

RECENT ADVANCES IN PEDIATRIC OTOLARYNGOLOGY

GUEST EDITORS: JEFFREY A. KOEMPEL, TOMISLAV BAUDOIN, ALAN T. L. CHENG,
DEBRA M. DON, AND AJOY M. VARGHESE





Recent Advances in Pediatric Otolaryngology

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Guest Editors: Jeffrey A. Koempel, Tomislav Baudoin,
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Editorial

Recent Advances in Pediatric Otolaryngology

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Ear, nose, and throat problems comprise a significant portion of patient visits to the primary care physicians' offices, urgent care facilities, emergency rooms, and children's hospitals. Since its beginnings in the 1970s, the specialty of pediatric otolaryngology has developed significantly and even more so in the last five to ten years. The aim of this special issue is to offer our pediatrician colleagues an opportunity to learn about recent advances in both diagnostic methods and therapeutic procedures that are now available to assist in the care of children with ear, nose, and throat disorders.

This special issue is comprised of both original clinical research and review articles from all areas of pediatric otolaryngology such as otologic disease and hearing loss, sinonasal disorders, airway issues, and head and neck masses. These papers emphasize how methods of diagnosis have improved for certain conditions, how existing surgical procedures have been modified to be less invasive and better tolerated, and finally, how new technology and operations allow clinicians to treat otolaryngologic disorders that were without treatment in the past.

The paper "Troublesome tinnitus in children: epidemiology, audiological profile, and preliminary Results of Treatment" by G. Bartnik et al. offers a very readable and practical approach to a common otologic problem in children while most pediatric textbooks often have no information on this subject. This group offers their experience with a treatment

called "Tinnitus Retraining Therapy." A. Koravand, B. Jutras, and M. Lassonde present their original research using the diagnostic tools of cortical auditory evoked potentials and mismatch responses (MMRs) to identify patterns of neural activity in the central auditory system of children with hearing loss.

The care of patients with nose and sinus complaints can be frustrating to the primary care physician. H. Ramadan's paper "Chronic rhinosinusitis in children" provides a simple, straightforward approach to the pediatric patient with these symptoms including the use of "real-life" examples to illustrate the important aspects of the history and physical exam that are necessary in the care of these patients. After reading this article, any health care practitioner will feel more confident about their decision-making in patients with sinus disease. Although juvenile angiofibroma is a rare clinical problem, P. Nicolai, A. Schreiber, and A. B. Villaret describe new, less invasive approaches to treatment of this sinonasal mass. This is in addition to a succinct review of the pathophysiology and recommended work-up including the relative advantages and disadvantages of various radiographic imaging techniques.

The airway section of this special issue will be of great value to the primary care practitioner. Included are three papers on stridor in the infant, one dedicated entirely to laryngomalacia, and lastly, a paper on a new diagnostic tool

called “sleep endoscopy.” M. Daniel and A. Cheng discuss the approach to an infant with noisy breathing or stridor; separating the material into three sections that allow for easy recall and use by the pediatrician. Novel approaches such as the EXIT procedure to treat disorders of the fetal airway are presented. A. M. Landry and D. M. Thompson’s review article on laryngomalacia will be equally relevant. The reader will find it to be complete yet easily digestible. Finally, any health care practitioner will be familiar with the frustration of seeing patients for persistent difficulty breathing at night after adenotonsillectomy for upper airway obstruction or obstructive sleep apnea. Although polysomnography can determine the presence and severity of any degree of obstruction, it cannot identify the location of obstruction. The paper by A. C. Lin and P. J. Koltai describe a new diagnostic tool called “sleep endoscopy” that will allow otolaryngologists the opportunity to identify such areas of obstruction and perhaps offer treatment options which were not obvious in the past.

The approach to a patient with a vascular malformation can be confusing. G. T. Richter’s review article on this clinical entity will be very helpful to the primary care practitioner. Nomenclature, relevant parts of the history and physical exam, diagnostic tools including radiographic imaging studies, and medical and surgical therapies are discussed. D. Dzepina’s paper on papillary thyroid carcinoma in children describes their approach and results with total thyroidectomy including neck dissection for lymphatic dissemination which is common in this type of thyroid cancer.

The editors of this special issue have worked hard with the authors to provide primary care practitioners with information that is relevant to their practice and, at the same time, very easy to read and understand. We hope the papers in this special issue will be of great help to primary care practitioners as they see pediatric patients with ear, nose, and throat problems.

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Review Article

Hemangiomas and Vascular Malformations: Current Theory and Management

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Vascular anomalies are a heterogeneous group of congenital blood vessel disorders more typically referred to as birthmarks. Subcategorized into vascular tumors and malformations, each anomaly is characterized by specific morphology, pathophysiology, clinical behavior, and management approach. Hemangiomas are the most common vascular tumor. Lymphatic, capillary, venous, and arteriovenous malformations make up the majority of vascular malformations. This paper reviews current theory and practice in the etiology, diagnosis, and treatment of these more common vascular anomalies.

1. Introduction

Vascular anomalies are congenital lesions of abnormal vascular development. Previously referred to as vascular birthmarks, vascular anomalies are now classified based on a system developed in 1982 by Mulliken and Glowacki that considers histology, biological behavior, and clinical presentation of these entities [1]. A primary distinction is made between a vascular tumor, which grows by cellular hyperplasia, and a vascular malformation, which represents a localized defect in vascular morphogenesis. Due to the differences in biologic and radiographic behavior, malformations are further divided into slow-flow and fast-flow lesions (Table 1).

Both vascular tumors and malformations may occur anywhere on the body. In brief, hemangiomas are vascular tumors that are rarely apparent at birth, grow rapidly during the first 6 months of life, involute with time and do not necessarily infiltrate but can sometimes be destructive. Vascular malformations are irregular vascular networks defined by their particular blood vessel type. In contrast to hemangiomas, they are present at birth, slow growing, infiltrative, and destructive. Almost all vascular malformations and nearly 40% of hemangiomas eventually require intervention. Thus, this paper offers pediatricians an update on recent

developments in the diagnosis, management, and pathogenesis of vascular anomalies. Due to their complexity, a multidisciplinary approach is frequently necessary in managing these lesions and includes a team of specialists in pediatric otolaryngology, dermatology, hematology, interventional radiology, surgery, orthopedics, and sometimes psychology.

2. Hemangiomas

Infantile hemangiomas are the most common tumor in infancy and occur in approximately 10% of the population. Identifiable risk factors include female sex, prematurity, low birth weight, and fair skin [2]. They consist of rapidly dividing endothelial cells. Because their growth is attributed to hyperplasia of endothelial cells, they are classified as, and are the most common, vascular tumors.

Hemangiomas are further categorized into two types: "infantile" or "congenital." The rare "congenital" hemangioma is less understood and present at birth. Congenital hemangiomas either rapidly involute (rapidly involuting congenital hemangioma (RICH)) over a very brief period in infancy or never involute (noninvoluting congenital hemangioma; (NICH)). The remaining sections will focus on the more common "infantile" hemangiomas.

TABLE 1: Classification of vascular anomalies.

Vascular tumors	Vascular malformations
	Slow-flow
Infantile hemangioma	Capillary malformations
Congenital hemangioma	Venous malformations
Tufted angioma	Lymphatic malformations
Kaposiform hemangioendothelioma	Fast-flow
	Arteriovenous malformations

The pathogenesis of infantile hemangiomas remains unclear, although two theories dominate current thought. The first theory suggests that hemangioma endothelial cells arise from disrupted placental tissue imbedded in fetal soft tissues during gestation or birth. Markers of hemangiomas have been shown to coincide with those found in placental tissue [3]. This is further supported by the fact that they are found more commonly in infants following chorionic villus sampling, placenta previa, and preeclampsia [2]. A second theory arose from the discovery of endothelial progenitor and stem cells in the circulation of patients with hemangiomas [4]. The development of hemangiomas in animals from stem cells isolated from human specimens supports this theory [5]. However, infantile hemangiomas most likely arise from hematopoietic progenitor cells (from placenta or stem cell) in the appropriate milieu of genetic alterations and cytokines. Abnormal levels of matrix metalloproteinases (MMP-9) and proangiogenic factors (VEGF, b-FGF, and TGF-beta 1) play a role in hemangioma pathogenesis [6]. Genetic errors in growth factor receptors have also been shown to affect development of hemangiomas [7].

2.1. Diagnosis. Infantile hemangiomas present shortly after birth most often as well-demarcated, flat, and erythematous red patches. At this stage, hemangiomas may be confused with other red lesions of birth, but rapid proliferation and vertical growth will trigger the diagnosis (Figure 1(a)). Generally speaking, hemangiomas do not spread outside their original anatomical boundaries. Hemangiomas follow a predictable course with three distinct developmental phases: proliferation, quiescence, and involution. In most hemangiomas, eighty percent of proliferation occurs by three months of life but may last longer [8]. During proliferation, rapid growth can lead to exhaustion of blood supply with resulting ischemia, necrosis, ulceration, and bleeding.

Hemangiomas can be superficial, deep, or compound. The superficial hemangioma is red and nodular with no subcutaneous component. A deep hemangioma presents as a protrusion with an overlying bluish tint or telangiectasia. Compound hemangiomas have both deep and superficial components (Figure 1(b)). This new nomenclature helps eliminate confusing older terms (Table 2).

Following proliferation, hemangiomas enter a slower or no growth phase, known as quiescence. This phase typically lasts from 9 to 12 months of age. The final and unique phase of the hemangioma lifecycle is involution. This phase is

marked by graying of the overlying skin and shrinking of the deeper components (Figure 1(b)). Historical reports suggest that involution of 50%, 70%, and 90% of the hemangioma occurs by 5, 7, and 9 years of age with some variability [9]. At the final stages of involution, a fibrofatty protuberance may remain (Figure 1(b)).

Another subclassification for hemangiomas is focal versus segmental disease. Focal hemangiomas are localized, unilocular lesions which adhere to the phases of growth and involution. Multifocal hemangiomatosis also exists, and infants with greater than 5 lesions should undergo workup to rule out visceral involvement. Segmental hemangiomas are more diffuse plaque-like and can lead to untoward functional and aesthetic outcomes. The limb and face are common locations for disease (Figure 2). Head and neck lesions frequently coincide with the distribution of the trigeminal nerve. A beard-like distribution is associated with a subglottic hemangioma 60% of the time [10]. Regardless, a stridulous child with either a focal or segmental hemangioma should be presumed to have subglottic disease until proven otherwise.

Patients with segmental hemangiomas should also undergo investigation to rule out PHACES syndrome (posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular anomalies, cardiovascular anomalies, eye anomalies, and sternal defects or supraumbilical raphe) [11].

The diagnosis of a hemangioma is best made by clinical history and physical exam. In cases of unclear diagnosis, the best radiographic modalities to use are either a Doppler ultrasound or MRI.

2.2. Management. Historically, hemangiomas have been managed with close observation over their lifecycle [9]. However, research suggests that nearly 40% of children require further intervention because of bleeding, ulceration, visual axis obstruction, airway obstruction, high-output cardiac failure, or risk for permanent disfigurement [12]. With novel therapeutic options as well as a better understanding of disease, observation is declining as the sole means of treating hemangiomas. Nonetheless, inconspicuous lesions are still best treated with observation alone.

Medical and surgical options are available for the treatment of “problematic” hemangiomas. Medical management includes one or more systemic therapies. Corticosteroids, interferon, and vincristine have been successful for massive and life-threatening disease [13–15]. These agents have also been used for multifocal disease, visceral involvement, segmental distribution, airway obstruction, and periorbital lesions. However, significant side effects accompany systemic therapy and have even led to the rejection of some agents as a treatment option.

Surgical management involves excision, laser treatment or both. Intralesional steroid treatment is also an option for focal hemangiomas of the parotid, nasal tip, subglottis, and eyelid. Repeat therapy is often required, but systemic side effects are limited [16].

Excision is the appropriate for localized lesions the fibrofatty remnants (residuum) of involuted hemangiomas. Elective subtotal excision of massive protuberant proliferating



FIGURE 1: (a) Proliferating hemangioma at 3 months of age. (b) Same hemangioma at involution at 4 years of age.

