackle cerebral ischemia better than old patients concerning short-term outcome, which is in contrast to recent observation made by a Swiss group [28]. Differences in methodology (e.g., stroke unit cohort versus population-based study) may account for this discrepancy. However, subanalyses suggested that patients >80 years may experience less improvement than patients <80 years (analysis not shown).

This is one of the largest studies making a hospital-based direct comparison between ischemic stroke patients <50 years and ≥50 years admitted to a single centre, which we consider to be one of its strengths. All patients underwent investigations and treatment according to one common protocol. Another strength was the frequent use of MRI which promotes high diagnostic precision. However, there are some limitations; using the Baltimore-Washington Cooperative Young Stroke Study Criteria may complicate comparison with other studies using other criteria such as the WHO criteria. However, specificity is high in our study due to the frequent use of MRI. As described in Section 2, certain risk factors were registered as present when diagnosed before stroke onset. We might have missed some patients with untreated hypertension, atrial fibrillation and diabetes here, especially in the young patient group. We did not register outcome at 3 months, which gives an incomplete impression about the patients' outcome in the different groups. Young patients may improve more in long-term outcome compared to old patients. Although investigations were thorough in most patients, not all patients underwent complete workup. We might have missed few patients with, for example, atrial fibrillation or carotid stenosis due to that fact.

In conclusion, there are important differences between young and old patients with respect to risk factors, etiology, and distribution of gender. However, severity of stroke on admittance and short-term outcome is similar among young and old patients.

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Research Article

Electroencephalography as a Tool for Assessment of Brain Ischemic Alterations after Open Heart Operations

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Cardiac surgery is commonly associated with brain ischemia. Few studies addressed brain electric activity changes after on-pump operations. Eyes closed EEG was performed in 22 patients (mean age: 45.2 ± 11.2) before and two weeks after valve replacement. Spouses of patients were invited to participate as controls. Generalized increase of beta power most prominent in beta-1 band was an unambiguous pathological sign of postoperative cortex dysfunction, probably, manifesting due to gamma-activity slowing ("beta buzz" symptom). Generalized postoperative increase of delta-1 mean frequency along with increase of slow-wave activity in right posterior region may be hypothesized to be a consequence of intraoperative ischemia as well. At the same time, significant changes of alpha activity were observed in both patient and control groups, and, therefore, may be considered as physiological. Unexpectedly, controls showed prominent increase of electric activity in left temporal region whereas patients were deficient in left hemisphere activity in comparison with controls at postoperative followup. Further research is needed in order to determine the true neurological meaning of the EEG findings after on-pump operations.

1. Introduction

Cardiac surgery is commonly associated with perioperative brain ischemia. Neuroimaging studies consistently demonstrated acute brain edema and global decrease of brain metabolism during first three days after on-pump surgery [1–4]. In addition, 20–45% of on-pump patients demonstrated multiple small ischemic lesions postoperatively [4–8]. Only 20% of patients with neuroimaging ischemic lesions showed clinical signs of stroke or acute encephalopathy. Nevertheless, the majority of on-pump patients reported memory decrease several months or even several years after surgery [9, 10]. Neuropsychological studies consistently confirmed mild cognitive decline in the majority of cardiac surgery patients at discharge and in 7–69% of patients at 1–3 months followup after surgery [11]. Hence, mild brain ischemic injury is common after on-pump surgery appearing as postoperative cognitive dysfunction. Overall, total volume of brain ischemic alterations correlated with clinical symptoms in the majority of neuroimaging studies [7, 8, 12, 13].

Many researchers pointed to the embolic genesis of the postoperative brain infarcts due to characteristic distribution of the latter ones [12, 14]. Significant associations between microembolic load and severity of postoperative brain injury were consistently shown [2, 15, 16]. In our relatively young patient cohort we found the threshold association between microembolic load and postoperative delirium, that is, patients with delirium were characterized by more than 900 microembolic signals during on-pump period [17]. Postoperative cognitive dysfunction was shown to be associated with intraoperative cerebral microembolic load in a range of studies as well [18–20]. Important, Stygall and colleagues [21] determined the association between cognitive decline at 5 years after CABG and the number of intraoperative microemboli in their study. Hence, cerebral microemboli appear to be a primary cause of brain ischemia in the majority of patients undergoing on-pump operations.

Microemboli are observed during on-pump procedures in nearly all patients [20, 22]. The number of microemboli considerably varies in different cases being the largest in open heart operations. In the study of Abu-Omar and colleagues [23], open heart procedures were associated with a 22-fold increase in microemboli in comparison with off-pump group. Several studies showed a 2–5-fold increase in microemboli during open heart operations in comparison with on-pump coronary surgery [20, 23–25]. It is not unexpected that prevalence of acute postoperative encephalopathy and cognitive dysfunction was reported to be higher after valve operations in comparison with coronary surgery [20, 26].

The inventor of electroencephalography (EEG), Hans Berger, hypothesized brain electric oscillations to be directly associated with cognitive activity [27]. However, until computer processing of EEG data became available, this suggestion was rejected by the majority of clinical neurologists and even scientists. Moreover, such striking EEG phenomenon as alpha-rhythm was widely interpreted as a "resting state" activity resulting from inhibitory thalamic effects, and slow-wave oscillations were considered to be an indicator of pathological or somnogenic brain states. Recent computer EEG studies showed that only small proportion of cortical alpha activity related to corticothalamic interactions, and the majority of alpha-band oscillations originated due to functional interconnectivity of cortical regions [28, 29]. The direct associations between slow-wave oscillations and cognitive activity were shown in neurologically healthy individuals as well [28, 30]. At present, it is widely accepted by the psychophysiological community that slow-wave activity, alpha- and high-frequency (beta and gamma) oscillations in healthy awaken subjects are directly involved in cognitive processing [28, 30, 31].

Brain oscillations during "resting" state were consistently shown to highly correlate with intelligence and a range of cognitive functions [31–33]. Clearly, the situation of EEG registration is completely unusual for the majority of patients and healthy subjects, and therefore induces intensive cognitive processing including internal representations and memorizing of a new environment of a neurophysiological lab, imaging of a personal localization, and associations of the present experience and past memories. Magnetic resonance functional neuroimaging demonstrated prominent activation of a range of brain structures (medial prefrontal cortex, posterior cingulate, inferior parietal cortex, precuneus, and medial temporal cortex) during awaken eyes closed state, which was conventionally called "resting" condition [34–36]. Hence, contemporary spectral EEG studies evidence that electric brain oscillations during "resting" state predominantly relate to cortex cognitive processing. Therefore, computer EEG is a perspective tool for assessment of mild postoperative ischemic brain alterations appearing as cognitive dysfunction.

Studies using intraoperative computer EEG monitoring evidence that brain electric activity demonstrates moderate sensitivity (0.55) and high specificity (1.0) in detecting brain ischemic alterations [37]. Decrease in EEG amplitude and/or EEG slowing manifest when mean cerebral blood flow falls below 22 ml/100 g/min. Initial decrease in fast activities (alpha and beta) is followed by appearance of delta rhythms. A further decrease in perfusion leads to flattening of the EEG activity [37]. Nevertheless, flattening of brain electric activity is typical for brain cooling during bypass and for general anesthetic effects [38]. Although, effects of brain ischemia and general anesthesia on brain electric activity are somewhat similar, intraoperative EEG characteristics appear to be predictive for postoperative cognitive dysfunction. Gugino and colleagues [39] found significant associations between intraoperative characteristics of brain electric activity and postoperative decrement of performance on two or more neuropsychological tests in 2-3 months after on-pump operations.

A handful of studies evaluated brain electric activity in patients after cardiac operations. Evoked auditory cognitive potential (P300) was consistently shown to be deteriorated during first weeks after valve and on-pump coronary operations [40–43]. Importantly, several studies found significant associations between severity of cardiac operations and postoperative impairment of evoked brain electric activity [41–43]. For instance, Grimm and colleagues [43] observed impairment of P300 after mitral valve replacement but not after valve repair. Zimpfer and colleagues [42] found prolongation of P300 in four months after aortic valve replacement but not after CABG. Kilo et al. [41] reported impairment of P300 after on-pump but not after off-pump CABG. The group means differed significantly at followups in all cited studies. Overall, the studies of evoked cognitive potentials showed that the operations with larger embolic load (valve replacement versus valve repair or CABG; on-pump CABG versus off-pump CABG) were associated with greater postoperative impairment of brain electric activity.

Characteristics of spontaneous (resting state) brain electric activity were demonstrated to change after cardiac operations as well [44–47]. Zeitlhofer and colleagues [44] found slight delta-theta relative power increase, alpha decrease and beta increase in 10 days after open heart surgery. In contrast, Hauser et al. [45] reported significant decrease of beta along with alpha-2 power in children after open heart surgery. Vanninen and colleagues [47] found slowing of background activity and increase of relative slow-wave activity at bipolar central and posterior derivations at three months after CABG. EEG slowing did not correlate with the occurrence of new cerebral lesions in the postoperative MRI scans or with deterioration in neuropsychological test performance in that study. Nevertheless, Toner and colleagues [46] reported significant decrease of relative delta and theta power at both 7-day and 2-month followups after CABG. Significant association between postoperative EEG slowing and neuropsychological deficits was found in the latter study. It should be noted that the discrepancies between findings in the cited reports may be partially attributed to the use of relative power parameters, which are less reliable EEG measures in comparison with absolute power [31]. Absence of repeated evaluations of healthy controls is a shortcoming of both studies as well.

Using EEG for repeated evaluations of neurological patients is problematic due to obligatory changes of brain

electric activity at followups in healthy subjects. This electrophysiological phenomenon is widely known for evoked potentials [48, 49] and was less investigated for "resting" brain activity. Corsi-Cabrera and colleagues [50] reported significant increase of theta power and decrease of beta-2 power at eyes closed condition, and decrease of alpha and beta at eyes open condition at 1-month followup in comparison with the first assessment in healthy women. Angelakis et al. [51] showed significant increase of alpha peak frequency at followup in healthy subjects. In our study of healthy subjects [52], presented here as a control group, we observed significant decrease of alpha and theta-2 power along with changes of alpha-1 and alpha-2 mean frequencies in right hemisphere at 2-week followup. In addition, increase of delta-2, theta and beta power was prominent in left temporal region in the majority of subjects. Slowing of delta-1 mean frequency in left hemisphere and slowing of theta-2 frequency in temporal region were also characteristic for followup EEG recordings. Hence, physiological changes of brain electric activity at repeated evaluations are prominent, and this fact should be correctly treated during clinical longitudinal studies using EEG.

The primary aim of the present study was to test the possibility of using the computer EEG as a tool for detecting and evaluating mild neurological alterations in patients after open heart operations. Here we present the data of the repeated EEG assessments of cardiac surgery patients in comparison with healthy controls. In addition, patients were repeatedly evaluated by a battery of neuropsychological tests, and the interrelationships between postoperative brain electric activity and cognitive changes are currently being analyzed and are going to be presented elsewhere. As correlations between brain electric activity and separate cognitive domains are region specific [32, 33], we investigated both global and regional postoperative dynamics of brain electric activity. Post hoc analyses at separate leads were undertaken as well, because this approach consistently showed similar correlations between performance on cognitive tests and brain electrical oscillations [32, 33]. We studied eight frequency bands instead of the usual four ones (delta, theta, alpha, and beta), as the narrow bands demonstrated more reliable neurophysiological correlates in a range of studies [32, 53, 54]. Both eight bands' power and mean frequency parameters were analysed as mean frequency was consistently shown to be a highly informative measure in investigating cognitive versus EEG associations [32, 33]. In addition, we tested associations between postoperative brain electric activity changes and the presence of risk factors of excessive intraoperative cerebral microembolic load.

2. Materials and Methods

2.1. Subjects. A total of 25 patients were included into the study; however, followup EEG recordings were completed only in 22 subjects. Inclusion criteria were age 16–59 years old and preoperative cardiac ejection fraction >40. Exclusion criteria were emergency and reoperative surgical procedures; previous cerebrovascular accident or other neuropsychiatric disorder; serious concomitant noncardiac disease. Ten spouses of patients were invited as controls; however, only eight of them returned for a followup. The preoperative and intraoperative characteristics of patients and demographic characteristics of controls are presented in Table 1.

2.2. Study Design. The present study protocols were reviewed and approved by the academic council of Bakulev's cardiovascular surgery center. The study design was explained to patients, and each patient gave informed consent to participate. Patients underwent clinical, EEG, and neuropsychological evaluation 2-3 days before surgery. Clinical examination included M-mode two-dimensional echocardiography for measuring a left ventricular end systolic dimension (absolute value was not normalized), because an enlarged left ventricular was associated with a high risk of elevated intraoperative cerebral microembolism in our previous study [55]. Mini-Mental State Examination was applied to evaluate overall cognitive status. In addition, subjects performed a set of cognitive tests (the data will be published elsewhere). The postoperative assessment was performed in 10–15 days after surgery. Controls were reevaluated with a 2-week interval as well.

2.3. Anesthesia, CPB, and Surgical Management. The protocols of anesthesia and surgical techniques were standardized. Diazepam and morphine served as premedication. Anesthesia was induced and maintained with propofol, fentanyl, and pancuronium. The perfusion apparatus consisted of the Stökert S3 roller pump (Germany), DIDECO-703 membrane oxygenator (Italy), and a 40 μm arterial filter. Nonpulsatile pump flow rates were maintained between 2.4 and 2.6 $\mathrm{L}*\mathrm{min}^{-1}*\ \mathrm{m}^{-2}$, and mean perfusion pressure at 60 mm Hg. The operations were accomplished during moderate hypothermia (28°C). All patients underwent median sternotomy, the aorta was cross-clamped and the heart was arrested with anterograde cold pharmacological cardioplegia by solution of custodiol. Topical ice saline was used as an adjuvant to myocardial protection. Aortic valve replacement was performed in 9 patients. Mitral valve was replaced in 10 patients. And 3 patients underwent combined valve surgery. Overall, the patients uneventfully underwent operations on aortic and/or mitral valve. Three patients demonstrated transitory mild psychotic symptoms (visual hallucinations and disorientation) during first postoperative day.

2.4. EEG Recordings and Analysis. Eyes closed resting EEG data were collected from the 21 monopolar electrode sites of the international 10/20 system (Fp1/Fp2, F3/F4, C3/C4, P3/P4, O1/O2, F7/F8, T3/T4, T5/T6, Fpz, Fz, Cz, Pz, Oz), referred to linked earlobes. EEG signal was amplified using EEG machine (Neuron-Spectr 4/EP, Neurosoft, Russia) with bandpass filter settings 0.5 and 35 Hz. All signals were digitized online at a sampling rate of 200 Hz. Electrode impedances were below 5 KΩ. Each recording comprised 7–10 min.

The resulting time series were inspected visually for body movements, eye blinks, eye movements, EMG, ECG, rheogram, and loose electrodes artifacts. Intervals identified

Table 1: Subject characteristics and operative data.

	Open heart surgery	Controls	*P*
Number of subjects	22	8	
Male/female sex (*n*)	11/11	1/7	NS
Age (years)	45.2 ± 11.2	39.4 ± 16.6	NS
Education (years)	14.5 ± 2.8	15.4 ± 3.4	NS
MMSE at first assessment (score)	27.3 ± 2.6	27.6 ± 3.3	NS
MMSE at followup (score)	27.0 ± 3.0	28.1 ± 3.7	NS
History of hypertension (*n*)	6	0	NS
History of diabetes (*n*)	1	0	NS
History of atrium fibrillation (*n*)	7	0	NS
NYHA class III and IV (*n*)	8	0	0.046
Ejection fraction (%)	62.3 ± 7.0		
End systolic size of left ventricular (mm)	35.6 ± 0.8		
Mitral valve replacement (*n*)	10		
Aortic valve replacement (*n*)	9		
Aortic and mitral valve replacement (*n*)	3		
Cardiopulmonary bypass time (minute)	115.6 ± 49.5		
Aortic cross-clamp time (minute)	73.9 ± 34.5		
Postoperative delirium (*n*)	3		

Data given as means and SD, unless otherwise indicated.
Abbreviations: *n:* number of patients; NS*:* not significant; NYHA*:* New York Heart Association.

as disturbed by artifacts were excluded from the spectral analysis. Finally, 4 sec with 50% overlap epochs were obtained from artifact-free EEG tracings and submitted to a fast Fourier transform. For each of the 21 monopolar derivations, absolute power and mean frequency were computed for the delta1 (1-2 Hz), delta2 (2–4 Hz), theta1 (4–6 Hz), theta2 (6–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz) frequency bands.

2.5. Statistical Analysis. Statistical analysis was performed using SPSS software for windows (SPSS 17.0, Chicago, IL, USA). Repeated-measures analyses of variance (ANOVAs) were used to analyze EEG power and mean frequency data at 12 leads with regions, that is, *laterality* (central (F3/F4, C3/C4, P3/P4), temporal (F7/F8, T3/T4, T5/T6)), *sagittality* (anterior (F3/F4, F7/F8), medial (C3/C4, T3/T4), posterior (P3/P4, T5/T6)), *hemisphere* (left (F3, C3, P3, F7, T3, T5), right (F4, C4, P4, F8, T4, T6), and time (preoperative versus postoperative) as within-subject factors. First, repeated-measures ANOVAs included only EEG variables of patients, and time effects (global changes) and interaction of time with regions (regional changes) were tested. Second, the same ANOVAs were conducted using the data of patients and controls with a group as a between-subject factor. The time ∗ group and region ∗ time ∗ group interactions were tested. When significant region ∗ time or region ∗ time ∗ group interactions were found, ANOVAs were conducted using only the data of the region of interest. Finally, post-hoc analyses of dynamics of EEG variables at separate leads were conducted to test time ∗ group interaction. As a small proportion of EEG variables tended to be nonparametric, we preferred to apply Wilcoxon test to explore time effects at separate leads in patient group.

In order to test effects of cardiopulmonary bypass duration on postoperative dynamics of brain electric activity, the patient sample was split into two groups according to the median of on-pump time: CPB <100 minutes and CPB >100 minutes. Repeated-measures ANOVAs were also used to analyze differences in dynamics of EEG power and mean frequency in two patient subgroups. The similar approach was used to explore effects of left ventricular end systolic size (LV) on postoperative brain electric activity. The patients were divided into two groups according to the median of LV: LV < 35.5 mm and LV > 35.5 mm. Then repeated-measures ANOVAs were conducted with regions and time as within-subject factor and group according to LV size as a between-subject factor. Post-hoc analyses at separate leads were undertaken as well.

3. Results

3.1. Characteristics of Electrical Brain Activity before Surgery. Preoperatively, patients differed significantly from controls by *lower beta-1 power* in right hemisphere (hemisphere ∗ group interaction: $F = 6.31$, $P = .018$) with the similar trend for delta-2, theta-2, alpha-1, and alpha2 activity (Fs > 3.5, Ps < .10, resp.). Group differences in total alpha-2 and beta-1 mean frequencies reached significance as well (Fs = 4.40 and 6.43, Ps = .045 and .017, resp.) with *higher alpha-2* and *lower beta-1 mean frequencies* in the patient group in all brain regions.

3.2. Global Changes of Brain Activity after Open Heart Operations. Global changes of brain electric activity after open heart operations are summarized in Table 2. After surgery

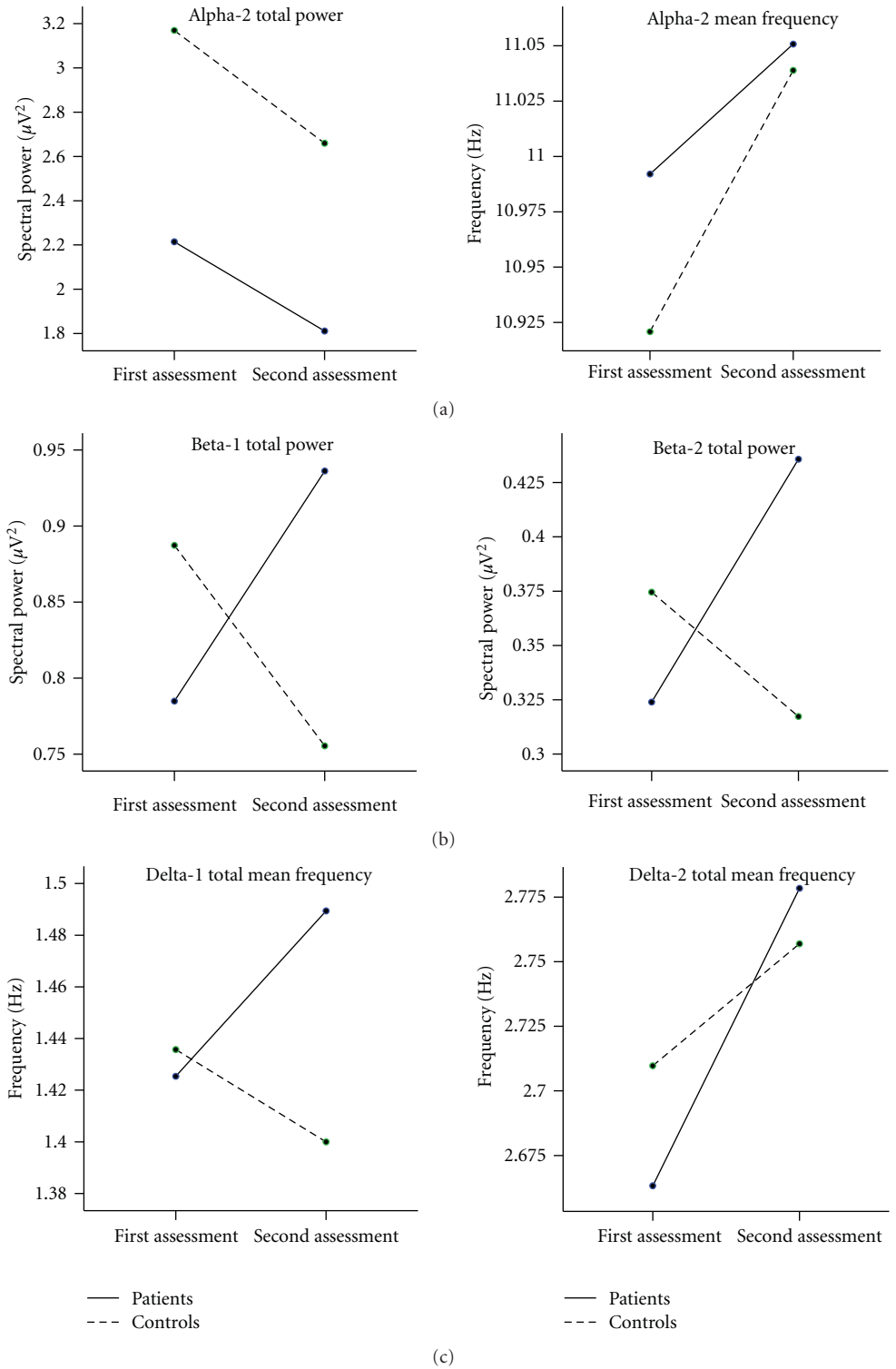

Figure 1: Global changes of alpha (a), beta (b), and delta (c) activity in patients after open heart operations and controls.

patients demonstrated significant decrease of alpha-2 power in all brain regions ($F = 5.28$, $P = .032$). Healthy controls showed significant decrease of alpha-2 power in right hemisphere, and therefore groups did not differ on global dynamics of alpha-2 power ($F = 0.037$, $P = .85$) (Figure 1(a)). Nevertheless, groups differed on regional dynamics of alpha-2 power due to somewhat larger decrease of alpha-2 power in right hemisphere in healthy controls and more prominent changes of this EEG variable in left hemisphere in patient group ($F = 6.90$, $P = .014$). It should be noted, that global

alpha-2 mean frequency increased in both groups at followup ($F = 4.25$, $P = .049$; Figure 1(a)).

As opposite to controls, patients demonstrated global increase of beta-1 and beta-2 power (Fs = 7.28 and 5.42, Ps = .013 and.030). Accordingly, patients differed significantly from controls on dynamics of beta-1 total power ($F = 6.11$, $P = .020$; Figure 1(b)) with the similar trend for beta-2 total power ($F = 3.41$, $P = .076$). Group effects were significant at C3, C4, Cz, P3, P4, Pz, O1, O2, F8, T4, and T6 (Fs > 4.2, Ps < .05) for changes of beta-1 power, and tended to be significant at Fpz, F3, C3, C4, Cz, P4, O1, T4, and T5 (Fs > 3.0, Ps < .10) for beta-2 power. It should be noted that maximal postoperative increase of beta-2 power was found at left posterior temporal and occipital region (leads T5 and O1, zs > 2.5, Ps < .01) along with concomitant increase of beta-2 mean frequency at T5 ($z = 2.05$, $P = .04$). No significant postoperative changes or group effects on global or regional dynamics of beta-1 or beta-2 mean frequencies were found.

Delta-1 mean frequency showed postoperative increase in all brain regions in open heart patients ($F = 15.8$, $P = .001$), and, accordingly, patients differed from controls on dynamics of total delta-1 mean frequency ($F = 10.2$, $P = .004$; Figure 1(c)). Postoperative changes of delta-1 mean frequency at Fp2, C3, C4, P4, Pz, O1, O2, F7, T3, T5, F8, T4, and T6 reached significance (zs < −2.00, Ps < .05). Group effects were significant at C3, C4, P3, Pz, O1, O2, Oz, F7, and T3 (Fs > 4.3, Ps < .05). Maximal increase of delta-1 mean frequency was registered in left (T3) and right (F8) temporal derivations (Ps < .005).

In addition, patients showed significant increase of delta-2 mean frequency in all brain regions ($F = 16.2$, $P = .001$). However, no group effects on dynamics of delta-2 mean frequency was found ($F = 1.32$, $P = .26$) as healthy controls demonstrated the similar global increase of this EEG parameter (Figure 1(c)).

3.3. Right Hemisphere Electrical Activity after Open Heart Surgery. As opposite to healthy controls, patients showed no regional changes of delta-1, delta-2, theta-1, theta-2, or alpha-1 power. Nevertheless, patients significantly differed from controls on dynamics of delta-1, delta-2. theta-2, and alpha-1 power in right hemisphere (Fs > 5.4, Ps < .03) due to significant decrease of brain activity power in right hemisphere in healthy subjects (Figure 2(a)). Analyses at separate leads showed group effects at T6 for delta-1; at C4, F8 and T6 for delta-2; at P4 and T6 for theta-2; at T4 for alpha-1 and alpha-2 (Fs > 4.5, Ps < 0.05).

Dynamics of theta-1 power was similar in left and right hemispheres in both groups ($F = 0.51$, P =.48). Nevertheless, groups differed on changes of theta-1 power in central region of right hemisphere ($F = 5.11$, $P = .032$; Figure 2(b)) due to postoperative increase of theta-1 power in the patient group. At the same time, patients and controls demonstrated similar increase of theta-1 power at right temporal derivations. Increase of theta-1 power at T4 and T6 was significant at postoperative followup in the patient group (zs = −2.90 and −2.71, Ps = .004 and .007, resp.). It should be noted, that delta-2 and theta-2 power increased at P4, T4, and T6 leads (zs < −1.7, Ps < .08) in patients but not in controls at followup. No concomitant regional changes or group effects on theta-1 and theta-2 mean frequencies were found. Nevertheless, analyses at separate leads showed significant slowing of theta-2 mean frequency at C4 and T6 in the patient group (zs < −2.00, Ps < .05) after surgery.