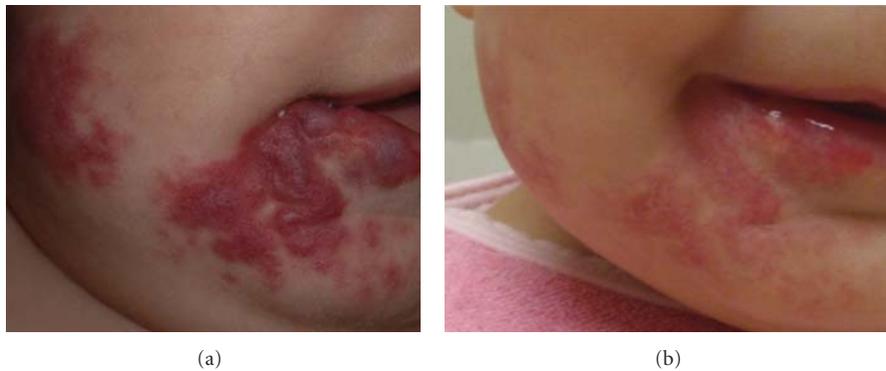


FIGURE 2: (a) Segmental hemangioma in trigeminal (V3) distribution. (b) Same hemangioma after 2 months of therapy with propranolol (2 mg/kg divided tid).

TABLE 2: Old versus current nomenclature for describing hemangioma types.

Old nomenclature	New nomenclature
Strawberry or capillary hemangioma	Superficial hemangioma
Cavernous hemangioma	Deep hemangioma
Capillary cavernous hemangioma	Compound hemangioma

hemangiomas can be employed in order to maintain aesthetic facial boundaries. Small remnants of disease are then left for involution. Residual erythema and telangiectasias frequently remain in involuted hemangiomas and are best treated by selective photothermolysis using the flash pulse dye laser (FPDL). Similarly, ulcerative lesions during proliferation can be treated with FPDL to induce healing and new epidermal growth.

2.3. Propranolol. A paradigm shift has occurred regarding the treatment of hemangiomas over the past few years. In 2008, propranolol, a nonselective β -adrenergic antagonist, was serendipitously discovered to cause regression of proliferating hemangiomas in newborns receiving treatment for cardiovascular disease [17]. Numerous studies demonstrating the success of propranolol for shrinking hemangiomas

have followed suit [17–19]. In fact, over ninety percent of patients have dramatic reduction in the size of their hemangiomas as early as 1-2 weeks following the first dose of propranolol (Figure 2(b)). Dosing for propranolol in treating hemangiomas is recommended to be 2-3 mg/kg separated into two or three-times-a-day regimens [20]. These doses are dramatically below the concentration employed for cardiovascular conditions in children. Thus, reported side effects of propranolol for hemangiomas have been minimal. Nonetheless, serious concerns for hypoglycemia and lethargy that can occur with this medicine should not be brushed aside [21, 22]. To address these concerns, parents are instructed to give propranolol with meals, report any unusual sleepiness, and not administer it during infections. Early and frequent visits to assess vital signs are recommended in young infants while on therapy. Exacerbation of gastroesophageal reflux may result due to beta-receptor blockade at the lower esophageal sphincter [18].

Monitoring the administration of propranolol varies among institutions and practitioners. A unified approach has not yet been determined. However, elective admission with cardiovascular monitoring may be necessary. Outpatient administration with close monitoring has also been successfully performed [23]. Nonetheless, an electrocardiogram must be reviewed by a pediatric cardiologist prior to

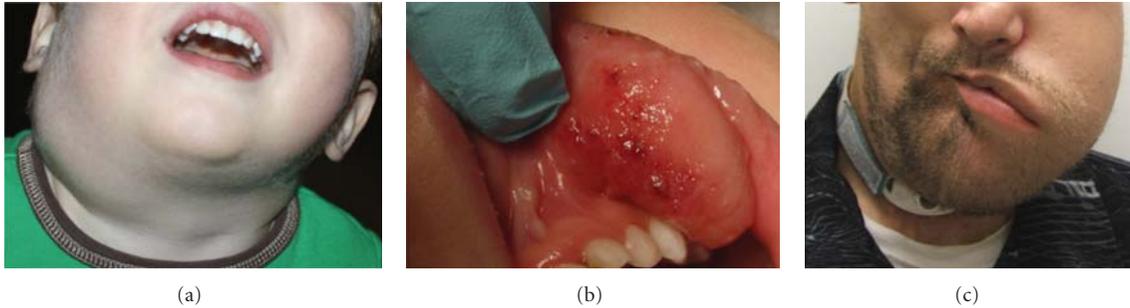


FIGURE 3: (a) Macrocytic lymphatic malformation (LM) of right neck in toddler. (b) Microcystic lip LM displaying mucosal vesicles. (c) Microcystic LM in older patient with bone involvement and mandibular hypertrophy.

administration. Cardiopulmonary conditions at risk for propranolol therapy such as heart block or reactive airway disease should draw careful consideration before administering. Consensus on patient monitoring and best dose regimens remains to be determined, but prospective research is underway.

Propranolol is currently employed for “problematic” hemangiomas, those that would have received either surgical or some other systemic therapy to prevent untoward side effects. Subglottic, periorbital, and massive hemangiomas seem to respond well [24]. Despite the success of propranolol in reducing hemangioma size, adjuvant therapy may be necessary in up to 50% of patients [17]. Propranolol’s mechanism on treating hemangiomas remains unclear but may involve the regulation of vascular growth factors and hemodynamic cytokines.

3. Vascular Malformations Overview

Vascular malformations are rare vascular anomalies composed of inappropriately connected vasculature. Any blood vessel type, or a combination thereof, can be affected in a vascular malformation. These lesions infiltrate normal tissue which makes them very difficult to manage. The most common vascular malformations include lymphatic malformations (LMs), capillary-venular malformations (CM), venous malformations (VMs) and arteriovenous malformations (AVMs) which have been selected to be covered in this paper (Table 1). While different in their biologic and clinical profile, as a whole, vascular malformations do not regress and continue to expand with time. Periods of rapid growth, infiltration, and soft tissue destruction will spur therapeutic approaches that depend upon the malformation involved.

4. Lymphatic Malformations

Lymphatic malformations (LMs) are composed of dilated lymphatic vessels with inappropriate communication, lined by endothelial cells and filled with lymphatic fluid. Their incidence is approximated to be 1 in 2000 to 4000 live births [25]. Lesions are classified as macrocystic (single or multiple cysts $>2\text{ cm}^3$), microcystic ($<2\text{ cm}^3$), or mixed [1]. Previous

terminology, that is no longer used, has included “cystic hygroma” and “lymphangioma” to describe these entities.

The etiology of LM is unclear. Although most are congenital, there have been reports of LM occurring after trauma or infection. Receptors involved in the formation of lymphatic vascular channels, such as VEGFR3 and Prox-1, may play a role in the development of this disease [26].

4.1. Diagnosis. Lymphatic malformations may be macrocystic, microcystic, or mixed. Gradual growth and expansion is typical. Approximately half of the lesions are present at birth and 80–90% by 2 years of age. Local infections approximating the course of lymphatic drainage will cause LM to swell, protrude, and sometimes become painful. This is a hallmark of a LM versus other vascular anomalies that do not present in this fashion.

Clinically, the appearance of macrocystic disease differs from that of microcystic. Macrocystic LMs present as a soft, fluid-filled swelling beneath normal or slightly discolored skin (Figure 3(a)). Intracystic bleeding or a mixed lymphatic venous malformation may result in blue discoloration of the overlying skin. Microcystic LMs are soft and noncompressible masses with an overlying area of small vesicles involving the skin or mucosa. These vesicles can weep and at times cause pain or minor bleeding (Figure 3(b)).

LM can occur anywhere on the body, and symptoms are determined by the extent of disease. Most LMs are found in the cervicofacial region and extend to involve the oral cavity or airway, especially when mixed or microcystic [27]. Symptoms secondary to bulky disease often include pain, dysphagia, odynophagia, impaired speech, or in severe cases, airway obstruction. When involving the skeletal framework in this area, LMs often cause osseous hypertrophy leading to dental or extremity abnormalities (Figure 3(c)).

Although these malformations can usually be diagnosed by physical examination, MRI is used to confirm diagnosis, identify cystic architecture, and determine extent of disease.

4.2. Management. An ideal option for treatment of LM does not exist. Several interventions may be required. There have been rare cases of sporadic resolution of a lesion although the majority of these malformations continue to enlarge with age [27]. Macrocystic lesions are more amenable to treatment

and have a better prognosis. Swelling from acute infection is best controlled with a short course of systemic steroids and antibiotics. Definitive treatment is delayed until resolution.

LM may be detected on prenatal ultrasound and may require special interventions during delivery. The EXIT (ex utero intrapartum treatment) procedure provides good airway control of the infant if compromise is suspected to occur at birth.

Sclerotherapy is frequently employed for lymphatic malformations, especially if deep seated and difficult to access surgically. It involves injection of a sclerosing agent directly into the lesion leading to fibrosis and ultimately regression of the cysts. Several treatments are usually required, and swelling is expected following therapy. Macrocystic lesions are more easily treated in this fashion, but there have been reports of success in microcystic lesions [28]. Several agents have been utilized for lymphatic malformations including ethanol, bleomycin, OK-432, and doxycycline [29, 30]. Complications include skin breakdown, pain, and swelling. Severe swelling can at times occur and may lead to airway obstruction requiring intensive care [31]. Risks to local nerves are also real but usually result in only transient loss of function.

Carbon dioxide laser therapy may also be employed in limited disease of the airway and oral mucosa [32]. Macrocystic disease is often cured with surgical extirpation. Surgical excision is also frequently employed for microcystic disease although it is more aggressive, invasive, and difficult to control [33, 34]. Infiltration of normal soft tissue and bone by extensive microcystic LM requires massive resections and local or free-flap reconstruction. Failure to completely excise microcystic LM often leads to recurrence. Surgery is also employed in the correction of secondary deformities caused by LM such as bony overgrowth of the facial skeleton [34].

Overall, treatment for LM should be aimed at complete elimination of disease. When this is not feasible, multiple treatment modalities are combined to control disease and provide satisfactory functional outcomes.

5. Capillary Malformations

Capillary malformations (CMs) are sporadic lesions consisting of dilated capillary-like channels. They occur in approximately 0.3% of children. CMs can present on any part of the body, but are mostly found in the cervicofacial region. They are categorized as medial or lateral lesions depending on their locations. Medial CM gradually lighten with time and eventually disappear. Colloquially they are referred to as stork bites on the nape of the neck and angel kisses on the forehead. Lateral lesions, commonly referred to as port-wine stains, have a more protracted course (Figure 4).

Pathogenesis of isolated capillary malformations is unknown. A genomewide linkage analysis has identified a locus on chromosome 5q associated with familial disease [35]. A rare autosomal dominant inherited disease consisting of a combination of CM and arteriovenous malformations (AVM) is associated with a loss-of-function mutation in RASA1 gene [36]. This has spurred further research into the cause of the more common sporadic form of CM.



FIGURE 4: Capillary malformation (port wine stain) of the left face in infant.

5.1. Diagnosis. CMs present at birth as flat, red or purple, cutaneous patches with irregular borders. They are painless and do not spontaneously bleed. Lateral CMs, or port-wine stains, usually involve the face and present along the distribution of the trigeminal nerve. CMs tend to progress with time as the vessel ectasia extends to involve deeper vessels to the level of the subcutaneous tissues. This causes the lesion to become darker in color, as well as more raised and nodular [37].

Although they are mostly solitary lesions, CM may exist as a part of a syndrome. The most common of these is the Sturge-Weber syndrome (SWS) and is characterized by a CM in the region of the ophthalmic branch of the trigeminal nerve, leptomeningeal angiomas, and choroid angioma. Symptoms of SWS are variable among cases and include intractable seizures, mental retardation, and glaucoma. CM may also be present in Klippel-Trenaunay Syndrome (KTS). This syndrome consists of a combination of multiple lymphatic, venous, and capillary abnormalities.

Diagnosis is usually made by physical examination alone. If there are findings inconsistent with CM exist, for example, pain or spontaneous bleeding, an MRI may be performed. An MRI of the brain as well as an annual ophthalmological exam is warranted when suspicion for SWS is present.

5.2. Treatment. The mainstay of treatment for CM is laser therapy. The FPDL is efficacious in treating these lesions. The laser slowly causes the redness of the lesion to fade; therefore, many treatments are often necessary [38]. Early treatment of these lesions appears to slow the progression of the disease. The argon, potassium-titanyl-phosphate (KTP) lasers, and 755 nm laser have also been utilized in more advanced lesions with good outcomes [39]. Surgical excision is also an option in lesions not amenable to laser therapy. This is especially true in advanced lesions which have become nodular [37].