In addition, patients showed significant slowing of alpha-1 mean frequency at O2 ($z = -2.89$, $P = .004$). However, this phenomenon was registered in healthy subjects as well, and analyses including both groups showed significant slowing of alpha-1 activity at O1, O2, and Oz at followup (Fs > 7.0, Ps ≤ .01).

3.4. Left Hemisphere Electrical Activity after Open Heart Surgery. After surgery, patients differed from controls on dynamics of delta-2, theta-1, and theta-2 power in central and temporal regions of left hemisphere (Fs > 4.3, Ps < .05) (Figure 3(a)). In central region power of slow-wave activity decreased in healthy controls and did not change in patients at followup. In temporal region, controls demonstrated increase of slow-wave activity power whereas patients did not show any changes. Analyses at separate leads showed group differences on dynamics of delta-1 ($F = 4.07$, $P = .05$) and delta-2 ($F = 4.31$, $P = .048$) power at left temporal derivation (T3). In addition, groups differed on dynamics of theta-2 mean frequency in central and temporal region of left hemisphere ($F = 5.30$, $P = .030$). No group effects at separate leads analyses were found.

3.5. Cardiopulmonary Bypass Length and Left Ventricular Size Effects on Brain Activity. Patients with prolonged CPB were characterized by increase of alpha-1 power in central region whereas patients with shorter CPB length showed decrease of alpha-1 activity in central derivations ($F = 8.94$, $P = .007$) (Figure 4(a)). Group differences reached significance only at P3 ($F = 5.73$, P =.027) with the similar trend for P4 and Pz (Fs = 3.63 and 3.92, Ps = .071 and .062, resp.).

Patients with enlarged left ventricular size showed increase of beta-1 mean frequency in right hemisphere whereas patients with smaller left ventricular were characterized by decrease of this EEG parameter ($F = 4.43$, $P = .048$) (Figure 4(b)). Group differences in dynamics of beta-1 mean frequency at C4 and P4 showed a trend to be significant (F = 3.28 and 3.21, Ps = .085 and .088, resp.).

4. Discussion

In the present study we observed both physiological and pathological phenomena of brain electric activity dynamics after open heart operations. Indeed, some prominent postoperative EEG changes in our patient cohort did not differ from dynamics of brain electric activity in healthy controls. At the same time, a range of EEG parameters abnormally altered after cardiac operations, and the latter were highly probable signs of perioperative brain ischemia.

Table 2: Global changes of BEA after open heart operation*.

	Patient group dynamics**	Group effect***	Local dynamics**	Local group effects***
Total alpha-2 power decrease	$F = 5.28$, $P = .032$	NS	F3, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, Oz,T5	T4 (larger decrease in controls)
Total beta-1 power increase	$F = 7.28$, $P = .013$	$F = 6.11$, $P = .020$	C3, C4, Cz, P3, P4, Pz, O1, O2, T3, T5, F8, T4, T6	C3, C4, Cz, P3, P4, Pz, O1, O2, F8, T4, T6
Total beta-2 power increase	$F = 5.42$, $P = .030$	$F = 3.41$, $P = .076$	C3, P3, P4, Pz, O1, O2, T3, T5, F8, T6	Fpz, F3, C3, C4, Cz, P4, T4
Total delta-1 mean frequency increase	$F = 15.8$, $P = .001$	$F = 10.2$, $P = .004$	Fp2, C3, C4, P4, Pz, O1, O2, F7, T3, T5, F8, T4, T6	C3, C4, P3, Pz, O1, O2, Oz, F7, T3
Total delta-2 mean frequency increase	$F = 16.2$, $P = .001$	NS	Fp2, Fpz, F3, F4, C3, C4, Cz, P4, O2, Oz, F7, T5, F8, T4, T6	Fp2, Fpz, Cz, T4
Total alpha-2 mean frequency increase	$F = 4.25$, $P = .049$	NS	P3, Pz, T3	NS

* Findings at $P < .1$ are presented.
** Repeated measures ANOVAs or Wilcoxon tests included only patients.
*** Repeated measures ANOVAs included patients and normal controls.

Table 3: Hemisphere effects on electric activity after open heart operations*.

	Patient group dynamics**	Group effect***	Local dynamics**	Local group effects***
Right hemisphere				
Delta-1 power did not change versus decrease in controls	NS	$F = 6.67$, $P = .016$	NS	C4, T4, T6 (decrease in controls)
Delta-2 power did not change versus decrease in controls	$F = 3.62$, $P = .071$	F = 5.95, $P = .022$	P4, T4 (increase)	C4, F8, T4, T6 (decrease in controls)
Theta-2 power did not change versus decrease in controls	NS	$F = 5.49$, $P = .027$	P4, T4, T6 (increase)	Fp2, C4, P4, T6 (decrease in controls)
Alpha-1 power did not change versus decrease in controls	NS	$F = 5.83$, $P = .023$	F8, T4 (increase)	T4 (decrease in controls)
Theta-1 power increase in central region	NS	$F = 5.11$, $P = .032$	P4, O2, T4, T6 (increase)	P4 (decrease in controls
*Left hemisphere***				
Delta-2 power increase in central region and no change in temporal region versus opposite dynamics in controls	NS	$F = 4.42$, $P = .045$	NS	T3 (increase in controls)
Theta-1 power did not change versus significant changes in controls	NS	$F = 4.33$, $P = .042$	NS	NS
Theta-2 power did not change versus significant changes in controls	NS	$F = 4.83$, $P = .037$	NS	NS
Alpha-2 power decrease	NS	$F = 6.90$, $P = .014$	F3, C3, P3, O1, T5	NS
Theta-2 mean frequency decrease in central region	NS	$F = 5.30$, $P = .030$	NS	NS

* Findings at $P < .1$ are presented.
**Repeated measures ANOVAs or Wilcoxon tests included only patients.
***Repeated measures ANOVAs included patients and normal controls.
****Statistics on interaction of time ∗central/temporal region ∗group factors in left hemisphere is presented.

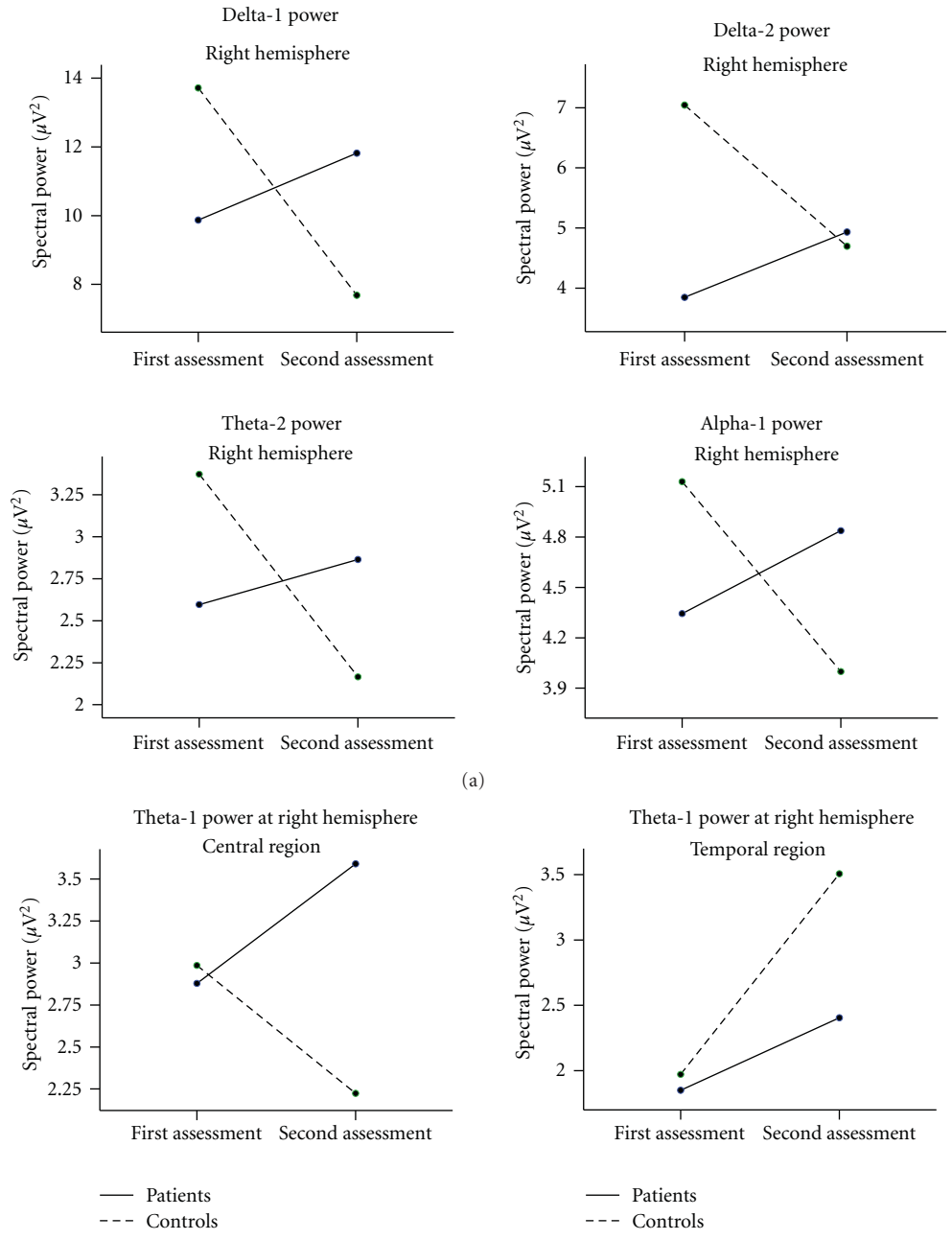

Figure 2: Group differences in dynamics of delta-1, delta-2, theta-2, and alpha-1 power in right hemisphere (a); group effects on dynamics of theta-1 power in central and temporal regions of right hemisphere (b).

4.1. Postoperative Beta Activity. Postoperative increase of beta power especially prominent in beta-1 band was a certain pathological phenomenon in our patient cohort. The similar postoperative increase of beta activity was previously reported after open heart operations [44] and on-pump coronary surgery [46]. Interestingly, increase of beta activity was reported in acute alcohol and heroin withdrawal, that is, conditions with pronounced neurochemical imbalances [48, 49]. Moreover, a "beta buzz" phenomenon with strong increase in EEG beta power was reported after administration of benzodiazepines and other GABA agonists [27, 56].

Porjesz and colleagues [27] explained the functional meaning of a "beta buzz" as a "slow gamma" activity. Normally, only excitatory neurons oscillate at beta frequency whereas inhibitory interneurons simultaneously oscillate at subharmonic gamma rate. GABA agonists synchronize excitatory and inhibitory neurons oscillations at beta frequency. In a range of studies (including our previous study

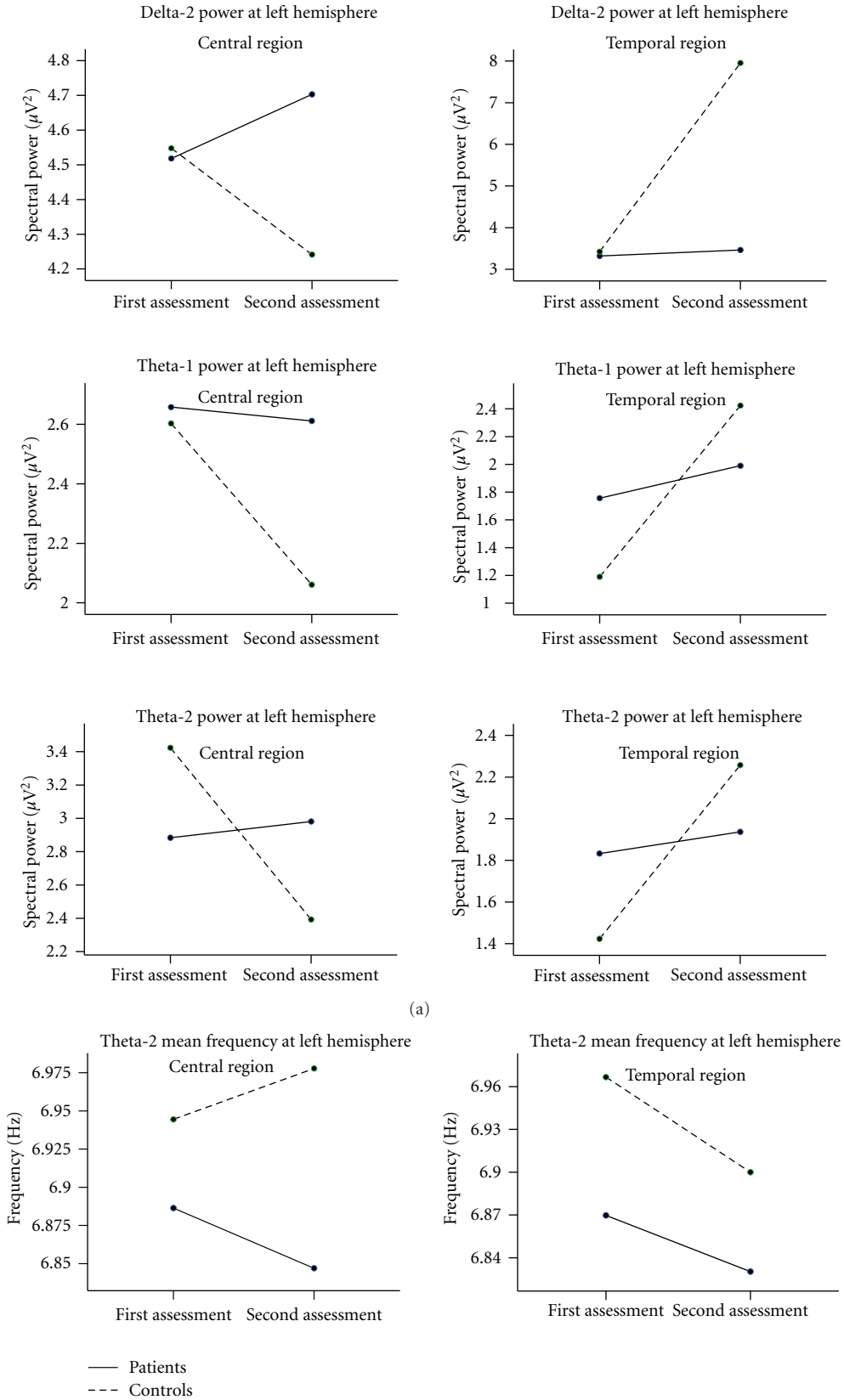

Figure 3: Group differences in dynamics of delta-2, theta-1, and theta-2 power (a); theta-2 mean frequency (b) in central and temporal regions of left hemisphere.

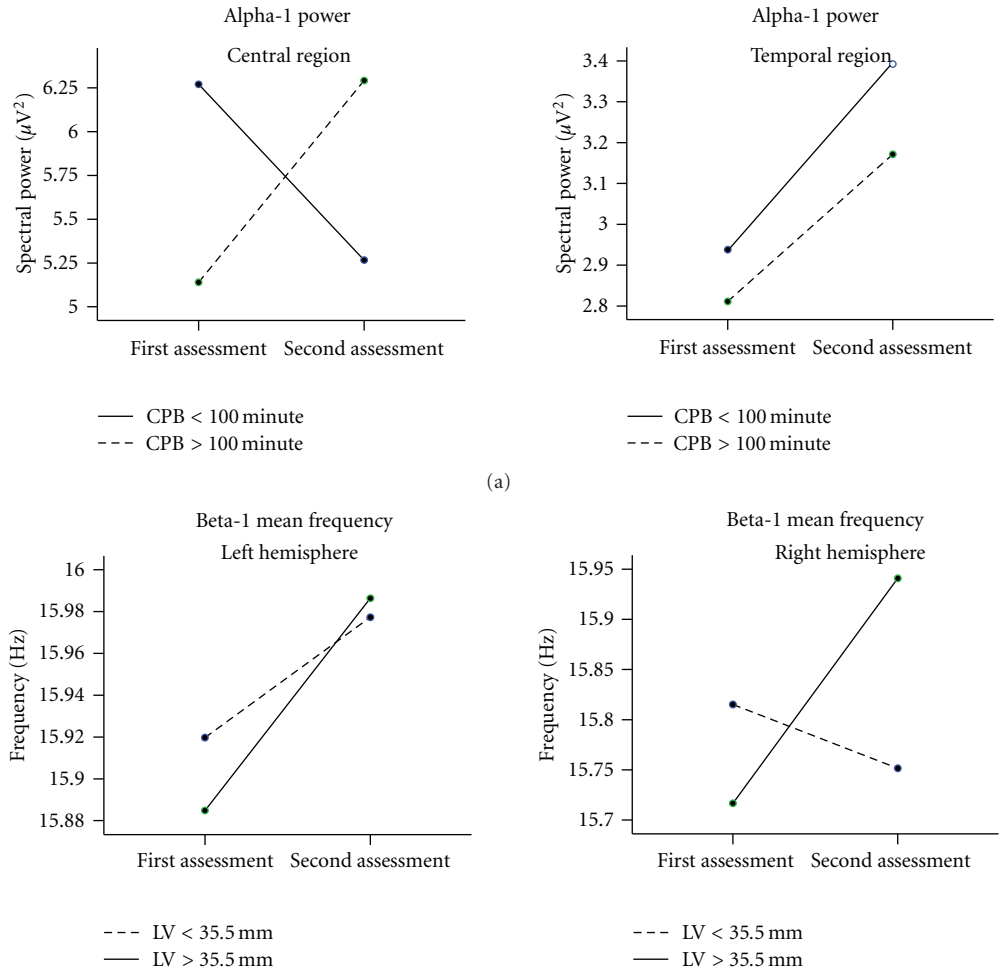

Figure 4: Effects of cardiopulmonary bypass length (a) and left ventricular size (b) on postoperative dynamics of brain electric activity.

of heroin addicts), strong association between beta power increase and slowing of psychomotor speed was observed [57–59]. Importantly, slowing of psychomotor speed is a very common postoperative deficit [11]. At the same time, postoperative increase of beta activity [46] and psychomotor slowing [11] were shown to be transitory, and this dynamics gives grounds to associate a postoperative "beta buzz" with global cortex edema and metabolism decrease reported by neuroimaging studies. Additional increase of beta-1 mean frequency in right hemisphere in patients with high risk of excessive embolism is logical, as previously we found asymmetrical distribution of emboli to right hemisphere in a similar cohort of patients [20]. The latter phenomenon may result from perfusion techniques.

4.2. Postoperative Alpha Activity. In agreement with almost all previous studies [44–47], we found prominent changes of alpha activity, especially, in fast (alpha-2) band. For instance, Hauser and colleagues [45] reported alpha-2 power decrease at 6-, 11-, and 44-day followups after open heart operations in children. Slowing of alpha-rhythm (alpha activity in occipital region) at followup was consistently reported in previous studies of postoperative EEG changes as well [44, 47]. Nevertheless, healthy subjects in our study demonstrated the similar decrease of alpha-2 activity at second assessment [52]. In addition, both patient and control groups showed analogous widespread alpha-2 mean frequency and localized alpha-1 mean frequency changes. Importantly, two more studies reported significant decrease of alpha activity and increase of peak alpha frequency in healthy subjects during repeated EEG evaluations [51, 60]. Thus, decrement of alpha activity along with alpha mean frequency shifts at repeated EEG is regularly observed in both healthy subjects and cardiac surgery patients. Therefore, alpha activity changes in our patient cohort appear to represent at least partially a physiological phenomenon.

It is widely known, that alpha rhythm is a dominating activity in adult subjects during eyes closed "resting" condition. In healthy young subjects, alpha-2 activity (10–12 Hz) dominates at occipital derivations, and the source of alpha-2 oscillations is lateralized to right hemisphere [61]. Previously, alpha rhythm was commonly considered

as an idling rhythm of visual cortex as it was blocked by eyes opening. However, this view is contradicted by the stimulus-related enhancement of alpha activity, which was consistently shown in a range of studies. For instance, alpha rhythm maximally synchronizes at rhythmic light stimulation, and in healthy subjects occipital cortex responds with 10–12 Hz wave forms [62, 63]. Intensive contemplating of complex pictures induces prominent increase of interhemispheric coherence of alpha-oscillations at occipital and posterior temporal derivations, and memorizing of the same pictures does not affect alpha activity coherence in comparison with "resting" background [53]. Enhancement of synchronization of alpha activity after simple auditory stimuli (tones) was consistently shown in a range of studies as well [28, 64, 65]. Overall, the cited studies evidenced that alpha activity is an intrinsic component of cortex cognitive processing rather than an "idling" cortex phenomenon. Not surprisingly, spectral characteristics of alpha-rhythm and overall spontaneous alpha-activity were consistently shown to highly correlate with a range of cognitive abilities [51, 66, 67].

Laufs and colleagues [68] showed positive correlations between alpha-oscillations and activation of cingulate and occipital cortex at fMRI scans during "resting" eyes closed condition. Sadaghiani et al. [36] found similar positive associations between global alpha-2 activity power at eyes closed resting state and activity at a network comprising dorsal anterior cingulated cortex, anterior insula, anterior prefrontal cortex, and thalamus. The latter brain structures are commonly designated as a "default-mode" network, which maximally activates during "resting" state. We could not identify MRI studies, which repeatedly evaluated a default-mode network functioning in healthy subjects. We just may hypothesize that activity of the former decreased at followup in our patients and healthy subjects, and therefore alpha-2 activity power decreased as well. As it was cited earlier, alpha oscillations are an intrinsic component of cognitive evoked potentials, and decrease of amplitude of the latter is a widely known phenomenon [48, 49]. Therefore, at least partially, alpha power decrease in our patient cohort appear to be physiological. Perhaps, only the elevation of alpha-1 power in central derivations in patients after prolonged bypass may be hypothesized to be pathological; however, further research is needed to determine the significance of the latter finding. We hope to elucidate the nature of alpha activity reduction in our patient cohort after analyses of interrelationships between postoperative EEG data and performance on cognitive tests.

4.3. Postoperative Delta and Theta Activity. Both patient and control groups demonstrated significant changes of slow-wave activity at followup assessment. Important, that healthy controls showed increase of delta-2, theta-1, and theta-2 power in left temporal region (T3) at followup. Patients did not demonstrate comparable dynamics of regional slow-wave activity in left hemisphere, and absence of the latter physiological EEG changes may be suggested to be a deficient neurological sign. As left hemisphere and posterior brain cortex were consistently shown to be highly vulnerable to ischemia during cardiac operations [7, 19, 69–72], we discuss the left temporal region deficit in our patient cohort in detail.

A range of experimental studies consistently demonstrated that delta/theta activity is an intrinsic component of information processing in normal human brain [30, 73–75]. At present, it is widely accepted that theta activity synchronizes during mnemonic processes in humans [73, 75]. For instance, Kirk and Mackay [75] showed that theta activity synchronized left temporally during digit span task and right temporally during spatial memory task. Complex calculations and concept formation were shown to be associated with prominent synchronization of delta activity over frontal and temporal regions as well [30, 75]. Although visual and auditory stimuli usually evoke a broadband response, delta-theta oscillations tend to demonstrate larger synchronization during processing of auditory information as opposed to alpha activity, which predominates during visual tasks over posterior brain regions [53, 76]. During eyes closed "resting" condition the source of delta and theta activity localizes anterior and somewhat leftward from midline, that is, closer to auditory cortex in comparison with alpha activity [61]. Importantly, Corsi-Cabrera and colleagues [50] showed significant increase of theta power at followup in their study of healthy women.

The cited above neurophysiological studies give grounds to hypothesize that electric brain activity in healthy subjects shifted from "visualizing" regimen during primary assessment to "internal speech" regimen, and therefore slow-wave activity at left temporal region increased along with concomitant alpha activity decrease. Patients did not demonstrate this physiological shift of electric brain activity probably due to ischemic alterations in left temporal cortex. At least two neuroimaging studies showed localized postoperative dysfunction of left temporal cortex in patients after on-pump coronary surgery [19, 72]. Moreover, verbal memory decline is the most common postoperative cognitive deficit in cardiac surgery patients [11, 19]. Interestingly, Zeitlhofer and colleagues [44] reported a trend for more pronounced EEG changes in left hemisphere after open heart surgery.

In addition, we observed significant postoperative increase of delta-1 and delta-2 mean frequencies in all brain regions without concomitant generalized changes of delta power. However, only dynamics of delta-1 mean frequency differed between patients and controls. A trend for region-specific postoperative elevation of delta-2 power was observed. Analyses at separate leads showed significant increase of delta-2 and theta activity in posterior derivations of right hemisphere after open heart operations. The latter EEG changes in the patient group differed significantly from controls, which showed the most prominent decrease of delta and theta-2 activity in this region. It should be noted that Vanninen and colleagues [47] found similar postoperative increase of delta activity in right posterior region (bipolar derivation T6-O2), along with increase of theta activity in bilateral central derivations. Moreover, overall mean frequency significantly slowed in right hemisphere in their study.

Slow-wave activity was traditionally associated with compromised brain states, and therefore was considered as an unambiguous pathological sign [37, 77]. Thatcher and colleagues [31] found opposite association between increase of delta amplitude and the severity of white matter alterations in patients after brain injury. It may be hypothesized, that generalized shift of delta-1 mean frequency and elevation of slow-wave activity in posterior right region were pathological in our patient cohort. Further research is needed in order to identify the mechanisms of slow-wave activity changes after cardiac operations.

4.4. Limitations of the Study. The small number of patient and control subjects makes the present results preliminary. A somewhat imbalanced gender distribution between patient and control groups may be a source of result bias in the present study, as gender was recently shown to affect brain electric activity characteristics. Preoperative abnormalities of brain electric activity in patients in comparison with healthy controls is the other limitation of this study. It should be noted that premorbid cognitive and electrophysiological dysfunction is a common problem for studies investigating patients with chronic diseases as good general health is an important contributor to normal brain functioning. Absence of direct measurements of intraoperative cerebral microembolism is an important limitation as well, and further research is needed in order to determine effects of intraoperative emboli on postoperative brain electrophysiology.

5. Conclusions

Both pathological and physiological changes of brain electric activity were observed after open heart operations. Generalized postoperative increase of beta power most prominent in beta-1 band was an unambiguous pathological sign of postoperative cortex dysfunction, probably, manifesting due to gamma-activity slowing ("beta buzz" symptom). Generalized increase of delta-1 mean frequency along with increase of slow-wave activity in right posterior region may be hypothesized to be a consequence of intraoperative ischemia as well. At the same time, significant changes of alpha activity were observed in both patient and control groups, and, therefore, may be considered as physiological. Unexpectedly, controls showed prominent increase of electric activity in left temporal region whereas patients were deficient in left hemisphere activity in comparison with controls at postoperative followup. Further research is needed in order to determine the true neurological meaning of the EEG findings after on-pump operations.