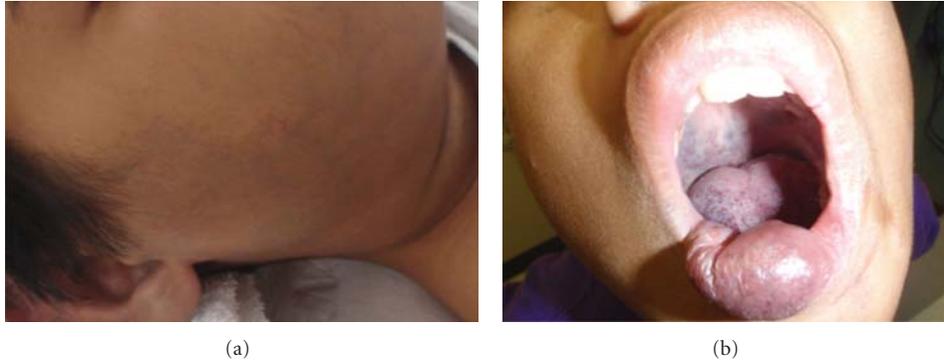


FIGURE 5: Cervicofacial venous malformation involving the right neck (a) and oropharyngeal mucosa (b).

6. Venous Malformations

Venous malformations (VMs) are slow-flow vascular anomalies composed of ectatic venous channels. These aberrant venous connections lead to venous congestion, thrombosis, and gradual expansion of these lesions. As a result, VMs persist and progress until therapeutic intervention. The incidence of VMs is approximately 1 in 10,000 [40]. VMs more commonly occur sporadically, but research into multifocal disease and familial patterns has helped discover suspected genetic loci involved in their development. There are inherited forms of VMs, the cause of which has been localized to chromosome 9p [41]. Recently a loss-of-function mutation was discovered on the angiopoietin receptor gene *TIE2/TEK* in many solitary and multiple sporadic venous malformations [42]. In addition, upregulation of several factors including tissue growth factor beta (TGF-beta) and basic fibroblast growth factor (beta-FGF) has been discovered in patients with venous malformations [26]. Progesterone receptors have been discovered in venous malformations. This likely explains their tendency to grow rapidly during hormonal changes [43].

6.1. Diagnosis. Venous malformations are often visible at birth but may present as a deep mass. Protrusion may be the only presenting symptom. They are known to grow proportionately with the child with sudden expansion in adulthood. Rapid growth may occur during puberty, pregnancy, or traumatic injury. VM can be either well localized or extensive. The overlying skin may appear normal or possess a bluish discoloration. With more cutaneous involvement, the lesions appear darker blue or purple (Figure 5(a)). Upper aerodigestive involvement is common, and VM are particularly evident when mucosa is affected (Figure 5(b)).

VMs are compressible and swell when the region is dependent or there is an increase in hydrostatic pressure such as during a valsalva maneuver. With time, pain and swelling will occur with the formation of phleboliths (calcified thrombi), or small clots, secondary to trauma or venous stasis. For very large lesions with significant thrombosis the risk of distal emboli remains low but real. D-dimers may be elevated and a marker of disease [44]. When isolated, VM are generally benign with slow growth. They expand secondary to

venous stasis and elastic vascular expansion. Airway obstruction, snoring, and sleep apnea may also be present with recumbence [45]. VM can occur anywhere in the body but often are found in the head and neck where they involve the oral cavity, airway, or cervical musculature. MRI is the imaging modality of choice when diagnosing VM and offers superior delineation of disease for treatment planning [46].

6.2. Treatment. No single treatment modality is favored in the treatment of VMs and often more than one modality is utilized [47]. Surgery, Nd:YAG laser therapy, and sclerotherapy (directed vascular injury) are all options for treating VM.

Conservative observation of small VM in children may be an option with the knowledge that growth is imminent. Elevating the involved area can decrease hydrostatic pressure and vascular expansion and may impede growth. In large lesions, elevation also decreases swelling and improves pain and airway obstruction. Similarly, compression garments are the initial treatment of choice for advanced limb lesions allowing risks from other treatment options to be avoided. Low-molecular-weight heparin can improve pain from thrombosis [44].

Treatment of larger airway and multifocal disease is often warranted. Symptom-directed therapy is the goal for these lesions. Management techniques typically aim to relieve airway symptoms, pain, and/or disfigurement. Surgical resection and sclerotherapy alone can, at times, be curative for smaller lesions. Local recurrence may occur years after treatment.

Laser therapy provides good control of VM [48]. Use of the Nd:Yag and KTP lasers has been described [47, 49]. The Nd:Yag laser can be used via a fiber attached to an endoscope to treat intraoral and airway venous malformations. Direct injury to deep venous malformations may also be performed by passing the laser directly into the lesion (interstitial therapy). The laser causes shrinking of the lesion along with thrombosis. Serial treatment with these lasers offers reduction and control of disease [48]. Nerve injury may occur with interstitial laser.

Sclerotherapy, as described above, has been used extensively for treatment of VM [50]. The sclerosants most commonly used include ethanol and sotradecol [51]. Complications of sclerotherapy include skin and mucosal injury,

swelling leading to airway compromise, infection, and nerve injury. In addition, each sclerosant has its own risk profile. Cardiovascular shock can occur with ethanol, shock-like symptoms with OK-432, interstitial pneumonia or pulmonary fibrosis with bleomycin, and tooth discoloration or electrolyte abnormalities with doxycycline [33].

Surgery remains one of the most superior treatment options and may offer a cure for localized VM. Excision of complex lesions remains difficult secondary to intraoperative bleeding. Preoperative sclerosant can be used prior to excision (24–48 hours) to decrease surgical risk. Patients with extensive disease will often require combined modality therapy. Cure is not common, but disease control for many years is often achieved.

7. Arteriovenous Malformations

Arteriovenous malformations (AVMs) are congenital high-flow vascular malformations composed of anomalous capillary beds shunting blood from the arterial system to the venous system. They are often misdiagnosed at birth as other vascular lesions because of the delay in presentation of characteristic signs of the malformation. Puberty and trauma trigger the growth of the lesion and manifestation of its troublesome symptoms [52]. They are infiltrative causing destruction of local tissue and often life-threatening secondary to massive bleeding. Extracranial AVMs are different from their intracranial counterpart and are found in several areas in the cervicofacial region.

Little is known about the origin and pathogenesis of AVM. A defect in vascular stabilization is thought to cause AVM, but it remains unclear whether these lesions are primarily congenital in origin. Most AVM, are present at birth, but there are several case reports of these lesions presenting after trauma in adults. Defects in TGF-beta signaling and a genetic two-hit hypothesis are the prevailing theories to the pathogenesis [53, 54]. Progesterone receptors have been isolated in AVMs explaining their expansion during puberty [43].

7.1. Diagnosis. Diagnosis of AVM is based upon clinical examination and imaging. A growing hypervascular lesion may have been present as a slight blush at birth. AVMs are often quiescent for many years and grow commensurate with the child. Intermittent expansion will suggest the diagnosis [52]. Hormonal changes are thought to influence growth [43]. The distinguishing characteristics of an AVM will be palpable warmth, pulse, or thrill due to its high vascular flow [55]. The overlying skin may have a well-demarcated blush with elevated temperature relative to adjacent skin (Figure 6).

The natural course of AVM is early quiescence, late expansion, and ultimately infiltration and destruction of local soft tissue and bone. Common sites for occurrence are the midface, oral cavity, and limbs [52]. Oral lesions can present early due to gingival involvement, disruption of deciduous teeth, and profuse periodontal bleeding. Although both focal (small vessel) and diffuse lesions exist, AVMs are by far the most difficult vascular anomaly to manage due to



FIGURE 6: Evidence of skin involvement in limb AVM. Patchy erythematous areas are palpably warmer and pulsatile relative to adjacent skin.

the replacement of normal tissue by disease vessels and very high recurrence rates [55, 56].

Imaging is essential in identifying the extent of AVM. MRI may be useful, but MRA and CTA can give a superior outline of these lesions [57]. Numerous hypolucent arterial flow voids are the hallmark of AVM by MRI. CTA allows evaluation of surrounding tissues and bones. Individual arterial feeders can be visualized with this imaging as well [58]. An arteriogram, the time-tested approach to diagnosing AVM, will provide good definition of central “nidus” of affected vessels and provide access for intravascular treatment when necessary [59].

7.2. Treatment. Treatment of AVM consists of embolization, surgical extirpation, or a combination of these modalities. Treatment and timing are often individualized to the patient and the extent of disease. For example, small-vessel AVMs are known to be localized and can be resected with good long-term outcomes [60]. Historically, young children were closely observed until disease expansion with the concept that the treatment should not be worse than the disease. However, this approach is currently being challenged due to the high recurrence rates experienced with AVM [61]. Diffuse lesions are a lifelong problem. Long-term followup with a dedicated multidisciplinary team is important for AVM management.

Intravascular embolization of AVM can be used alone or in combination with surgical excision. Absolute ethanol, polyvinyl alcohol, and ONYX have been employed as AVM embolization materials [62]. These agents selectively obstruct and destroy the arteries treated. Complications of this approach include local skin ulceration, soft tissue necrosis, mucosal sloughing, or nerve injury. Embolization provides temporary control of disease, but recurrence is high [61]. This is theoretically due to collateralization and recruitment of new vessels to support an undetected portion of the “nidus.” Frequent serial embolizations may improve patient outcomes.

In general, surgical management of AVMs requires preoperative supraselective embolization, judicious removal of tissue, and complex reconstructive techniques. In focal lesions, surgical excision has been shown to cure AVM [56, 63]. However, diffuse AVMs have recurrence rates as high as 93% [61]. Excision is performed 24–48 hours after embolization. This helps control blood loss and define surgical margins of the lesion. Close postoperative observation with expected

management of local recurrence is required. Recruitment of new vessels occurs after excision as well. In essence, AVMs are debilitating vascular malformations that are often misdiagnosed early in life. Despite successful initial therapy, these lesions may recur many years later making vigilant management necessary.

8. Conclusions

Vascular anomalies embody a myriad of blood vessels abnormalities that are thought to occur perinatally. Correct diagnosis is imperative for appropriate treatment. The most common vascular anomalies in order of presentation include hemangiomas, lymphatic malformations, capillary malformations (port-wine stains), venous malformations, and arteriovenous malformations. Treatment of vascular anomalies is complex and often involves multiple disciplines and therapeutic options. Referral to a vascular anomalies team is recommended when considering therapy for “problematic” hemangiomas and vascular malformations.

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Review Article

Laryngomalacia: Disease Presentation, Spectrum, and Management

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Laryngomalacia is the most common cause of stridor in newborns, affecting 45–75% of all infants with congenital stridor. The spectrum of disease presentation, progression, and outcomes is varied. Identifying symptoms and patient factors that influence disease severity helps predict outcomes. *Findings.* Infants with stridor who do not have significant feeding-related symptoms can be managed expectantly without intervention. Infants with stridor and feeding-related symptoms benefit from acid suppression treatment. Those with additional symptoms of aspiration, failure to thrive, and consequences of airway obstruction and hypoxia require surgical intervention. The presence of an additional level of airway obstruction worsens symptoms and has a 4.5x risk of requiring surgical intervention, usually supraglottoplasty. The presence of medical comorbidities predicts worse symptoms. *Summary.* Most with laryngomalacia will have mild-to-moderate symptoms and not require surgical intervention. Those with gastroesophageal reflux and/or laryngopharyngeal reflux have symptom improvement from acid suppression therapy. Those with severe enough disease to require supraglottoplasty will have minimal complications and good outcomes if multiple medical comorbidities are not present. Identifying patient factors that influence disease severity is an important aspect of care provided to infants with laryngomalacia.

1. Introduction

Laryngomalacia is the most common cause of stridor in newborns, affecting 45–75% of all infants with congenital stridor [1]. The stridor can be overwhelming to parents and caregivers. The high-pitched noise of stridor is created by airflow through an area of obstruction. In laryngomalacia the supraglottic structures collapse into the airway during the inspiratory phase of respiration which produces inspiratory stridor. Most infants with laryngomalacia will have mild symptoms and a benign disease course that resolves by the age of 12 to 24 months; however, it is important to recognize that not all cases of laryngomalacia have a benign course [1]. Once the condition is diagnosed and differentiated from other causes of stridor, most mild cases can be followed expectantly by their pediatrician and referred back to an otolaryngologist if symptoms worsen. The purpose of this paper

is to review the disease presentation spectrum, highlighting symptoms and patient factors that predict which infants may worsen and require intervention or comanagement with an otolaryngologist. Supraglottoplasty is the mainstay surgical management. Tracheotomy to bypass the obstruction is rarely performed and reserved for surgical failures or children with multiple medical comorbidities.

2. Presentation

Laryngomalacia presents with inspiratory stridor that typically worsens with feeding, crying, supine positioning, and agitation. The symptoms begin at birth or within the first few weeks of life, peak at 6 to 8 months, and typically resolve by 12 to 24 months [1]. Laryngomalacia is usually diagnosed within the first 4 months of life [2]. Although

inspiratory stridor is the classic symptom of laryngomalacia, there are a number of associated symptoms. The most common associated symptoms are related to feeding which include regurgitation, emesis, cough, choking, and slow feedings. Infants with laryngomalacia may have a difficult time coordinating the suck swallow breath sequence needed for feeding as a result of their airway obstruction [3]. The increased metabolic demand of coordinating eating and breathing against the obstruction can be so severe that it results in weight loss and failure to thrive. Other less common but concerning associated symptoms are tachypnea, suprasternal and substernal retractions, cyanosis, pectus excavatum, and obstructive sleep apnea. Chronic hypoxia from airway obstruction can lead to pulmonary hypertension if not recognized and managed.

It is important for a clinician to differentiate laryngomalacia from other conditions that cause noisy breathing. All too often the diagnosis of tracheomalacia, asthma, bronchiolitis, and reactive airway disease may precede the correct diagnosis of laryngomalacia. Because infants are often misdiagnosed with these conditions, understanding patterns and characteristics of breathing will aid the clinician in differentiating the noisy breathing of laryngomalacia from others. Identifying which phase of the respiratory cycle will also help determine the level of obstruction. Wheezing, stertor, and stridor are the types of noisy breathing. Wheezing is typified as a coarse whistling sound heard on the phase of expiration and is usually due to lung disease. Stertor is a grunting or a snoring sound and is loudest during inspiration. In children it is typically caused by adenotonsillar disease. The high-pitched noise of stridor can occur during the respiratory phase of inspiration, expiration, or both (biphasic). Inspiratory stridor is caused by airway obstruction at the vocal cords or higher. Biphasic stridor is caused by obstruction below the vocal cords. The most common cause of biphasic stridor in children is viral croup. Expiratory stridor is caused by obstruction in the trachea. The most common cause of expiratory stridor in children is tracheomalacia. Infants and children who have chronic stridor should be referred to an otolaryngologist for accurate diagnosis.

3. Diagnosis

The diagnosis of laryngomalacia is suspected by the typical clinical history but is confirmed by flexible laryngoscopy in an awake infant. Flexible laryngoscopy is easily performed in the otolaryngology office with the help of a caregiver. The infant is held in the caregivers lap in an upright or semireclined position, and a flexible laryngoscope is passed through the nose, pharynx, and positioned above the larynx. The otolaryngologist is able to examine the dynamic movement of the laryngeal structures during spontaneous respiration and differentiate laryngomalacia from other cause of inspiratory stridor such as vocal cord paralysis or a laryngeal cyst. Supraglottic tissue collapse and obstruction during inspiration is the hallmark of laryngomalacia. The epiglottis, false vocal cords, arytenoids, ventricle, and aryepiglottic folds

are the structures making up the supraglottis. As seen in Figures 1(a) and 1(b), the common findings seen on exam are prolapse of the posteriorly positioned arytenoid cartilages and mucosa into the airway during inspiration, shortening of the distance between the arytenoid and epiglottis, and an “omega-shaped” or retroflexed epiglottis.

4. Etiology

The exact etiology of laryngomalacia is unknown and continues to be an area of great interest and research. Theories of etiology include the anatomic, cartilaginous, and neurologic theories. The anatomic theory proposes that there is an abnormal placement of flaccid tissue resulting in stridor. The challenge with the anatomic theory is there are infants who have the typical anatomic laryngeal findings of laryngomalacia who do not have symptoms of airway obstruction. The cartilaginous theory proposes that the cartilages of the larynx are immature and abnormally pliable. This theory has been refuted by the finding of histologically normal cartilage in infants with symptomatic laryngomalacia. The neurologic theory is the best supported by the literature and as a result is the prevailing etiologic theory [2].

The neurologic theory recognizes that laryngomalacia may be a consequence of an underdeveloped or abnormally integrated CNS system, particularly the peripheral nerves and brainstem nuclei responsible for breathing and airway patency. As the infant matures laryngomalacia likely resolves secondary to the maturation of the CNS system. The laryngeal adductor reflex is a vagal nerve reflex responsible for laryngeal function and tone. The afferent activation of the reflex is mediated by the superior laryngeal nerve which is located in the aryepiglottic fold [2]. Sensory information from this nerve is then transmitted to the brainstem nuclei that regulate respiration and swallowing. A motor response to sensory stimulation is mediated by the vagus nerve resulting in glottic closure, inhibition of respiration, and swallow. An alteration in this pathway has a role in the etiology of laryngomalacia and the associated feeding symptoms. Laryngeal sensory testing in infants with laryngomalacia has demonstrated that the sensory stimulus threshold needed to elicit the typical motor response is elevated in those with moderate-to-severe disease versus those with mild disease. This testing supports the notion of an underdeveloped or abnormally integrated peripheral and central nervous system mechanism of laryngeal function and tone [2].

5. Spectrum of Disease

Laryngomalacia has a disease spectrum that can be divided into mild, moderate, and severe categories [2]. These categories are not based on the quantity of stridor but rather by the associated feeding and obstructive symptoms. Those with mild disease usually have inconsequential inspiratory stridor. Those with moderate disease usually have stridor with feeding-related symptoms and often improve on acid

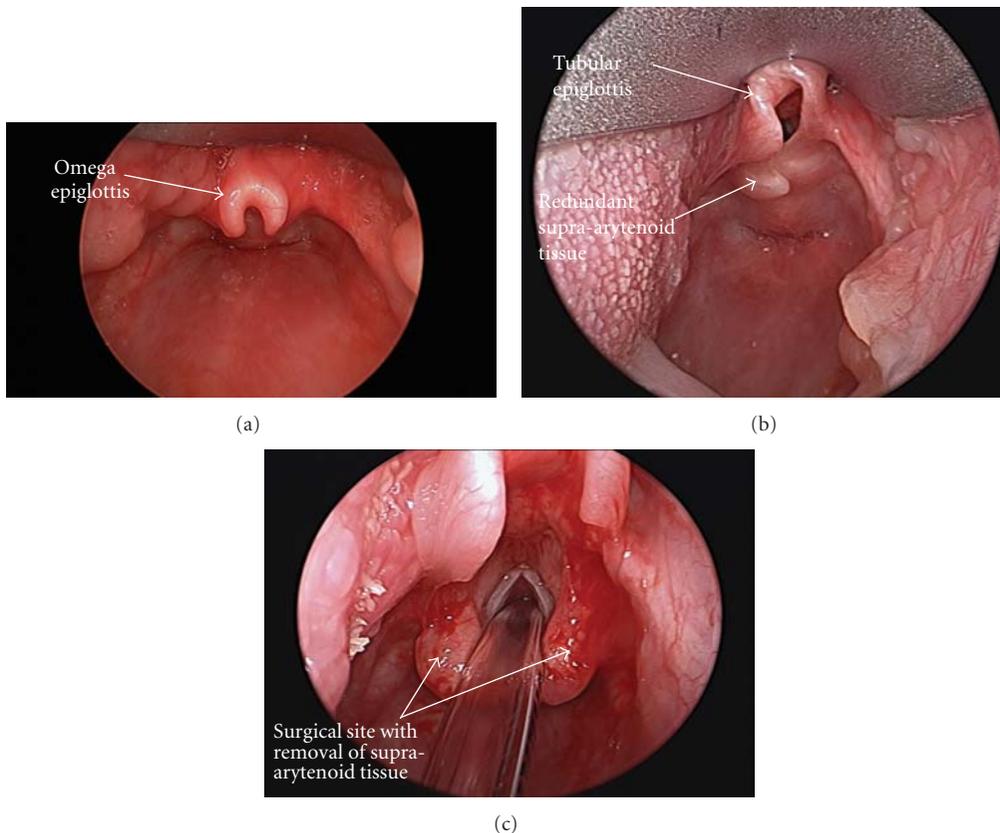


FIGURE 1: (a) Omega-shaped epiglottis. (b) A tubular-shaped epiglottis along with redundant supra-arytenoid tissue which is obstructing the glottis during inspiration. (c) the site of redundant supra-arytenoid tissue after surgical removal.

suppression treatment. Those with severe disease require surgical intervention, usually supraglottoplasty. Understanding the spectrum of symptoms and unique patient factors that influence disease severity will help determine which patients may worsen and require referral to an otolaryngologist for further management.

At the time of presentation to a health care provider approximately 40% of infants will have mild laryngomalacia. They present with inspiratory stridor and the occasional feeding-associated symptoms of cough, choking, and regurgitation. They have a coordinated suck swallow breath sequence and feed comfortably. Airway obstruction does not lead to hypoxia. They have an average resting oxygen saturation of 98–100% [4]. Seventy percent of those that present as mild disease will have an uneventful disease course and resolution and can be managed expectantly. The remaining 30% who present with worsening reflux symptoms that interfere with feeding will progress to the moderate disease category. In addition to reflux-related symptoms, those with mild disease and baseline resting SAO_2 of $\leq 96\%$ are predicted to progress to the moderate disease category [2, 4].

At the time of presentation up to 40% will have moderate laryngomalacia. Those in this category present with the typical stridor but are described by their caregivers as fussy and hard to feed. They have frequent feeding-associated

symptoms of cough, choking, regurgitation, and cyanosis during feeding. If not recognized and managed, feeding problems can lead to aspiration, weight loss, and laborious feedings. Strategies to improve feeding symptoms include pacing, texture modification by thickening formula/breast milk, and upright position for feeding. Acid suppression treatment is effective for which the mechanism is discussed below. Up to 72% percent of infants will have resolution of their symptoms by 12 months utilizing this management strategy. Infants with moderate laryngomalacia are not hypoxic; however they have a lower average resting SAO_2 of 96% [2, 4]. It is important to carefully monitor this group of infants as up to 28% develop severe disease and have worsening symptoms despite feeding modification and acid suppression therapy. These patients require surgical intervention [3]. An infant with moderate disease and an average resting SAO_2 of $\leq 91\%$ is also more likely to require surgical intervention, usually supraglottoplasty [2, 4].

Twenty percent of infants have severe laryngomalacia at the time of presentation to a health care provider. They present with inspiratory stridor and other associated symptoms that include recurrent cyanosis, apneic pauses, feeding difficulty, aspiration, and failure to thrive. Suprasternal and subcostal retractions can lead to pectus excavatum. The average resting baseline SAO_2 in those with severe disease is 86% [2, 4]. If not recognized and managed, chronic hypoxia

can lead to pulmonary hypertension and cor pulmonale. As discussed below those with severe disease will likely require surgical intervention in addition to acid suppression treatment for management. The mainstay for surgical intervention is supraglottoplasty whereby the obstructing collapsing tissue is removed through an endoscope. Tracheotomy is rarely indicated and is reserved for supraglottoplasty failures and those with multiple medical comorbidities [2, 4].

6. Medical Comorbidities

In addition to associated symptoms it is important for members of the health care team to recognize that the presence of medical comorbidities impacts symptoms and disease course. Gastroesophageal reflux disease (GERD) and neurologic disease are the most common medical comorbidities. Other comorbidities that influence the outcome are the presence of an additional airway lesion, congenital heart disease, and the presence of a syndrome or genetic disorder.

6.1. Gastroesophageal and Laryngopharyngeal Reflux. Gastroesophageal reflux is noted in 65–100% of infants with laryngomalacia [4]. The airway obstruction of laryngomalacia generates negative intrathoracic pressure which promotes gastric acid reflux onto the laryngopharyngeal tissues leading to laryngopharyngeal reflux. The laryngeal tissues are sensitive to the acid exposure and become edematous as a response. Increased supraglottic edema results in further collapsing of these tissues into the airway and further obstructive symptoms. A vicious cycle of increased obstruction, GERD, and edema then ensues. Prolonged acid exposure also blunts laryngeal sensation which decreases the motor response to swallow in response to secretions. Decreased laryngeal sensation explains the coughing and choking during feedings which are commonly seen with laryngomalacia. The vagal reflex responsible for laryngeal tone is also responsible for lower esophageal sphincter tone and esophageal motility [2]. Decreased lower esophageal tone and esophageal dysmotility are known risk factors for GERD and could be a factor in the GERD seen in laryngomalacia patients.

GERD should be treated in all patients with laryngomalacia and feeding symptoms. Upright positioning during feeding and bottles that minimize aerophagia may decrease the number of reflux events. Acid suppression therapy improves symptoms and may shorten the duration of the natural course. There are no controlled studies demonstrating the most effective GERD treatment regimen in laryngomalacia patients. The senior author's experience is to begin infants with feeding symptoms on high-dose histamine type-2 receptor antagonist therapy (ranitidine 3 mg/kg, 3 times a day). A proton pump inhibitor is added for refractory symptoms and breakthrough symptoms. At times a combination of daytime proton pump inhibitor therapy and nighttime histamine type-2 receptor antagonist therapy is used. Most infants are kept on acid suppression therapy for an average of 9 months [4].