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Clinical Study

Neckties and Cerebrovascular Reactivity in Young Healthy Males: A Pilot Randomised Crossover Trial

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Background. A necktie may elevate intracranial pressure through compression of venous return. We hypothesised that a tight necktie would deleteriously alter cerebrovascular reactivity. *Materials and Methods*. A necktie was simulated using bespoke apparatus comprising pneumatic inner-tube with aneroid pressure-gauge. Using a randomised crossover design, cerebrovascular reactivity was measured with the "pseudo-tie" worn inflated or deflated for 5 minutes (simulating tight/loose necktie resp.). Reactivity was calculated using breath hold index (BHI) and paired "t" testing used for comparative analysis. *Results*. We enrolled 40 healthy male volunteers. There was a reduction in cerebrovascular reactivity of 0.23 units with "tight" pseudotie (BHI loose 1.44 (SD 0.48); BHI *tight* 1.21 (SD 0.38) $P < .001$). *Conclusion*. Impairment in cerebrovascular reactivity was found with inflated pseudo-tie. However, mean BHI is still within a range of considered normal. The situation may differ in patients with vascular risk factors, and confirmatory work is recommended.

1. Introduction

Pathogenesis and treatment of stroke in young adults remain poorly understood. Management strategies are often based on evidence from studies of older patient cohorts however risk factors and prognosis are not equivalent for these two groups. Certain risk factors, for example, patent foramen ovale or illicit drug use, may be pertinent in younger populations, but even for these conditions there is no consensus on relative importance or optimal management [1–4]. Thus identification of novel risk factors for cerebrovascular disease in young adults remains an important area of study. Based on basic anatomy and physiology, extrapolation of data from other medical disciplines, and a degree of "lateral" thinking, we sought to characterise one such novel risk factor.

Many young professionals, including doctors, wear neckties. Recent media coverage has focussed on potential bacterial transmission via a necktie vector. The risk of neckties may not be confined to patients—a further possible "danger" of this sartorial habit is suggested by reports of pathologically increased intraocular pressures in individuals wearing tight neckties, the postulated mechanism being impairment of ocular venous drainage [5, 6]. If neckties cause haemodynamic effects in retinal vasculature, it seems reasonable to suppose that impairment of venous drainage could occur in other supracervical vascular beds including the cerebral vessels. Although an effect of circumferential neck pressure on stroke risk has been previously hypothesised [7], a "real-time" demonstration of the cerebrovascular effect of a tight necktie has not previously been demonstrated.

We hypothesized that, via jugular venous compression, a tight necktie may elevate intracranial venous pressure and impair reactivity in the cerebral circulation—a surrogate marker of cerebrovascular risk. We performed a randomised crossover study to describe the effect of wearing a tight necktie on cerebrovascular reactivity.

2. Materials and Methods

The study was conducted in the cerebrovascular investigation laboratory of our university hospital. The Local Research and Ethics Committee granted ethical approval prior to study

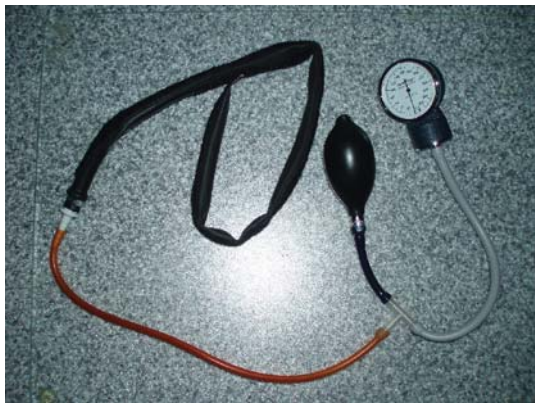

Figure 1: Artificial necktie apparatus.

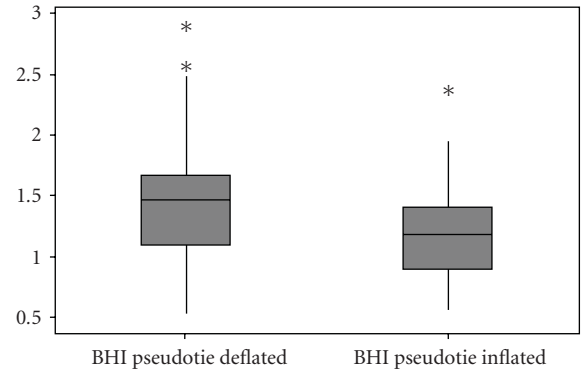

Figure 2: Cerebrovascular reactivity as measured by Breath hold index (BHI) with pseudo-tie deflated and inflated (tight).

commencing. All subjects gave informed consent and were allowed to withdraw from the study at any time. As this was a pilot study and as we were interested in novel risk factors, we invited healthy men with no known history of vascular disease and on no regular medication to participate.

For our primary outcome, we used a noninvasive surrogate measure of cerebrovascular reactivity—the Breath Hold Index (BHI). BHI is a validated and commonly used measure, which has been described in detail elsewhere [8]. In brief, breath holding yields a hypercapnic stimulus, which causes vasodilatation of cerebral resistance vessels. This in turn increases blood mean flow velocity in the middle cerebral artery (MCAv). To calculate BHI, the MCAv was measured at rest and after 30 seconds of breath holding. The change in MCAv was then used to calculate BHI using the formula:

$$\text{BHI} = \frac{[\text{MCAv(end of BH)} - \text{MCAv(rest)}]}{\text{MCAv(rest)}} \times \frac{100}{\text{Breath Hold(sec)}}. \quad (1)$$

To simulate and quantify the circumferential pressure applied by a necktie, a novel, purpose built apparatus was used, consisting of a pneumatic inner tube and aneroid pressure gauge (Figure 1).

All patients rested for five minutes in a quiet, temperature-controlled room prior to initial seated measurements. The middle cerebral artery (MCA) was insonated using a transtemporal approach. A Spencer M100 TCD machine (Spencer Technologies, Seattle USA) with 2 MHz transducer was used for the study. End tidal carbon dioxide concentration was measured to ensure that breath holds were adequate. To avoid valsalva, breath holding was undertaken following normal inspiration.

Participants were randomly allocated to begin wearing the purpose-built necktie inflated or deflated (to simulate a tight and loose necktie, resp.). Randomisation was performed using a simple coin tossing procedure. Inflation pressure was determined by the volunteer's perception of how a "tight" but not excessively uncomfortable necktie would feel. BHI was calculated after 5-minute exposure to tight/loose necktie, with 5-minute "washout" between measurements. This was achieved by measuring the change in MCAv over a 30-second breath hold and calculated using the stated BHI formula. The pressure gauge was concealed from the participant throughout the study, and the same operator performed all measures.

Our primary outcome measure was changed in BHI. Initial descriptive statistics suggested a reasonable parametric distribution, thus a paired t-test was used to compare BHI with necktie inflated and deflated. A sample size of 40 volunteers was deemed necessary to detect a difference in mean BHI of 0.20 units, with 90% power. Post hoc analyses of relationship between BHI (tight) and age; body mass index (BMI), and diastolic blood pressure (mmHg) were performed using chi-square or Pearson correlation as appropriate. All statistics were performed using Minitab software (version 14.0, Minitab Inc, PA, USA).

3. Results

We enrolled 40 healthy males; all subjects approached consented to the study with no "drop-outs" by study completion. Mean age was 31.5 (SD 10.5, range 20–59) years. Mean inflation pressure with the tight necktie was 63.5 (SD 12.3) mmHg. There were no adverse events from use of the necktie. MCAv at rest was similar with the necktie inflated (45.72 cms^{-1}) and deflated (45.00 cms^{-1}). The mean increase in MCAv during the breath hold was 16.49 cms^{-1} with the necktie inflated compared to 19.27 cms^{-1} with the necktie deflated. Cerebrovascular reactivity as measured by the BHI was reduced during necktie inflation (BHI = 1.44 with necktie deflated versus 1.21 when necktie inflated, $P < .001$) (Figure 2). Comparing older (age > 30 years; $n = 20$) and younger volunteers revealed a nonsignificant trend towards reduction in cerebrovascular reactivity (difference 0.07; 95% CI: −0.25 to 0.13) between the groups. Correlation coefficients calculated for blood pressure and BMI were $r = 0.23$ and $r = 0.003$, respectively.

4. Discussion

We hypothesised that wearing a tight collar or tie may compromise the venous drainage of the brain and thus impair cerebrovascular reactivity. Using a novel necktie apparatus we confirmed a significant reduction in cerebrovascular reactivity in healthy individuals wearing a tight necktie.

It is, of course, important to determine the clinical significance of this novel observation. The reduction in BHI seen when wearing the tight necktie (0.23 units) was clinically modest. Even with the necktie fully inflated, observed BHI values lay within values accepted as normal. This suggests that the changes seen are of little clinical significance in young healthy males and are unlikely to contribute to stroke risk in younger cohorts.

However, minor changes in cerebrovascular reactivity may be of importance in populations with higher baseline risk. Several cohorts with coexistent cerebrovascular risk factors and tight tie exposure can be postulated—for example, the cardiovascular risk of the obesity-hypoventilation phenotype is well recognised; with their increased neck girth this population may further increase their risk through wearing a tight necktie [9, 10]. The prevalence of tight neckties/collars should not be underestimated; a recent American study suggested that 70% of middle aged men wear a shirt collar at least one size too small [11].

In a cohort of healthy volunteers, analysis of differential effects of necktie pressure by classical vascular risk factors is not possible. We performed a post-hoc analysis to determine possible effects of certain factors. For age, the most powerful vascular risk marker, a trend towards increased pressure of necktie and greater reduction in reactivity was observed. Statistical significance was not achieved, a reflection of the small numbers in each group, but still an intriguing possibility of greater vascular risk with necktie exposure in older age is suggested. Positive correlation between increasing blood pressure and decreasing reactivity was small, and there was no significant relationship between body mass index and reactivity. Again interpretation of these data must be cautious due to low numbers, "healthy" subjects, and the post hoc nature of these analyses.

We accept that these are preliminary data and this initial hypothesis generating study had certain methodological weaknesses. Our choice of outcome measure is open to criticism. BHI is a surrogate marker of future cerebrovascular disease; a definitive statement on neckties and risk would require a more robust outcome. However, noninvasive measures of cerebrovascular reactivity have been shown to be strongly predictive of future stroke risk and as such are suitable as surrogate endpoint, especially in younger cohorts [12, 13]. Other measures of BHI are described but involve further intervention, for example, administration of a vasoactive substrate [14]; for this initial "pilot" study we felt BHI was a suitable compromise.

BHI measurements were performed after only 5 minutes of necktie exposure. Cerebral vasculature may autocorrect if a tie is worn over a more prolonged period, such as a working day, and the significance of a transiently induced reduction in reactivity is unknown. With a single "dose exposure", our study was unable to define the cumulative effect of repeatedly wearing a necktie. Thus it could be argued that in our study, we have demonstrated the cerebral vascular effects of attempted asphyxiation rather than daily necktie exposure. The pressure defined as "tight" was subjective, with inflation pressures of the "tight" necktie varying by as much as 60 mmHg between participants. This suggests that in a cohort of necktie wearers, some may routinely wear the tie at pressures that may interfere with cerebrovascular reactivity. As discussed, a more informative study may have been to measure cerebrovascular effects in a cohort with prevalent vascular risk factors; for safety reasons a healthy male population was considered for this preliminary analysis.

5. Conclusions

Our data suggest a detrimental effect of tight neckties on the cerebral vasculature. The clinical significance remains to be determined, and it seems unlikely that circumferential neck pressure from a necktie or similar garment is an important contributor to stroke risk in young males. In fact any clinical effect of neckties may be seen only in older patients with concomitant cardiovascular risk factors. The search for important, novel risk factors for stroke in young adults continues. These initial "neutral" findings give some scientific credence to wearing neckties "loose"—if at all.

Acknowledgments

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Review Article

The Psychology of Stroke in Young Adults: The Roles of Service Provision and Return to Work

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Literature about the psychological consequences of stroke in those under 65 is reviewed focussing on services and work. Despite similarities, young and old survivors have different experiences and needs. These are attributable to the effects of stroke on age-normative roles and activities, self-image, and the young person's stage in the life-cycle, especially family and work. "Hidden" cognitive impairments, a disrupted sense of self, and the incongruity of suffering an "older person's" disease are salient. Young survivors benefit from services, but experience lack of congruence between their needs and service philosophy, methods, and aims, and consequently have unmet needs. Employment is psychologically salient, and the evidence about return rates, factors that affect return, and the adequacy of employment-related service provision is reviewed. Specific and general recommendations are made for increasing congruence between young survivors' needs and service provision and also for facilitating their return to work.

1. Definitions and Scope

In this paper a "young" stroke survivor will be considered to be someone aged 18 to 65 years. The lower boundary ties in with the current dividing line between childhood and adulthood, and the upper boundary with the division between working age and old age health services in many countries. This paper is based upon literature searches of several data bases (ASSIA, AMED, British Nursing Index, Cochrane database of systematic reviews, MEDLINE, PsychInfo, SCOPUS, Zetoc, Google Scholar). Reference lists of relevant articles were scanned, and papers that cited articles were also examined to supplement these searches. Reviews and original articles that included material of psychological relevance were selected for further scrutiny and possible inclusion. The focus of the paper is upon factors that affect the psychological adjustment of stroke survivors, particularly service provision and employment.

2. Introduction

The risk of stroke increases with age, and the relationship with age is universally found across nations [1]. The incidence of stroke in younger people is low, but the population demographics of age mean that a significant proportion of new strokes occur in the under 65s. This proportion has been estimated as 21% in the UK [2]. As an example, a country of the size of England, with a population of about 50 million, and about 29 million under 45, would expect around 5,800 new strokes in people under 45 each year. Since people who have a stroke when young are likely to live longer than their elderly counterparts, the prevalence rate for younger strokes is about 25% [2, 3]. Younger people have proportionately more haemorrhagic strokes [4, 5], and ethnic differences in the risk of stroke are accentuated in younger age groups [6].