In infants with moderate-to-severe disease, complementary gastrointestinal studies may be beneficial in prognosis and management. An esophagram with small bowel follow-through is useful in evaluating reflux and aspiration along with ruling out containment gastrointestinal disorders such as pyloric stenosis. Aspiration during feedings can be evaluated by a videofluoroscopic swallow study or a functional endoscopic swallow study. Aspiration seen on these swallow evaluations may prompt surgical management of the laryngomalacia in order to decrease the respiratory consequences of chronic aspiration into the lung [3]. Twenty-four-hour pH studies and impedance studies may be useful in determining management strategies for the infant with severe reflux despite acid suppression therapy. Impedance testing is a method to detect esophageal bolus movement. When combined with pH studies it is helpful in detecting both acidic and nonacidic gastroesophageal reflux events. Depending on the results of these studies, expanded medical management or fundoplication surgery may be warranted for reflux control.

6.2. Neurologic Disease. Neurologic disease is present in 20–45% of infants with laryngomalacia and includes seizure disorder, hypotonia, developmental delay, cerebral palsy, mental retardation, microcephaly, quadriparesis, and Chiari malformation. Neurologic disease may decrease vagal nerve function at the brainstem level contributing to decreased laryngeal tone. Infants with neurologic disease require surgical intervention at higher rates than those without [4]. Neuromuscular hypotonia also leads to collapse of the supporting muscles in the pharynx and swallowing mechanism leading to airway obstruction and feeding symptoms. Those with neurologic disease will often have worse symptoms or a prolonged course of symptoms. Some may not have resolution of their symptoms despite medical intervention or supraglottoplasty. These patients may require accessory routes for feeding and breathing, usually a tracheostomy.

6.3. Secondary Airway Lesions. The incidence of secondary or synchronous airway lesions (SAL) in laryngomalacia ranges from 7.5 to 64% [5–9]. The higher range of SAL is likely explained by the technique used for diagnosis and the indication for looking for another lesion. The presence of a SAL can be screened by using airway fluoroscopy for tracheomalacia and high-kilovoltage airway radiographs for fixed structural lesions such as subglottic stenosis. Tracheomalacia is the most common synchronous airway lesion followed by subglottic stenosis. SAL have an accumulative effect on airway obstruction. Airway obstruction from laryngomalacia combined with a SAL can lead to greater airway obstruction with increased negative intrathoracic pressure. Negative intrathoracic pressure potentiates gastroesophageal and laryngopharyngeal reflux. Gastroesophageal and laryngopharyngeal reflux and its complications add to the severity of symptoms previously described [2, 6]. Infants with mild or moderate disease that have a SAL are 4.8 times more likely to require surgical intervention [6]. Diagnosis of SAL may lead to earlier intervention and ultimately affect progression

of disease. By surgically addressing laryngomalacia, the resultant effect of SAL on the airway may become less significant. If a SAL is suspected on screening radiographs, the infant will benefit from a referral to an otolaryngologist for clinical correlation.

6.4. Congenital Heart Disease. Congenital heart disease is reported in 10% of infants with laryngomalacia. These infants are more likely to have moderate-to-severe disease at the time of presentation. The additive effect of airway obstruction on compromised cardiovascular function likely tips these infants towards worsening symptoms. Up to 34% of infants with both laryngomalacia and congenital heart disease will require surgical management [2].

6.5. Congenital Anomalies/Syndromes/Genetic Disorders. Congenital anomalies and genetic disorders occur with an estimated incidence of 8–20% [2, 10, 11]. The incidence is as high as 40% of infants with severe laryngomalacia that require surgical intervention [2, 12]. Infants with congenital anomalies and genetic disorders often have other medical comorbidities such as synchronous airway lesions, cardiac disease, and neurologic disease that confound oxygenation and breathing; this makes any degree of airway obstruction more of problematic for these patients. Infants with severe laryngomalacia, an isolated anomaly or syndrome, and minimal comorbidities can be managed successfully with supraglottoplasty [2, 12]. Of those infants, Down syndrome appears to be the most commonly reported associated genetic disorder with laryngomalacia. Fifty percent of those that have respiratory symptoms also have laryngomalacia [13–15]. The senior author's experience with supraglottoplasty in Down syndrome children is that if no coexisting cardiac disease or neurologic disease is present, they do well with aggressive acid suppression therapy and supraglottoplasty even if a synchronous airway lesion is present. Those with cardiac disease, neurologic disease, and synchronous airway lesions often fail supraglottoplasty and may require a tracheostomy until cardiac disease is treated.

Those with laryngomalacia and syndromes associated with micrognathia such as CHARGE association and Pierre Robin sequence will do worse due to the retrodisplacement of the tongue base. The retrodisplaced tongue base collapses on the epiglottis in addition to supra-arytenoid tissue redundancy and short aryepiglottic folds. Supraglottoplasty or epiglottic suspension procedures usually are unsuccessful [16], and most with severe airway obstruction and laryngomalacia will require a tracheostomy until they grow into the micrognathia or surgical intervention is performed to correct it. Laryngomalacia and variants of 22q11.2 microdeletion syndrome are described to have severe upper airway obstruction [17–19] and can be successfully managed with supraglottoplasty [17]. Because cervical vertebral anomalies are common in this patient population, cervicomedullary compression of the brainstem should be investigated as a potentiating cause of symptoms. A recent case series describes a child who had laryngomalacia symptom reversal

and improvement in laryngeal tone after brainstem decompression and did not require supraglottoplasty [19].

If micrognathia is not present, a syndrome or anomaly should not preclude supraglottoplasty in those with severe laryngomalacia that require intervention. The rates of failure and tracheostomy placement however may be higher in these patients and should be taken into consideration when counseling parents and managing this unique group of infants.

7. Surgical Management

Surgical management is indicated in those with severe disease. The most common indications for surgery are stridor with respiratory compromise and feeding difficulties with failure to thrive [1]. Severe airway obstruction with significant retractions, pectus excavatum, cor pulmonale, pulmonary hypertension, and hypoxia are all considered absolute indications for surgery. The relative indications are aspiration with recurrent pneumonia, weight loss without true failure to thrive, and a difficult to feed child who has not responded to acid suppression therapy. The decision to operate is individualized and based on the trend of the infants overall health and development. Supraglottoplasty is the mainstay of surgical treatment for laryngomalacia. The patient is anesthetized with a combination of mask and intravenous anesthesia. The airway is first evaluated by rigid endoscopy (microdirect laryngoscopy and bronchoscopy) to rule out secondary lesions of the subglottis and trachea. The supraglottis is visualized during spontaneous respiration, and the major areas of collapse are noted. The larynx is then exposed with operating laryngoscopes, and the supraglottoplasty is performed focusing on removal of the redundant arytenoid mucosa. As seen in Figure 1(c), the procedure is tailored to the patient's areas of obstruction, and care is taken to preserve mucosa in areas prone to stenosis. The success of supraglottoplasty approximates 94% and has a low complication rate [1]. Revision supraglottoplasty or tracheostomy will be required in 19–45% of infants and is directly influenced by the number and type of medical comorbidities [2]. Tracheostomy is reserved for patients who continue to have life-threatening airway obstruction and who fail to improve after supraglottoplasty.

8. Conclusion

Laryngomalacia is a common disease of infancy where the diagnosis is suspected by primary care providers based on history. Those with mild disease can be managed expectantly. Continued monitoring of the symptoms is necessary as symptoms can progress over the natural course of the disease. Recognizing patient factors and symptoms associated with moderate and severe disease helps determine which infants will benefit from otolaryngology consultation. Identifying patient factors that influence disease severity and outcomes is an important aspect of counseling care givers and providing care to infants with laryngomalacia.

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Review Article

Sleep Endoscopy in the Evaluation of Pediatric Obstructive Sleep Apnea

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Pediatric obstructive sleep apnea (OSA) is not always resolved or improved with adenotonsillectomy. Persistent or complex cases of pediatric OSA may be due to sites of obstruction in the airway other than the tonsils and adenoids. Identifying these areas in the past has been problematic, and therefore, therapy for OSA in children who have failed adenotonsillectomy has often been unsatisfactory. Sleep endoscopy is a technique that can enable the surgeon to determine the level of obstruction in a sleeping child with OSA. With this knowledge, site-specific surgical therapy for persistent and complex pediatric OSA may be possible.

1. Introduction

Obstructive sleep apnea (OSA) has been estimated to affect 1–4% of all children in the United States [1] and is linked to a number of health-related issues and behavioral problems such as daytime sleepiness, enuresis, cardiovascular problems, poor growth, hyperactivity, academic difficulties, and attention issues [2, 3]. Pediatric OSA is characterized by recurrent obstruction of the airway resulting in snoring, gasping, and apneic events, and OSA in children has been recognized as a significant disorder warranting evaluation and management. In many cases, adenotonsillar hypertrophy is the primary cause of OSA in children. Therefore, tonsillectomy and adenoidectomy (T&A) is the preferred surgical method to treat OSA in most pediatric patients.

With the increased use of polysomnography (PSG), studies have shown that 15–20% of children will have persistent OSA with postoperative symptoms of obstruction [4, 5]. Children with comorbidities such as obesity, Down syndrome, and craniofacial abnormalities may have obstruction unrelated to the tonsils and adenoids; these patients are at even higher risk for persistent apnea after T&A. In addition, healthy children with OSA may have small tonsils and adenoids that are unlikely to be completely

responsible for their obstruction [6]. There are a variety of causes for persistent and complex cases of OSA; these include obesity, hypotonia, craniofacial disproportion, lingual tonsillar hypertrophy, and occult laryngomalacia [7–10]. One solution to these difficult cases is the use of continuous positive airway pressure (CPAP). CPAP is generally effective in managing persistent OSA after adenotonsillectomy or complex OSA unrelated to the tonsils and adenoids, and its use is widely adopted in adults. Unfortunately, the use of CPAP in children can be difficult, and many children do not tolerate it [11]. Tracheotomy may be necessary in some severe cases of OSA.

The evaluation of children suspected of having complex OSA or persistent OSA after adenotonsillectomy should include polysomnography to confirm obstruction during sleep. Once OSA is diagnosed, identifying the site of airway obstruction during sleep may allow further interventions beyond tonsillectomy and adenoidectomy and CPAP. Flexible fiberoptic laryngoscopy is a useful tool that can be performed in the office to look for any potential levels of airway obstruction. Adenoid regrowth, lingual tonsillar hypertrophy, tongue base prolapsed, or laryngeal causes of obstruction can be seen with office fiberoptic laryngoscopy. However, this evaluation is limited by the fact that patients

are awake and upright when examined; potential sites of obstruction may be missed.

Sleep endoscopy has been previously described in the adult and pediatric populations for the purpose of evaluating the dynamic airway in the supine position during a sleep-like state [6, 12, 13]. It is an increasingly useful tool in the evaluation of children with persistent OSA after initial therapy, children with OSA without tonsil or adenoid hypertrophy, or children with significant craniofacial anomalies.

2. Method

Sleep endoscopy is performed in the operating room under general anesthesia and is performed in conjunction with direct laryngoscopy and bronchoscopy. The child is given inhalational anesthesia by mask. The IV is then placed, and anesthesia is then maintained with an infusion of dexmedetomidine at 1-2 mcg/kg/hr without a loading dose, as well as with a concurrent ketamine bolus of 1 mg/kg as our primary anesthetic cocktail. In the past, a propofol infusion was used to maintain anesthesia. However, we have found that there is less muscular relaxation and a more sustained respiratory effort with this current technique. We also vasoconstrict and anesthetize the nose with a half and half mixture of oxymetazoline and 1% xylocaine delivered on a 1 cm × 4 cm cottonoid pledget. Spontaneous respiration is supported by oxygen (2L/min) delivered via nasal canula. The child should be in the supine position without a shoulder roll, mimicking the position of natural sleep as much as possible.

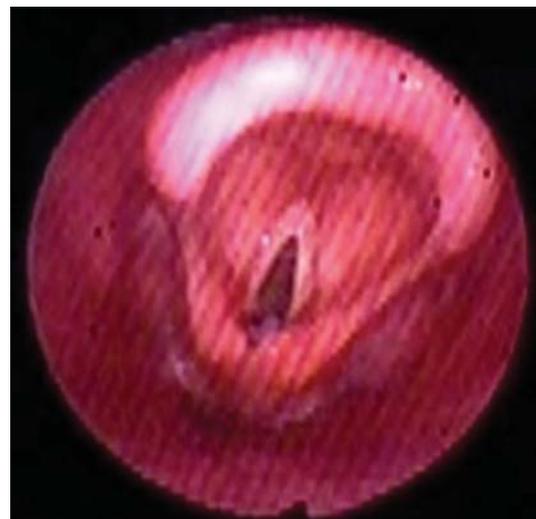
Once a rhythmic pattern of respiration is established, a flexible fiberoptic laryngoscope is passed directly into the child's nose, passing posteriorly toward the nasopharynx. For visualization and documentation, a digital video camera is used with the endoscope.

At the nasopharynx, the adenoids are examined as a potential site of obstruction. The position of the palate and uvula in relation to the posterior pharyngeal wall can be seen. The scope is then passed into the oropharynx where the tongue base, lingual tonsils, and pharyngeal tonsils (if still present) are examined. The position of the base of tongue, vallecula, and epiglottis in relation to the posterior pharyngeal wall is noted. In some cases, the tongue base can be seen collapsed against the posterior pharyngeal wall; visualizing the improvement in airway patency by lifting the tongue base with jaw thrust can be quite dramatic (Figures 1(a) and 1(b)). The dynamics of lateral pharyngeal wall motion can be seen. The scope is then passed under the epiglottis where the dynamics of the supraglottic soft tissues, as well as the motion of the vocal cords, are observed. At the completion of the sleep endoscopy, the scope is removed. Direct laryngoscopy and bronchoscopy can then be performed to complete the airway evaluation.

During sleep endoscopy, dynamic airway obstruction potentially can be observed at several levels. In the nasopharynx, the normal velopharyngeal opening should remain patent during inspiration and expiration. However, adenoid hypertrophy, adenoid regrowth, and midfacial hypoplasia



(a)

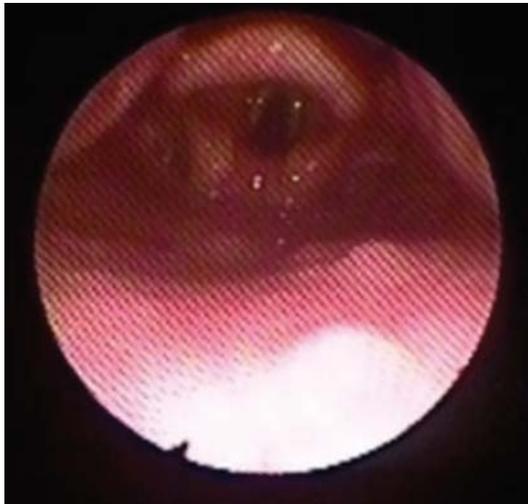


(b)

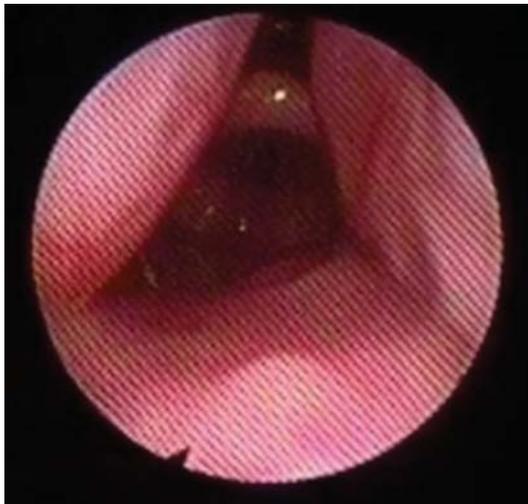
FIGURE 1: (a) Posteriorly displaced epiglottis secondary to tongue base collapse. (b) Dramatic improvement of the airway upon lifting the tongue base anteriorly using jaw thrust.

can obstruct this opening and reduce nasal airflow. In the oropharynx, the airway can be narrowed by the lateral pharyngeal wall and tonsils. This space collapses and expands during respiration but normally should not result in obstruction. Not surprisingly, tonsillar hypertrophy can significantly narrow and obstruct this space (Figures 2(a), 2(b), and 2(c)). Collapse of the lateral pharyngeal walls can occur during inspiration in children with hypotonia.

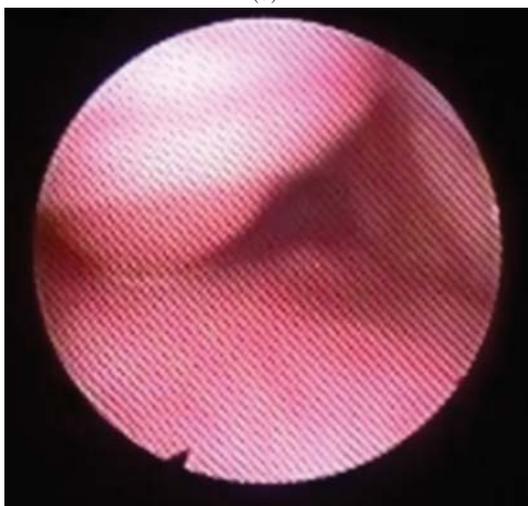
The tongue base should not rest on the posterior pharyngeal wall or displace the epiglottis posteriorly, allowing air to flow under and around the edges of the epiglottis. Again, hypotonia can result in collapse and obstruction at the tongue base, displacing the epiglottis against the posterior pharyngeal wall (Figure 3). Similarly, lingual tonsillar hypertrophy can crowd the entire vallecula with lymphoid tissue and displace the epiglottis against the posterior



(a)



(b)



(c)

FIGURE 2: (a) Supraglottic larynx with the pharyngeal tonsils seen laterally. (b) Rapid collapse of the pharyngeal tonsils medially on inspiration. (c) Complete obstruction of the airway by the pharyngeal tonsils on inspiration. On the expiration, the tonsils returned to their normal positions as in Figure 2(a).

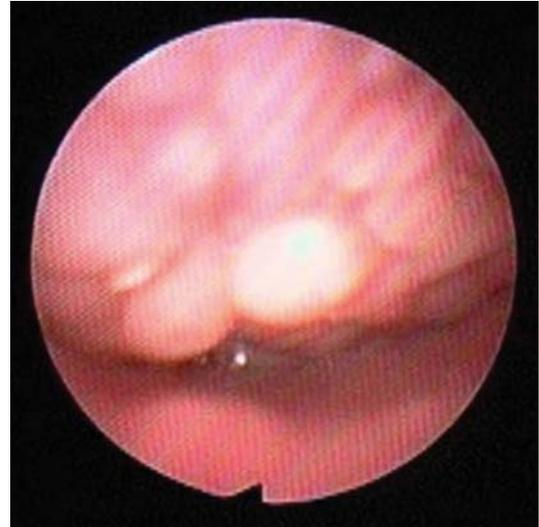


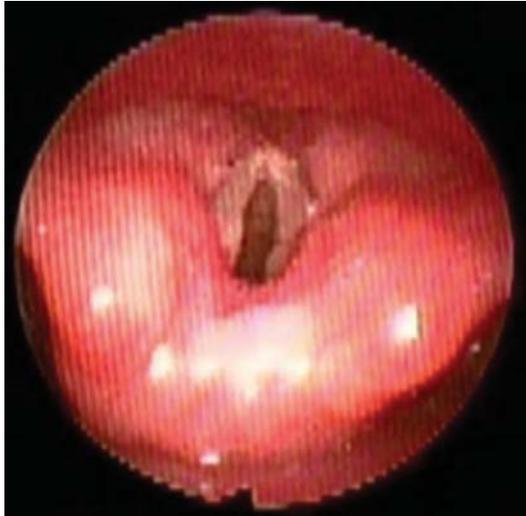
FIGURE 3: Tongue base collapsed against the posterior pharyngeal wall. The tip of the epiglottis is barely seen.



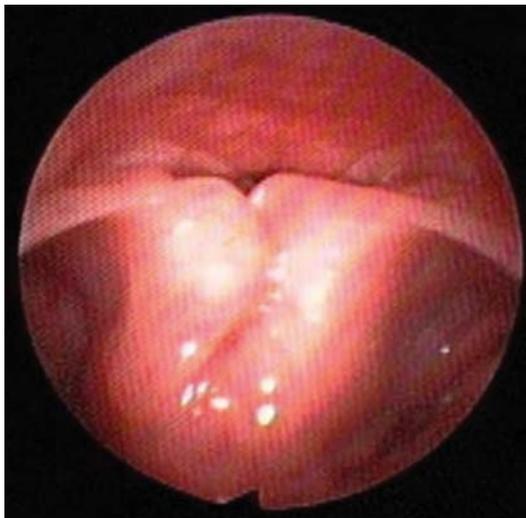
FIGURE 4: Lymphoid tissue of the lingual tonsils displacing the epiglottis posteriorly.

pharyngeal wall during inspiration (Figure 4). This is also seen in children with micrognathia or retrognathia where the tongue base is displaced posteriorly by the underdeveloped mandible.

If not displaced posteriorly by the tongue base, the normal supraglottis should remain patent during inspiration and expiration. In infants, airway obstruction may result from laryngomalacia characterized by floppy arytenoid mucosa and short aryepiglottic folds; this is present both while awake and during sleep. In some older children with persistent OSA, dynamics similar to laryngomalacia can be seen where excessive mucosal folds above the arytenoids prolapse into the glottis on inspiration. However, as opposed to infantile laryngomalacia, this form of obstruction only



(a)



(b)

FIGURE 5: (a) Supraglottis of an older child with occult laryngomalacia prior to inspiration. (b) Upon inspiration, the redundant arytenoid mucosa prolapses into the laryngeal introitus causing obstruction.

manifests during sleep; we call this “occult” laryngomalacia (Figures 5(a) and 5(b)).

3. Discussion

Sleep endoscopy was first described in 1991 by Croft and Pringle [12]. Since then, many studies have shown sleep endoscopy to be a safe and useful tool in the evaluation of the upper airway obstruction [14–16]. The findings in sleep endoscopy can assist in the management of persistent or difficult cases of pediatric OSA. Factors other than adenotonsillar hypertrophy which are known to contribute to airway obstruction during sleep include craniofacial disproportion such as midface hypoplasia or micrognathia, hypotonia, obesity resulting in oropharyngeal

soft-tissue redundancy, laryngomalacia, and lingual tonsillar hypertrophy. Historically, the exact site or sites of obstruction have been difficult to evaluate and identify in the pediatric population. The use of flexible fiberoptic laryngoscopy in the office as well as rigid laryngoscopy and bronchoscopy in the operating room has aided the workup of persistent and complex pediatric OSA. However, sleep endoscopy has the advantage of visualizing dynamic collapse and obstruction of the airway during a sleep-like state.

A number of studies have examined the utility of sleep endoscopy in the management of complex and persistent OSA. Various scoring schemes have been proposed to grade and classify obstruction seen during sleep endoscopy [14–17]. Yet the ultimate goal has been to identify the site of obstruction in order to direct further interventions. Simple site-specific identification of obstructing structures (e.g., lingual tonsils or arytenoids) is likely to be most useful as any potential surgical procedures (e.g., lingual tonsillectomy or supraglottoplasty) can be directed towards these structures to relieve obstruction [18].

Lingual tonsillectomy is one example. Lingual tonsillar hypertrophy has been well described in the anesthesia literature as a potential area of airway obstruction [7–10]. The lingual tonsils and the base of tongue are particularly concerning in Down syndrome with macroglossia and glossoptosis, although healthy children may have isolated lingual tonsillar hypertrophy as well [19, 20]. Using sleep endoscopy, Lin and Koltai conducted a study in which 26 children with persistent OSA were found to have lingual tonsillar hypertrophy. They reported a significant improvement in symptoms and polysomnogram scores after performing endoscopic-assisted coblation lingual tonsillectomy [20] (Figures 6(a) and 6(b)).

Another unexpected and recently described area of obstruction in older children with OSA is at the supraglottic larynx. Laryngomalacia, normally seen in infants, can be present in older children and can cause obstruction on inspiration. However, unlike infantile laryngomalacia, occult laryngomalacia is seen only in sleep. Richter et al. reported 7 patients with a mean age of 6.3 years with OSA secondary to laryngomalacia. All were treated successfully with supraglottoplasty [21]. Similarly, Revell and Clark diagnosed 19 children with a mean age of 7.3 years with laryngomalacia and OSA. Supraglottoplasty was offered to these children as well with the majority resulting in improvement or resolution of OSA [22].

The historic criticism of sleep endoscopy was related to the use of propofol [23, 24]. This drug has been shown to cause excessive hypotonia and muscle relaxation with altered airway dynamics resulting in an inaccurate model of natural slumber. While still imperfect, the combination of dexmedetomidine and ketamine provides a better simulacrum of sleep and consequently more accurate diagnosis.