3. Stroke and Psychological Adjustment in the Young

The psychological effects of stroke and the evidence for their occurrence are summarised in Table 1.

Quality of life after stroke for all age groups was impaired in comparison with comparable healthy adults [7, 8], and studies comparing the quality of life of younger and older

Table 1: Psychological adjustment in young stroke survivors.

Attribute	Evidence
Reduced quality of life. Associated with dependence, depression, being single, fatigue, and being unemployed.	[7–9]
Specific problems	
(i) Loss of home	
(ii) Loss of employment	
(iii) "Psychological paralysis"	
(iv) Problems fulfilling roles, for example, parent	
(v) Financial stress	
(vi) Conflict with spouse	[2, 4, 10–15]
(vii) Conflict with children	
(viii) Childcare difficulties	
(ix) Sexual problems	
(x) Separation or divorce	
(xi) Reduced social and leisure activity	
Psychological disorders/reactions	
(i) Depression	
(ii) Fatigue	
(iii) Anxiety	
(iv) Anger	[4, 11, 13, 16]
(v) Denial	
(vi) Anger/frustration	
(vii) Negative body image	
(viii) Impaired self-efficacy and self-esteem (e.g., through a sense of permanent impairment)	
Lack of acknowledgment of covert impairments (e.g., cognitive)	[11, 14, 17]
Disruption of self and identity	
(i) Changed self-perception	[14, 15, 18–20]
(ii) Acquiring an untimely, old-person's disease.	
Reduced life satisfaction. Associated with impaired concentration (men and women) and being single and not working (only men)	[13]
New perspectives and new roles, helpful to adjustment.	[11]
Self-efficacy determined and maintained by perspectives about the aims of rehabilitation and engagement in the process.	[21]

stroke survivors have produced inconsistent findings [7]. Reduced quality of life in young survivors was associated with dependence, depression, being single, fatigue, and being unemployed [9], and different factors, including type of stroke, visual field impairment, and seizures may be associated with quality of life only in older survivors [8].

Young and old stroke survivors have much in common, but young survivors have particular needs, both practical and psychological. A study of stroke survivors under 50 years of age [4] found that family conflict and loss of home, employment, and spouse were common practical problems. In the case of employment loss the rate was 80%–90%. Staff reported that about half of survivors had psychological disorders, especially depression or anxiety. The anxiety mainly focussed on work, but also related to recovery and childcare. Around a quarter to a third exhibited denial, anger, frustration, or hostility. Problems with employment, finances, and social participation, as well as marital difficulties, including sexual problems, were also reported in a UK questionnaire survey [2]. These results were echoed in the conclusions of a review of 78 studies of young stroke survivors [10], and this review also noted that problems were frequently attributed to the stroke. However, the percentage of survivors reporting problems varied considerably across studies and problems, typically from 5% to around 70%. Body image was found to decline following stroke in a mixed gender group under 40 years old [16]. This was most marked in those with left hemisphere strokes and was associated with a reduction in physical and global measures of self-esteem. Frustration was a core theme found in a qualitative study of survivors under 55 years old, for up to two years after a first stroke [11]. The frustration was related to a sense of psychological paralysis stemming from omnipresent fatigue that affected everyday activities and gender roles, particularly the roles of mother, father, provider, and housekeeper. It was also fuelled by the sense of being "outside and invisible" which revolved around lack of information, lack of consideration of young survivors' needs, a shortage of age-appropriate activities, and their awareness of their "invisible" cognitive impairments. This study also reported positive outcomes of stroke, including new roles and perspectives that improved adjustment. The small sample limited the generality of the results, but there was corroboration from large-scale follow-up studies [12, 13] as well as independent research [14]. More than half of young survivors perceived themselves to have enduring physical and cognitive disabilities and were dissatisfied with life after stroke [13] and many experienced problems caused by paralysis due to fatigue and the "invisibility" of disabilities which predisposed colleagues, family, or friends to discount, ignore, or deny the "authenticity" of the survivor's limitations [14]. Objective evidence for cognitive difficulties in younger stroke survivors (under 45 at time of stroke) was provided by a comparison of neuropsychological test performance of young stroke survivors and matched controls, and there was also a marked contrast between the good recovery of function and mobility in the stroke survivors and the poor recovery of cognition [22]. A study of people with mild stroke [17] further supported these findings and concluded that life satisfaction in this group was affected by subtle impairments including impaired executive function, attention, and other neurological deficits: the rapid recovery of overt, noticeable physical functions created a false impression of generalised recovery that was not paralleled in the less obvious cognitive domain. Finally, a synthesis of four qualitative studies proposed that the experience of young stroke survivors may be encompassed by three overarching domains: "disorientation" due to the sudden effects of stroke, "disrupted sense of self" due to changed self-perception and "loss of control" which may in turn lead to changed priorities, and finally "roles and relationships"

which change due to dependency and impaired functioning [15].

Young survivors face the added psychological task of reconciling the perceived incongruity of suffering an older person's disease at an early age [14] and being treated in services in which older people predominate. This challenges self-identity, or social identity; the way that a person views and experiences themselves and their relationships with significant others and social groups [23]. Identity is a general, central aspect of psychological adjustment, and is important in the efforts of brain injured people to make sense of themselves and their circumstances [18]. Continuity in self-identity has been demonstrated to impact on the psychological well-being of stroke survivors [19, 20].

Sense of self-efficacy, or competence, emerged as an important aspect of identity in a study of young neurological and stroke patients [21]. The patients understood their own and others' roles in relation to rehabilitation in several ways; independence and self-reliance were important, as were determination, pushing limits, and recognition of progress. Professionals and rehabilitation processes were perceived as vital factors influencing self-efficacy, as were vicarious experiences through contact with other patients. However, a singular feature was the way in which a higher-order understanding of the purpose of rehabilitation influenced adjustment. Survivors adopted contrasting views of rehabilitation, as either a process that led to "restitution" of former life, or a process that enabled and supported adaptation, adjustment and change to meet the demands of new circumstances. Taking the perspective of rehabilitation as supporting adaptation was considered to improve adaptation, reduce disappointment, and was more congruent with the aims of professionals.

4. Young Stroke Survivors' Experiences of Services

Young stroke survivors' access to components of stroke care such as specialist stroke units and time with professional staff differed sharply between countries and world regions, as did their fatality rates and functional outcomes [24]. The national stroke strategies and guidelines of wealthier nations generally recognise the special and different needs of younger stroke survivors. For example, the UK National Clinical Guidelines for Stroke [3] state that "*Some younger adults feel that general stroke services, of which the majority of users are older adults, do not meet their needs*" (page 32) and recommend that the particular needs of this group are considered, especially vocational rehabilitation and child care, and that services are "*provided in an environment suited to their specific social needs*" (page 32). However, national stroke strategies around the world do not recommend separate care services for young stroke survivors (e.g., the European Stroke Strategy [25]; the Australian Stroke Strategy [26, 27]; the Canadian Stoke Strategy [28]). Consequently, young stroke survivors receive treatment within stroke care services in which the majority of patients are over 65.

As for stroke survivors in general [29], the quality of life, physical function, and cognition of young survivors all improved when specialist stroke care was provided [30]. It has been suggested that the outcomes of younger and older stroke survivors may be comparable and that the needs of the two groups are substantially similar [31]. This received support from the finding that, although greater age did predict lower absolute functional scores at discharge, the effect of age alone on *improvement* in functioning was small and accounted for less than 2% of variation [32]. Moreover, there is evidence demonstrating that age interacts with other factors to determine outcome; survivors under 75 years old achieved better outcomes than older survivors when treated on specialist stroke units, but not when treated on general wards [33]. A review of 13 studies examining the influence of age on outcome noted that results were inconsistent. One large-scale survey demonstrated that differential treatment for younger and older stroke patients may underpin outcome differences; the greater functional improvement and chances of returning home of young patients may have been a consequence of them receiving, on average, substantially longer hospital treatment than older patients [34].

Few studies have compared the services experienced by younger and older stroke survivors. A study in a neurovascular clinic for people with TIAs or mild strokes compared patients over and under 75 years and found no differences in appointment times, preventative treatments offered, or in rates of receiving CT scans [35]. However younger people were more often given life-style advice about diet and weight, they were CT scanned sooner, and more of them received MRI scans and carotid Doppler investigations (but older people received carotid endarterectomy more rapidly). Two studies that compared age groups (18–45 and 46–65) found that younger patients had more unmet needs in relation to holidays, intellectual fulfilment, and family support, despite having the same number of unmet needs overall [2, 36]. Unfortunately these two studies drew participants from several different services in an unsystematic way, so service factors could account for the age differences.

A questionnaire survey of young survivors at a median of three years after stroke [2] found that GP services were widely used by their informants (77% had consulted within the 12 months before the survey), 24% had utilised third sector stroke organisations (Different Strokes and the Stroke Association), and 15% to 38% received specialist rehabilitation input, with physiotherapy being the most frequent. However, the median number of unmet needs was two, with the most common being personalised information about their stroke and assistance with finances, noncare activities, intellectual fulfilment, adaptations, vehicles and social contacts. Those with impaired mobility and those who did not return to work reported more unmet needs. Employment and sexual difficulties were additional needs, and sexual difficulty rates were much higher than the 40% for women and 30% for men found in the general population [37]. A survey conducted in young stroke groups [36] found results concordant with those above, except that there was a higher rate of unmet needs (median 5). The most often reported service shortfalls were once again personalised

information about the person's stroke, help with finances, assistance with social activities, and assistance in achieving intellectual fulfilment. An in-depth study of response to service provision in 50 survivors (18–49 years old), their relatives, and care staff, covering the period from stroke onset to returning to the community and "moving on," found some additional needs. Young survivors wanted services that focussed on the needs of younger people and considered their family responsibilities, need for employment rehabilitation, difficulties in claiming welfare benefits, child-care problems, and issues regarding employment for their spouse carers. Two further in-depth studies [11, 38] using interviews or case notes suggested that rehabilitation staff were not attuned to the concerns and needs of young stroke survivors and did not formulate their problems effectively or set appropriate goals; while the survivors were preoccupied with loss of control, fatigue, and fear of another stroke, the staff focussed upon functional deficits and training. There was a perceived lack of age-appropriate activities and environments and lack of attention to "invisible" cognitive impairments. Qualitative analyses of separate focus groups of survivors and staff [39] also identified differences between staff and survivors' perceptions of needs. This study included older as well as younger survivors, suggesting that this disparity is not unique to young survivors and many of the service deficits identified in young survivors [40] were shared by older survivors including service variation, poor communication, lack of personalised information, lack of understanding of effects of stroke on patient and family, low involvement in decision-making, gaps in postdischarge support, and gaps in community support.

While the negative service experiences of younger stroke survivors may be partly attributable to failure to identify and respond to their particular needs, the dissatisfaction and distress arising from the experiences of young stroke survivors in health services may not be entirely a function of the services themselves, and may be partly psychological in origin, stemming from the threats to a young person's self-concept and identity [14, 15, 18–20] posed by being treated in services where older people predominate.

4.1. Implications for Services Supporting Young Stroke Survivors. There are currently no evidence-based, interventions specifically designed for young stroke survivors. However, a few general recommendations can be made on the basis of the evidence reviewed above. Caring for young children, relationships with spouse, sexuality, invisible cognitive disabilities, fatigue that affects engagement in age-appropriate activities, loss of employment, reduced intellectual fulfilment, and financial problems seem to be especially salient practical issues. Addressing these adequately not only requires skilled therapists but also networking with nonhealthcare agencies such as employers, social services, job-centres, marital counselling services, and community-based education or leisure facilities. Second, young stroke survivors experience major threats to their self-identity through being isolated from their peers, being unable to meet normal expectations for the leisure and employment activities of young people, having a reduced sense of self-efficacy due to their disabilities and restrictions, experiencing a sharp discontinuity between their prestroke self and their current self, and finally by having what is perceived as an "old person's disease." Young survivors should be afforded opportunities for psychologically oriented counselling and support when well-being is affected by change in identity and a sense of discontinuity. Young stroke survivors require help to understand the wider goal of rehabilitation as a process of adjustment and adaptation to changed capabilities and circumstances rather than simply the "restitution" of former patterns of activity. Peer support is widely employed to assist the adjustment of stroke survivors by voluntary stroke groups, but has been only sparsely researched and its benefits for stoke survivors are not fully established. However, it was included in the National Stroke Strategy for England [41], and there is some evidence for its effectiveness in supporting the psychological well-being of stroke carers (see Section 5.2.)

5. Work after Stroke

The total economic cost of stroke to the UK economy has been estimated as exceeding £8.9 billion per year and a substantial proportion of the total is attributable to the cost of loss of employment and benefits payments (£2.2 billion) [42]. In addition to its economic importance, the benefit of work for individual health and well-being has been recognised. It is an important source of income essential for material well-being and participation in society, and it also meets psychosocial needs, helps develop and maintain individual identity, social roles, and social status, and is associated with physical and mental health and longevity. Conversely, worklessness is associated with greater mortality, poorer mental and physical health, and greater use of health-care resources [43].

5.1. Work and Young Stroke Survivors. Work is valued and a salient issue for stroke survivors, even for those not working prior to their stroke [55, 64], and not having work after stroke is often perceived as a major problem [64]. Many young stroke survivors were working at the time of the stroke and, perhaps just as important, so were their partners. For some the stroke may present an opportunity to change lifestyle, take early or medical retirement, or to explore eligibility for age-related benefits. For others, particularly those with dependent children, these routes may not be an option. Reported rates of return to work after stroke vary widely, due to contextual and methodological differences between studies. A review of 16 studies conducted in 12 developed countries [65] identified rates ranging from 14% to 73% with a median value of around 50%. Most of those returning to work did so quickly, usually in 3–6 months, but there were reports of a second peak at 12–18 months, perhaps when the consequences of long-term unemployment began to impact. Daniel et al. [10] found the mean percentage returning to work to be 44% (range 0 to 100%) in a review

Table 2: Facilitators and barriers for return to work.