4. Conclusion

Sleep endoscopy is a valuable tool for the treatment of complex or persistent pediatric OSA by identifying the site



(a)



(b)

FIGURE 6: (a) Lingual tonsils prior to endoscopic-assisted coblation lingual tonsillectomy. (b) After lingual tonsillectomy, the epiglottis can now be seen.

of airway obstruction. This enhanced diagnostic capability provides opportunities for site-specific interventions; additional options in the management of pediatric OSA other than CPAP and adenotonsillectomy may become available.

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Research Article

Cortical Auditory Evoked Potentials in Children with a Hearing Loss: A Pilot Study

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Objective. This study examined the patterns of neural activity in the central auditory system in children with hearing loss. *Methods.* Cortical potentials and mismatch responses (MMRs) were recorded from ten children aged between 9 and 10 years: five with hearing loss and five with normal hearing in passive oddball paradigms using verbal and nonverbal stimuli. *Results.* Results indicate a trend toward larger P1 amplitude, a significant reduction in amplitude, and latency of N2 in children with hearing loss compared to control. No significant group differences were observed for the majority of the MMRs conditions. *Conclusions.* Data suggest that the reduced auditory input affects the pattern of cortical-auditory-evoked potentials in children with a mild to moderately severe hearing loss. Results suggest maturational delays and/or deficits in central auditory processing in children with hearing loss, as indicated by the neurophysiological markers P1 and N2. In contrast, negative MMR data suggest that the amplification provided by the hearing aids could have allowed children with hearing loss to develop adequate discriminative abilities.

1. Introduction

Sensory hearing loss often affects speech perception due to a decreased audibility of the signal as well as decreased temporal analysis ability [1–3]. Studies have demonstrated the influence of hearing loss on auditory temporal ordering, a task which involves the central auditory system [4–6]. The lower performance of children with hearing loss in this task could be caused by central auditory neurophysiological deficits.

Auditory neurophysiological functions have been measured in adults and children with hearing loss [7–11]. Sensory hearing loss in adults induced a delay in the latency of N1, N2, and a reduction in N2-P2 amplitude [8]. Oates et al. [7] investigated the N1, N2, MMN, and P3, presented at 65 and 80 dB SPL, and found a latency prolongation and an amplitude reduction of these components in adults with hearing loss compared to those of the control group at both levels of presentation. However, an earlier study did not reveal

any significant differences in the latencies of N1, P2, and P3 components between adults with hearing loss and their normal-hearing controls [11]. Several factors could account for these differential findings, such as participants' age, age at onset of hearing loss, type and/or degree of hearing loss, level of stimulus presentation, and type of stimuli used.

In children, latency changes in the cortical-auditory-evoked potentials (CAEPs) have been used to document auditory system plasticity and recovery from auditory deprivation following cochlear implantation [10, 12]. Congenitally deaf children who are fitted with cochlear implants during a sensitive period of early childhood show normal central auditory maturation within six months of implant use as demonstrated by changes in P1 latency [10, 12]. Interestingly, in children with sensory hearing loss and those with auditory neuropathy, the P1, N1, and P2 components are present only in those children exhibiting good speech perception skills [9]. However, the children with and without good speech perception skills were not age-matched and this factor could

have influenced the results, since CAEPs show substantial changes with maturation [13, 14].

To determine CAEPs potential clinical benefits in assessing central auditory functions in children with hearing loss, a clear understanding of the effects of a sensory hearing loss on CAEPs is needed. The main objective of the present study is to explore central auditory neurophysiological functions in children with hearing loss wearing hearing aids. If CAEPs are affected by sensory hearing loss, cortical auditory measures could become neurophysiological markers in clinical audiology for evaluating young children for whom central auditory functions are difficult to assess behaviourally.

2. Materials and Methods

2.1. Participants. Two groups of nine-to-ten years old female children participated in the study: five with sensory hearing loss (mean age: 9:10 years, SD = ± 3 mo) and five with normal hearing (mean age: 9:11 years, SD = ± 3 mo). Participants with normal hearing had auditory detection threshold at 15 dB HL or less between 500 Hz and 8 kHz, bilaterally (re: ANSI, 1996 [15]). Average hearing sensitivity thresholds of children with hearing loss, based on the average of 500, 1000, and 2000 Hz thresholds, were within the limits of mild to moderately severe hearing loss (according to Clark (1981) classifications [16]). All participants were right handed, as measured by an adapted protocol to assess laterality dominance [17]. The study was approved by the Ethics Committee of the Sainte-Justine Hospital.

2.2. Stimuli. Three pairs of synthetic stimuli were used for this study: one verbal and two nonverbal pairs. The verbal stimuli consisted of two syllables: /ba/ and /da/. These stimuli were selected from the CD-ROM, Speech Production, and Perception I [18]. The first pair of nonverbal stimuli consisted of synthesized transformations of /ba/-/da/, generated using two softwares, Dr. Speech and Mitsyn [19, 20]. Only the second and third formants were used to create the nonverbal stimuli (for more detail on the syllable transformation, see Mody et al. [21]). Using only these two formants, the stimuli are recognized as nonverbal sounds [21]. The second pair of nonverbal stimuli was the pair of a 1 kHz pure tone and a wide-band noise. Stimuli were 250 ms in duration with 2.2 ms rise and fall times.

The stimuli were presented with a computer (DELL) using Stimaudio (NeuroScan Inc.) and the *Stim²* software. They were presented to the right ear through insert-earphone (E-A-RTONE 3A), connected to an audiometer (Interacoustics, AD229b model), at 70 dB HL for children with normal hearing and between 85 and 105 dB HL for those with hearing loss (See Table 1). Stimuli were presented in a passive oddball paradigm, with standard stimuli (syllable /ba/, nonverbal /ba/ and a 1 kHz pure tone) of 85% probability of occurrence and deviant stimuli (syllable /da/, nonverbal /da/ and wide-band noise) with a 15% probability of occurrence. The interstimulus interval (ISI) was one second. The order of stimulus presentation was pseudorandomized within a run, with no two deviants occurring in succession and no run beginning with a deviant stimulus. Any deviant stimulus was

always preceded by at least three standard stimuli. A thousand counterbalanced trials for each pair of stimuli were recorded.

2.3. Electrophysiological Recordings. The cortical responses were digitally recorded using a high-density system, Scan 4.0 software (NeuroScan, Inc., USA), with SynAmps amplifiers and from 128 Ag/AgCl electrodes. Electrophysiological signals were acquired at a sampling rate of 250 Hz, with an analog online bandpass filtering from 0.1 to 100 Hz using the SynAmps amplifiers running on a Dell computer. An electrode located on the forehead (Fpz) served as ground and reference was located at the vertex. Electrode impedance was kept under 7 k Ω for mastoid, central, and frontal regions and below 15 k Ω for ocular and peripheral regions.

2.4. Procedure. The children were seated in a chair in a double-walled sound-proof booth. Participants watched a movie or cartoon of their choice on a computer monitor with the sound off. They were told to ignore the auditory input and to focus their attention on the movie. Total testing duration was approximately between 90 and 120 minutes.

2.5. Data Analysis. Using BrainVision Analyser program on an IBM computer, the data were corrected for eye movements using Gratton and Coles algorithm [22]. They were next digitally filtered using a filter of 1–15 Hz at 24 dB/octave. These data were rereferenced to both mastoids electrodes. Eye movements and epochs with other artefacts were rejected based on voltage criteria ($\pm 100 \mu V$). The timeframe of analysis was from –100 ms to 700 ms. Data were baseline corrected to –50 ms. Auditory cortical components were defined as followed: P1 and N1 were the first positive and negative waveforms in the time window of 50–100 ms and 80–120 ms, respectively. They are followed by a positive peak, defined as P2 within the time window of 100–160 ms, and N2, the second negative peak at 200–280 ms. Amplitude values were measured from baseline to peak for each component, and latency values were measured relative to the onset of stimulus presentation.

MMRs were computed according to the following procedure: ERPs evoked by a standard stimulus were subtracted from ERPs evoked by the presentation of a deviant stimulus for each participant. Responses to standard stimuli that immediately followed the presentation of deviant stimuli were excluded from the standard stimulus average. Two MMRs were observed with the pair 1 kHz pure tone wide-band noise; a first negative peak was measured from 115 to 200 ms and a positive slope was observed from 200 to 330 ms. However, only one prevalent negative response from 115 to 260 ms was observed with the nonverbal and verbal pairs. For each participant, the latency of the most negative or positive peak was measured for the MMRs by using a peak amplitude automatic detection.

3. Results

3.1. CAEP Components. Statistical analyses were conducted on the amplitude and latency values of the standard sound

TABLE 1: Data of nine-to ten-year-old children with hearing loss: age (years; months); age of hearing aids fitting (H/A); sex and hearing loss measured in the right ear at 250 to 8000 Hz (NT: not tested); and stimulus presentation level (dB HL).

Participant	Age	H/A	Sex	Hearing threshold (dB HL)						Presentation level (HL)
				250	500	1000	2000	4000	8000	
1	9;07	3;00	F	35	50	60	60	60	NT	90
2	9;08	5;00	F	30	30	65	65	30	15	85
3	10;04	1;08	F	80	100	100	95	85	75	105
4	9;10	5;00	F	30	40	50	60	50	NT	85
5	9;11	4;00	F	40	40	45	50	45	30	85

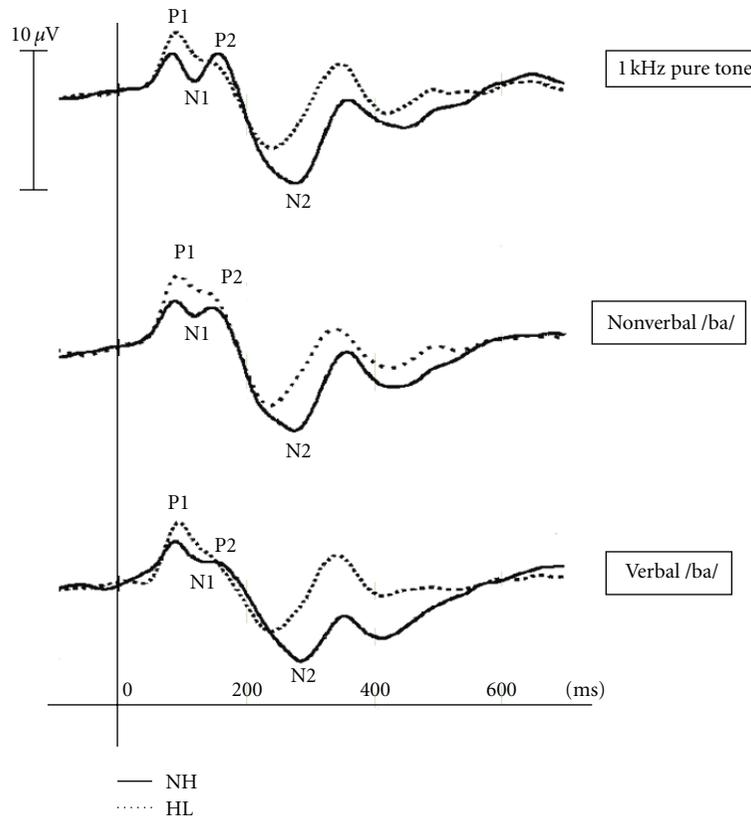


FIGURE 1: Waveforms recorded at FCz electrode from five children with normal hearing—NH (solid line) and five with hearing loss—HL (dashed line) with 1 kHz pure tone (top), nonverbal /ba/ (middle) and /ba/ (bottom) stimuli.

waveforms because they were better defined and had a clearer morphology compared to those obtained from deviant waveforms. P1, N1, P2, and N2 were observed clearly in children with normal hearing with the three stimuli (Figure 1). By contrast, the N1 and P2 components were not well defined in some children with hearing loss. Therefore, only the P1 and N2 components, which were clearly identified in all participants, were analyzed.

3.2. P1 and N2 Latency and Amplitude. Using SPSS software, a two-way ANOVA was performed (Group, Stimulus type) with repeated measures on the second factor, for both P1 and N2 latency and amplitude measures (Figures 2 and 3).

3.2.1. Latency. With regard to P1 latency, results revealed a significant effect for the main Type factor only (verbal /ba/,

nonverbal /ba/ and 1 kHz pure tone) [$F(2, 16) = 7.85, P < .01$]. t -tests were conducted, applying Bonferroni corrections to adjust for multiple comparisons ($P < .016$). Results revealed only a significant latency prolongation for the verbal /ba/ than the 1 kHz pure tone [$t(9) = 3.2, P < .016$] and for the nonverbal /ba/ than 1 kHz pure tone [$t(9) = 3.95, P < .016$].