Dimension			Evidence
Better functioning versus impaired functioning.			[44–51]
Holding a full-time job versus a part-time job			[52]
Having an office-based rather than a manual job			[45, 46, 49, 50]
Being male, white, or of high socioeconomic status versus being female, black, or of low socioeconomic status			[51, 53, 54]
Preserved cognitive ability versus cognitive impairments			[45, 46, 48–50]
Sympathetic flexible employers versus inflexible employer			[55–58]
Specific Facilitators	Evidence	Specific Barriers	Evidence
Positive personal attributes (patience, determination)	[56]	Stroke symptoms that impair specific work competences	[57–59]
Support from families and social networks	[55, 56]	Fatigue	[11, 56]
Support from health care professionals	[56]	Having a psychological disorders	[52, 60]
Disability legislation and statutory sick leave	[61]	Perceived stressfulness of work	[55, 59]
Employment tasks that can be flexibly configured.	[55, 56]	Benefits systems that encourage nonreturn to work	[57, 58, 61]
Previous positive experience of work	[55]	Lack of understanding of stroke by employers	[61]
Valuing work and its intrinsic rewards	[53, 61–63]	Lack of information about returning to work	[61]

that included 70 studies, but studies of return at 6–12 months after stroke found the rate to be slightly over 50%.

Several studies have attempted to identify factors that influence return to work after stroke. Successful return to work has been shown to be associated with individual factors such as absence of dysphasia [44], higher functioning on discharge [44–51], shorter rehabilitation stay [44, 48], lack of apraxia [45, 46], freedom from psychological disorders [52, 60], preserved cognitive abilities [48–50], and low alcohol intake prior to stroke [44]. Employment factors were also important determinants of return to work, and blue-collar (manual) workers returned sooner [45, 46], but white-collar (office) workers were more likely to return to work in the long term [45, 46, 49, 50]. Being in full-time employment prior to stroke [52] and having a positive attitude to work [53] were also associated with successful return, as were higher socioeconomic status [53], not being black [51], being male [51, 54], and receiving support from others [53]. Stroke location was not predictive of resumption of work in one study that examined this relationship [46]. Return to work was found to be associated with higher quality of life [47], well-being, and life-satisfaction [49]. A questionnaire survey [57, 58] of stroke survivors found that 75% of respondents said they would like to return to work, but 36% felt that they could not, and 43% had not been able to return to work, although 31% had worked since their stroke. Reasons given for not returning to work included: forced to retire by employer; cannot meet expectations; cannot drive/use public transport; afraid of losing benefits; not fit enough to work; can no longer do previous job.

Several studies have used in-depth qualitative methods to explore experiences of work in stroke survivors. Interviews with 43 survivors under 60 found that returning to work was a salient issue for the participants and a benchmark for successful recovery. The participants valued work and its benefits, including those not working before their stroke [55]. Another study of right hemisphere stroke survivors and their carers found that the stroke precipitated employment changes for all, and these employment changes had a substantial psychosocial impact on both the stroke survivor and the carer [56]. Lock et al. [61] studied stroke survivors and carers and reported four principal themes of relevance to work: rehabilitation process, employer agency, social-structural factors, and personal factors. Rehabilitation process was seen as being focussed on minimal physical recovery, time-limited and not sufficiently oriented to employment. Survivors responded to the shortfall in rehabilitation by taking control and pursuing their own goals, but also acknowledged the importance of family support and support from co-workers. The benefits system militated against return to work, and, in addition, information about support and opportunities for returning to work was limited. The UK Disability Discrimination Act [66] and sick leave arrangements were considered to facilitate return, but employers' inflexibility, ignorance about stroke, and negative attitudes were barriers. This latter finding is echoed by studies demonstrating that flexible, sympathetic work environments and practices, and supportive social networks facilitated return to work [55, 56], as did instrumental and emotional support from healthcare professionals [56]. As in other studies [11, 56], fatigue was seen as the major personal factor in returning to work, and perceived cognitive impairments were also implicated. One study [55] reported that return to work hinged upon the relative impact of barriers and facilitators; stress, and its possible consequences for health, was one such factor, as were past experiences with working or not working and severe residual disabilities which could make working impossible. Lock et al. [61] also identified

Table 3: Promoting return to work.

Consideration/Factor	Evidence	Implications
A very high proportion of young survivors wish to return to work. Employment is a central life role, bringing intrinsic rewards. Return to work is associated with better life-satisfaction and quality of life.	[49, 55, 62, 64]	(i) Consider employment in rehabilitation goal planning for all working-age stroke survivors.
A significant proportion of those working before stroke will not return to work. Many of these will want to return.	[2, 4, 52, 56, 57, 64]	(i) Psychological therapy should consider this as a major and sudden "loss". (ii) Such survivors and their carers may require help with adjustment to new circumstances. (iii) Encourage survivors to explore creative approaches to developing alternative activities.
Many survivors return to different types of work, including voluntary work.	[2, 49, 59–61]	(i) Provide vocational advice on suitable types of work. (ii) Encourage flexibility and exploration of options in survivors. (iii) Develop awareness of the Disability Discrimination Act and flexible provisions for disabled employees. (iv) Develop connections with potential employers including voluntary organizations.
A positive attitude to return to work is important.	[53, 55, 63]	(i) Individual and group therapeutic interventions to promote the benefits of work and influence attitudes may be beneficial.
Social, demographic and economic factors are important. (i) Wide variation in return rates between different countries. (ii) Socioeconomic status predicts return to work (iii) Gender, ethnicity, and age are associated with return	[65] [53] [51, 54]	(i) Professionals require good awareness of national employment disability legislation, benefits systems and employment practices. (ii) Individual demographic and socioeconomic factors and should be considered when planning support.
Employers' attitude and support are important determinant of return	[53, 55, 56, 63, 64]	(i) Advocacy should be available for those who wish to return to work. (ii) Stroke service should network with agencies that find employment, retrain, or support employment. (iii) Network with employers and/or human resources departments to build support for return to work.
Residual disabilities, physical ability and especially weakness are related to return.	[44–46, 48, 53, 54, 56, 59, 64]	(i) Return to original employment may not be realistic in all cases. (ii) Professionals should provide realistic feedback, considering the survivors readiness to accept it. Premature pessimistic prognosis should be avoided. (iii) Flexible, phased return may be helpful. (iv) Long-term support may be required.
Fatigue is an important factor in return.	[11, 56, 61, 64]	(i) Recognise fatigue as a common barrier to returning to work. (ii) Consider fatigue management as part of psychological therapy. (iii) Plan return to work allowing for effects of fatigue. A phased return may be helpful.
"Hidden" cognitive deficits are a concern for survivors.	[11, 14, 48–50, 53, 56, 61]	(i) Cognitive assessment for all intending to return to work. (ii) Consider cognitive rehabilitation. (iii) Consider "information prosthesis" and compensatory measures (diaries, pagers, electronic aids). (iv) Incorporate into psychological therapy to develop insight and promote adjustment.

Table 3: Continued.

Consideration/Factor	Evidence	Implications
Stress due to work is a factor when survivors consider return.	[55]	(i) Concern about work stress and its possible effects on health should be considered. (ii) Medical and psychological advice may be helpful.
Assets and resources are influential factors in return.	[55, 56, 61]	(i) Encourage survivors and carers to "audit" their assets and incorporate into their plans. (ii) Assets may include; family and social networks, healthcare agencies, employers (managers and human resources/personnel, occupational health).
Psychological disorders are a factor in stroke patients' return to work.	[52, 60]	(i) Offer treatment for any psychological conditions such as depression, anxiety or PTSD.

the intrinsic rewards of work as an incentive for survivors to take employment, and this is concordant with the results of Scandinavian studies [62, 63]. Those who valued the intrinsic rewards of work were also the most satisfied [62]. Further individual psychological factors implicated in returning to work were the personal attributes of patience, determination, and sense of humour [56]. Salient work-related concerns expressed by survivors included symptoms that prevented them from working, uncertainty and fear about returning, and the challenges of changing jobs [59].

On the basis of the research reviewed above, some dimensions and specific factors associated with return to work are summarised in Table 2.

5.2. Helping Stroke Survivors Return to Work: The Evidence and Its Implications. Work is a major issue for younger stroke survivors and their carers, and rehabilitation should adapt goals to meet their needs and aspirations in this area. There are several employment-related considerations and influential factors that those involved in service development and rehabilitation should consider (Table 3). It is likely that the factors illustrated in Table 3 interact, and case studies and in-depth interviews [64, 67] illustrate how outcomes depended on the interplay of personal factors, and disaffection with alternatives to not working, financial incentives and job characteristics.

In addition to the recommendations in Table 3, Wolfenden and Grace [68] made 13 recommendations for facilitating the return to work of high-functioning working-aged stroke survivors. These were based on a review of the literature and the experiences of one of the authors who was a stroke survivor. These recommendations called for education to raise awareness of the aspirations and needs of stroke survivors, a greater focus on rehabilitation directed towards nonmedical needs such as returning to work, and for rehabilitation to continue for longer after discharge. They also focussed on the workplace and proposed that greater consideration be given to the special needs of the survivor.

Unfortunately, the recommendations in Table 3, and those of Wolfenden and Grace [68], do not map clearly on the roles and responsibilities of multiprofessional stroke rehabilitation teams in many nations (e.g., the UK National Service Framework for older people [69]) and involve areas of expertise and a degree of interagency working not currently common in rehabilitation services. One promising approach is the development of vocational rehabilitation programmes encompassing the needs of young stroke survivors. Radford and Walker [70] reviewed work after stroke and included studies of vocational rehabilitation for brain-injured people. They concluded that vocational rehabilitation has considerable potential both in terms of individual and cost benefit, but that its application to stroke has been under-researched, and service provision has been patchy, poorly organised and meets only a fraction of the need.

Another development with relevance to the employment of stroke survivors and their carers was the incorporation of peer support into the National Stroke Strategy for England [41]. Peer support for stroke survivors has not been studied, but it has been used successfully with stroke carers [71, 72] and been shown to be beneficial for other health conditions [73, 74]. As well as enhancing the experience of new stroke survivors and their carers, participation as a peer supporter fulfils the intrinsic functions of work and has potential for enhancing quality of life and re-engaging participants in the benefit and challenges of employment [75, 76].

Finally, the use of internet-based resources may help to encourage stroke survivors and inform employers about the employment potential of stroke survivors. These resources may also serve to inform survivors, employers, and carers about practical aspects of return to work. Such information is published on the Different Strokes website in three "Returning to Work After Stroke" documents, one for survivors, one for families and friends, and one for employers [77].

6. Conclusions and Future Research

Young stroke survivors have psychological needs which overlap with those of older survivors, but some areas are more prominent in this group. These are mainly associated with being at an earlier life stage, but also stem from the effects of stroke which make them feel "different" and isolated from their young peers and "changed" from their former selves.

Many of these needs are not met by current stroke services. At an international level there seem to be no plans for separate, dedicated, services for young stroke survivors, therefore it is vital that existing stroke services recognise the special needs of this group and take appropriate action. This will require staff training to develop the capacity to deliver the prerequisite therapies as well as service reconfiguration to enable networking with relevant nonhealth service agencies.

There are no specific psychological interventions designed for young stroke survivors, and while it may not be practicable to develop new age-specific and stroke-specific therapies, there is potential to develop guidelines for adapting psychological therapies to meet the particular needs of this group.

With regard to re-engagement with employment, a number of specific recommendations were made on the basis of the literature and are summarised in Table 3. The number and importance of these recommendations, and the singular lack of provision of vocational rehabilitation within existing services, highlights the urgent need for research that will lead to the development of integrated service models and increase access to this vital resource.

The provision of peer support has the potential to meet some of the needs of recovering stroke survivors and of those who have completed their recovery by involvement as volunteers or paid supporters.

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Review Article

Long-Term Prognosis of Ischemic Stroke in Young Adults

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There is limited information about long-term prognosis of ischemic stroke in young adults. Giving the potentially negative impact in physical, social, and emotional aspects of an ischemic stroke in young people, providing early accurate long-term prognostic information is very important in this clinical setting. Moreover, detection of factors associated with bad outcomes (death, recurrence, moderate-to-severe disability) help physicians in optimizing secondary prevention strategies. The present paper reviews the most relevant published information concerning long-term prognosis and predictors of unfavorable outcomes of ischemic stroke affecting young adults. As a summary, we can conclude that, in the long term, stroke in the young adult increases slightly the risk of mortality, implies higher risk of future cardiovascular events, and determines functional limitations in a significant percentage of patients. Nevertheless, in every individual case the prognosis has to be considered depending on several factors (stroke subtype, initial severity, cardiovascular risk factors) that determine the long-term outcomes.

1. Introduction

Ischemic stroke in young adults (15–45 years) is not exceptional and accounts for up to 12% of all first ischemic strokes, with a wide diversity of etiologies [1–8]. Moreover, the impact on years of potential life lost and on socioeconomic cost is very important in this range of ages.

Many series have reported a favorable prognosis, but only the short-term prognosis has been widely evaluated and there are few investigations about long-term functional recovery of young adults with first-ever ischemic stroke.

Most of the investigations in long-term prognosis have described good functional recovery in young adults with ischemic stroke, since most patients are independent and at least 50% return to work [8–12]. Moreover, some predictive factors for mortality, recurrence, and good/poor functional recovery have been identified [12].

In the main series, the mean followup after the initial episode ranges between 1 and 16 years (Table 1) [9–33]. The most important methodological limitations in most of these studies are the retrospective design, but it is not so important to evaluate the long-term consequences of stroke, since events as recurrence, death, and disability can be easyly and accurately evaluated with this methodology. The review of the clinical records (including periodic outpatient reviews) complemented with telephone interviews is the main tools for obtaining information about the patients' functional status after the stroke in the main studies about consequences of stroke in the young [9–14], including prospective series [10, 11].

The prognosis of ischemic stroke in the young is much better than in the elderly, with lower mortality and recurrence and better functional recovery [12]. Thus, prognosis of stroke in young as a whole has been described as favorable in most of the series [12, 17–21], but the long-term prognosis is notably worse when compared with the general population of the same age, with higher death rate, higher risk of cardiovascular events, and significant limitations in quality of life [12]. Moreover, in our series (with a mean followup of almost 12 years and mean age of 36 years old), only 57% of the patients followed for more than 3 years are alive, free of significant disability, stroke recurrence or other vascular event [12].

2. Mortality

The overall risk of long-term death after an acute ischemic stroke in young adults is low. The reported cumulative risk

Table 1: Long-term followup series in young adults with ischemic stroke.

	Number of patients	Mean followup [years]	Type of study
Varona et al. [12]	272	11.7	Retrospective
Putaala et al. [31]	731	5	Prospective
Hindfelt and Nilsson [13]	74	16	Prospective
Marini et al. [10]	330	8	Prospective
Kappelle et al. [9]	296	6	Retrospective
Lanzino et al. [20]	155	5.8	Prospective
Camerlingo et al. [21]	135	5.7	Prospective
Bogousslavsky and Regli [18]	38	3.8	Consecutive cases
Ferro and Crespo [14]	215	3.5	Prospective
Leys et al. [11]	287	3	Prospective
Chancellor et al. [29]	59	3	Retrospective
Matias-Guiu et al. [22]	386	2.8	Prospective
Grindal et al. [26]	34	2.7	Retrospective
Snyder and Ramirez-Lassepas [27]	52	2.4	Retrospective
Srinivasan [28]	46	2	Retrospective
Nedeltchev et al. [32]	136	2.1	Prospective
Musolino et al. [30]	60	6.1	Prospective
Naess et al. [33]	232	5.7	Retrospective

Table 2: Annual and cumulative rates of mortality and recurrent stroke in young adults after a first-ever ischemic stroke, based on data of study of Varona et al. [12].

	0-1 year	2–5 years	2–10 years	2–20 years
Mean annual mortality (%)	4.9	1	0.8	0.9
Cumulative mortality (%)	4.9	9	12.1	21.7
Mean annual recurrence (%)	3.6	3	2.3	1.7
Cumulative recurrence (%)	3.6	15.4	24.2	36.4

of mortality is about 2% (95% confidence interval [CI], 1.5% to 3.9%) at 1 month, about 5% (3.1% to 6.5%) at 1 year, 9%-10% (8.5% to 11.5%) at 5 years, and 12% (11.2% to 13.0%) at 10 years [12, 31] (Table 2).

The mortality rate is higher in the first year (about 4%-5%; 95% CI: 1.8% to 6.0%) and decreases in following years (about 1.0% annually; 95% CI: 0.3% to 1.7%) [10–12, 21, 34]. Also the risk of vascular mortality is higher in the first year after stroke and then falls to lower risk in subsequent years. Thus, the mean vascular mortality rate is lower as longer is the followup.

The cumulative risk of mortality at 10 years in young adults with ischemic stroke is about almost 10 times higher than in the general population of the same age [12, 34], as shown in Figure 1, which compares the survival of young

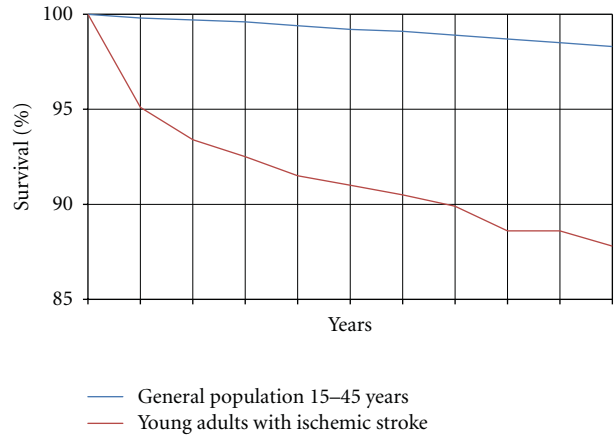

Figure 1: Graph showing a comparative approximation of the different probabilities of survival at 10 years in young adult patients (15–45 years) with ischemic stroke and the general population aged 15–45 years. (based on data of study of Varona et al. [12]).

patients with ischemic stroke in our series against the survival of persons between 15–45 years in the Madrid Community [35, 36], indicating the negative impact on survival for suffering from ischemic stroke in the young [12].

However, the mortality of young adults with ischemic stroke is much lower than in older patients, since survival at five years is more than 90% in the young and only 40% in the elderly [37].

Among the survivors after a first-ever ischemic stroke, the main causes of death are stroke recurrence (20%–30%), other cardiovascular events (20%–50%), malignancies (15%–35%), and infections (10%) [9, 12, 31].

2.1. Risk Factors for Mortality. Apart from patients with malignancies, several subgroups of patients and some factors have been identified as associated with notably higher risk of death: increasing age (above 35 years; relative risk [RR] of 2.0 and hazard ratio [HR] of 2.5), male gender (RR of 1.9; HR of 2.1), the presence of cardiovascular risk factors, in particular arterial hypertension (HR 1.3), completed stroke, with total anterior circulation involvement (HR: 3.3), heart failure (HR: 5.2), heart and/or vascular disease (HR: 1.7), heavy drinking (HR: 2.8), large artery atherosclerosis (HR: 4.4), smoking (HR: 1.4), and severe neurological deficit at presentation (RR of 5.1) have been associated with mortality in young adults with ischemic stroke [10, 12, 31, 33]. The majority of these factors are associated with an atherosclerotic risk profile, which is present in older and male patients in whom premature atherosclerosis is much more prevalent [38] and prognosis is worse.

As "protective" factors, the following have been reported as associated with lower long-term mortality: stroke due to dissection of extracranial arteries, stroke associated with migraine, permanent poststroke anticoagulation therapy (in patients with cardioembolic stroke or potential cardiac sources of emboli and patients with hypercoagulable states) (RR 0.3), and hypercholesterolemia (RR 0.3). The protective role of hypercholesterolemia therapy has been reported in

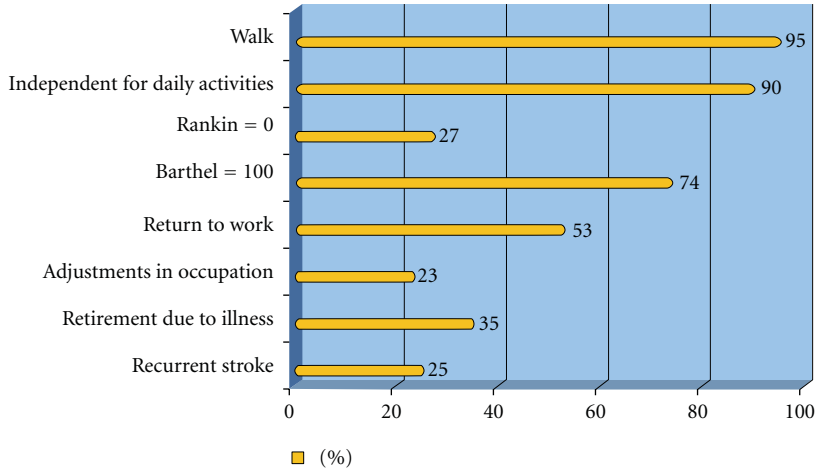

Figure 2: Functional outcome after long-term followup of young adults with ischemic stroke (number of patients: 240; mean followup time: 11.7 years), based on data of study of Varona et al. [12].

young [10, 12] as well as in elderly [39]. This is due to the neuroprotective effect of drugs such as statins or fibrates, which are prescribed in young adults with stroke and hypercholesterolemia.

Ischemic stroke in relation to atherothrombotic (HR: 4.4) and cardioembolic (HR: 2.8) causes has been associated in some series with a poor prognosis. Conversely, several etiologies have been associated with better prognosis and lower percentages of mortality: lacunar infarct, nonatherosclerotic vasculopathy, hypercoagulable state, and undetermined/unknown etiology [9, 10, 31, 40].

3. Long-Term Functional Deficits

With respect to functional recovery, the prognosis for young adults with stroke is good, especially compared with the elderly. Some series have reported that up to 90% of patients with a long-term followup are independent for all activities of daily living and 95% are able to walk without any assistance in spite of previous stroke (Figure 2) [9–12].

Functional recovery and residual disability outcomes are often rated with modified Rankin scale (MRS), Barthel Index (BI), and Glasgow Outcome Scale (GOS). According to these scales, in the long-term followup even more than 70%–80% of the patients report no significant problems for daily activities (MRS = 0–2; IB = 100), about 10%–20% report moderate handicaps (MRS = 3), and only about 10% report major handicaps and residual dependency after ischemic stroke (MRS score higher than 3 and/or BI score less than 90) [12, 30, 41].

These figures contrast with the figures in the elderly, in whom 35%–40% of patients with stroke are dependent on other persons after the stroke [42, 43].

The reported predictive factors for better long-term functional recovery have been: age below 35, transient ischemic stroke, favorable initial course without severe handicaps at discharge, and stroke associated with migraine and/or oral contraceptives [11, 12]. No etiology has been significantly associated with a better or poorer functional recovery, but lacunar infarct and unknown etiology have been associated to a slightly better prognosis.

4. Occupational Status

Ischemic stroke in the young originates limitations in the quality of life and occupational status [9, 12, 20, 21, 40, 44]. Series have reported that between 50%–70% of young adults with stroke return to work, with a time period ranging from several days after stroke to 40 months, with a mean of 8 months. However, about 25% of them need adjustments [other job or part-time employment] in their occupation due to their inability after stroke to perform the prior activity, so less than half of the patients return to their previous work (Figure 2) [9, 10, 12, 30, 40, 45].

Transient ischemia (71%), undetermined stroke (69%), and nonatherosclerotic vasculopathy (64%) had been associated with a higher probability of returning to work [12].

5. Other Sequelae

In the reported series, between 20%–50% of patients have poststroke depression (using DSM-IIIR criteria and/or The Montgomery Asberg Depression Rating Scale). Most of these patients need specific psychiatric assistance. Stroke localization on carotid artery territory, a severe disability, and absence of return to work have been reported as associated with poststroke depression [12, 41].

The poststroke headache has been reported in about 15%–20%, while poststroke seizures have been reported in about 10% [12, 33, 41].

6. Quality of Life

Few studies have evaluated specifically the quality of life after ischemic stroke in young people. In a Norwegian report, stroke had only moderate effects on self-reported health-related quality of life (HRQoL) among young adults with

ischemic stroke as a group (the most affected domain was physical functioning), although some factors were associated with marked reduction in HRQoL: functionally dependant status, fatigue, depression, unmarried status, and unemployment [46]. Other series conclude that aside from residual disability (mainly rated by MRS scale and BI), other factors which affect the quality of life are unemployment, motor impairment, aphasia, dysarthria, and dysphagia [47].

Thus, early identification and improved therapy for conditions such depression, fatigue, and physical disability may improve quality of life among young adults with ischemic stroke [46].

7. Recurrence

Recurrent stroke is frequent in the young, but lower compared with older patients, so cumulative recurrence rate at 5 years is almost 2 times lower in young (15%) than in older (29.5%) patients (Table 2) [12, 48].

The recurrence rate is higher in the first year (3%–5%) and decreases in following years (2%–5%). Thus, the annual recurrence rate between the second and twentieth year after stroke is less than 2% [10–12, 21, 33, 49] (Table 2).

Recurrence is more frequent in patients with atherothrombotic stroke (about 5% annual) than in those with stroke due to non-atherosclerotic vasculopathy (about 2%) [12].

Recurrent stroke may result in an important limitation in vital and functional prognosis, so about 15%–20% of patients died as the result of the recurrence, 30%–40% had severe handicaps with residual dependent status, and more than 50% receive permanent disability pension as a result of the recurrent stroke. These findings underline the importance of a properly secondary prevention therapy to avoid recurrence.

The predictive factors for recurrence in most of the studies are age over 35 years (RR: 1.7), the presence of cardiovascular risk factors (especially, diabetes mellitus, RR: 2.5), previous transient ischemic attack (RR: 1.5), and atherothrombotic stroke in the carotid territory (RR: 1.7). Stroke associated with migraine, stroke due to extracranial artery dissection, and patients with an unknown etiology have been associated with lower risk of recurrence [2, 12, 13, 20, 32, 33].

8. Conclusions

Although global risk of long-term death is low, first-ever ischemic stroke in young people has severe prognostic implications. The mortality risk is higher than general population, the risk of recurrent vascular events is considerable, and only about 50% of patients recover fully (without significant disability) and return to work after first-ever ischemic stroke. Several subgroups have notably increased risk of unfavorable outcomes in the long term and therefore need special attention. Thus, while the atherosclerotic risk profile is associated with the highest risk of recurrent stroke and mortality, age under 35 years and the stroke associated with dissection, migraine and/or contraceptives are associated with a good long-term outcome. Regarding young people with a long expected life span ahead, identifying factors associated to higher mortality is essential, because we can modify some of these factors with strict pharmacological control and/or invasive cardiovascular procedures in selected patients.

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