As pertains to N2 latency, a significant latency reduction was observed in children with hearing loss comparatively to the latency value of children with normal hearing [$F(1, 8) = 9.01, P < .01$]. Results revealed a significant effect for the Type factor too [$F(2, 16) = 3.9, P < .05$]. However, no significant difference was observed between the three types of stimuli when t -tests with Bonferroni corrections ($P < .016$) were applied.

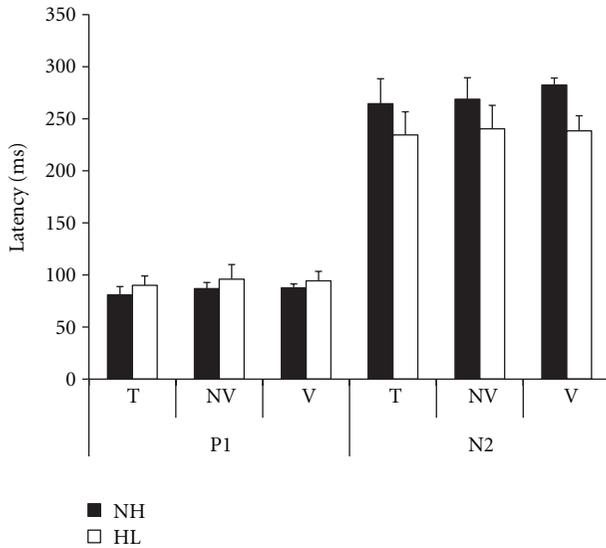


FIGURE 2: P1 and N2 mean latency values and standard deviation recorded of five children with hearing loss (HL) and five children with normal hearing (NH) with 1 kHz pure tone (T), nonverbal /ba/ (NV), and verbal /ba/ (V) stimuli.

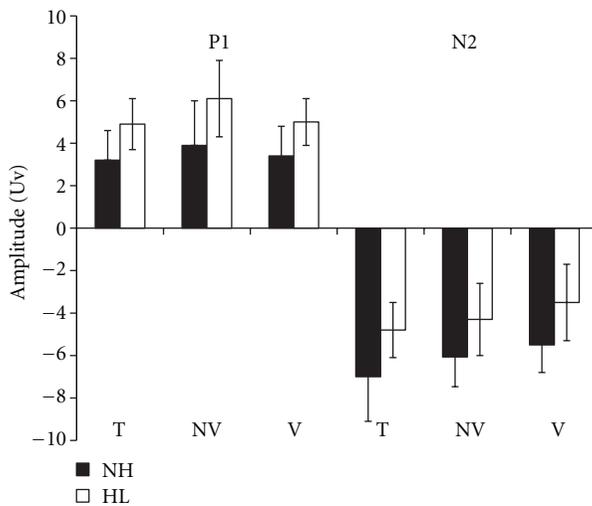


FIGURE 3: P1 and N2 mean amplitude values and standard deviation of five children with hearing loss (HL) and five children with normal hearing (NH) with 1 kHz pure tone (T), nonverbal /ba/ (NV), and verbal /ba/ (V) stimuli.

3.3.2. *Amplitude.* Regarding P1 amplitude, results revealed a significant effect for the Type factor only [$F(2, 16) = 5.5, P < .01$]. The main Group factor failed to reach significance but a trend was observed [$F(1, 8) = 4.03, P = .08$]. For the significant Type factor, a t -tests, with Bonferroni corrections ($P < .016$), revealed a significant greater amplitude for the 1 kHz pure tone than the nonverbal /ba/ [$t(9) = 3, P < .016$] only.

For the N2 amplitude, a significant amplitude reduction was observed in children with hearing loss comparatively to the amplitude value of children with normal hearing [$F(1, 8) = 5.8, P < .05$]. Results also showed a significant

effect for the type factor [$F(2, 16) = 3.8, P < .05$]. t -tests with Bonferroni corrections ($P < .016$) demonstrated a significant greater amplitude for the 1 kHz pure tone than the verbal /ba/ [$t(9) = 3.1, P < .016$] only.

3.3. *Mismatch Responses (MMRs).* A two-way ANOVA was performed (Group, Stimulus type) with repeated measures on the second factor, for both the MMR latency and amplitude measures (Figure 4).

3.3.1. *Latency.* With regard to negative MMR latency, results revealed a significant effect only for the main Type factor (verbal /ba-/da/ pair, nonverbal /ba-/da/ pair and 1 kHz pure tone and wide-band noise pair) [$F(2, 16) = 23.3, P < .001$]. A t -test with Bonferroni corrections ($P < .016$) demonstrated a significant latency prolongation for the verbal /ba-/da/ pair as compared with the 1 kHz pure tone and wide-band noise pair [$t(9) = 6.9, P < .016$] and also comparatively to the nonverbal /ba-/da/ pairs [$t(9) = 4.3, P < .016$].

3.3.2. *Amplitude.* Regarding the negative MMR amplitude, results revealed no significant effect for the two main factors nor for the two-way interaction Group \times Type. A positive MMR component was observed with the pair of 1 kHz pure tone and wide-band noise (Figure 4). A t -test was conducted on the amplitude and latency values. Results revealed a significant difference between the two groups for the amplitude value [$t(8) = 1.8, P < .05$], but not for the latency value [$t(8) = .53, P = .23$].

4. Discussion

The aim of the present research was to study the patterns of the neurophysiological activity in the central auditory system in children with hearing loss as compared with children with normal hearing. Differential findings were observed with regard to the principal cortical components and the MMR results.

4.1. *Cortical Principal Components.* P1 amplitude tended to be greater, N1 and P2 components less defined, and amplitude and latency of N2 reduced in children with hearing loss compared with the results of the children with normal hearing. These findings will be discussed according to three factors: the presentation level, the maturation of the central auditory system, and the deficit in the central auditory system.

4.2. *Presentation Level.* The stimuli were presented between 80 and 105 dB HL for the children with hearing loss and at 70 dB HL for the children with normal hearing. The higher level of stimulus presentation (in dB HL) could have contributed to the large amplitude of P1 and to the shorter latency of N2. Oates et al. (2002) found that the amplitude of the N1 and the P300 was larger and their latency shorter at 80 dB SPL compared to 65 dB SPL in adults with hearing loss [7]. In normal-hearing adults, as the intensity increases, peak latencies of P1, N1, P2, and N2 decrease and their peak amplitudes increase [23].

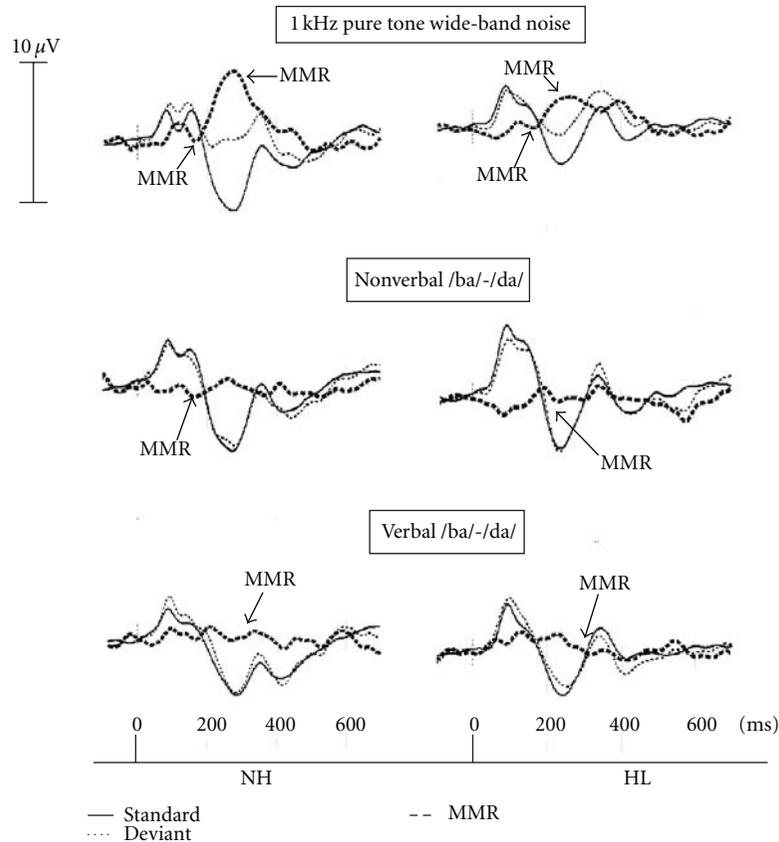


FIGURE 4: The grand average ERPs of five children with normal hearing (NH) and the five children with hearing loss (HL), elicited by the standard stimuli (solid lines): 1 kHz pure tone (top), nonverbal /ba/ (middle), and /ba/ (bottom); by the deviant stimuli (dotted lines): wide-band noise (top), nonverbal /da/ (middle), and /da/ (bottom). The mismatch response (MMR) is represented by a bold dashed line.

However, the results of the present study were partially in agreement with those results. There were only two indications that the level of presentation could modulate waveform characteristics. In fact, P1 amplitude was larger and N2 latency was shorter in children with hearing loss comparatively to children with normal hearing. The findings indicate that the level of presentation could affect differently the two components.

4.3. Maturation of the Central Auditory System. The P1 waveform changes in a complex manner in children. P1 decreases systematically in latency and/or amplitude to reach adult values almost at the age of 14-15 years [24] or 20 years [25]. The maturation of CAEPs has been investigated in children who received their cochlear implant between 18 months and six years of age, with the average age of implantation being 4.5 years [26]. The CAEPs, and in particular, the peak latency of P1, appeared to mature at the same rate as in children with normal hearing but were approximately delayed by the corresponding length of auditory deprivation [26]. This finding emphasizes that once adequate auditory stimulation is provided, the central auditory pathway continues to develop, but it is delayed by the duration of deafness, suggesting a limited form of auditory plasticity. Other studies further suggest that the plasticity of central auditory pathways is maximal only for a restricted period of about 3.5 years in early child-

hood [10, 12]. If the hearing system is stimulated within that period, the P1 morphology and latency reach age-normal values within 3 to 6 months following the beginning of auditory stimulation. By contrast, if the auditory system does not receive adequate stimulation for more than 7 years, then most children exhibit a delayed P1 latency and an abnormal large P1, even after years of implant use [10, 12].

In the present study, all children with hearing loss experienced a period without any stimulation with hearing aids, since their hearing loss was identified between the age of 20 months and 5 years (Table 1). During this period of deprivation, the maturation of the central auditory nervous system could have been slowed down. The P1 amplitude observed in children with hearing loss could be the reflection of limited plasticity. However, the amplification provided by the hearing aids could have certainly contributed to get under way the maturational processes but it was not probably sufficient to supply entirely the effect of the auditory deprivation.

Two out of four cortical auditory potential components—N1 and P2—were less defined in children with hearing loss compared to their peers with normal hearing. These two components do not emerge consistently until the age of 8 to 11 years in children with normal hearing [13, 24, 26]. The absence of these peaks or their affected morphology in children with hearing loss could be another manifestation of

a delayed maturation of the central auditory nervous system. This interpretation is consistent with a study reporting that N1 and P2 are either delayed in developing or absent in children with a cochlear implant [26].

Regarding the N2 maturation in children with normal hearing, N2 amplitude has an initial increase between the age of 5 to 11 years [24] followed by a gradual decline from late childhood to midadolescence [27, 28] and finally N2 amplitude reaches adult values by age 17 [24]. However, there is no general consensus regarding the development of peak latency, with some studies showing a decline [29], no change, [27] or an increase in latency with age [24]. The maturation effect was examined at central (Cz, C3, and C4) and at frontal (Fz) electrodes in 118 subjects [24]. The N2 latency increased significantly as a function of age at central electrodes with no maturational change at the frontal electrode. However, for the children between 9 and 10 years old, the latency values were similar at the four electrode sites [24]. Based on this study [24], the reduction in amplitude and in latency of N2 in children with hearing loss in the present set of data could be explained by a delay in maturation of the central auditory nervous system. Alternately, based on other studies (e.g., [13, 29]), the reduction of N2 latency could be related to a more mature system. However, it seems counter-intuitive that the late component (N2) should mature more rapidly in children with hearing loss than in children with normal hearing. Taking into account the increased P1 amplitude and the abnormal morphology of N1 and P2, the N2 changes would rather militate in favor of delayed maturation in children with hearing loss.

4.4. Deficit in the Central Auditory System. The greater amplitude of P1 with a concomitant reduction in N2 amplitude and the less well-defined N1-P2 components could also indicate a deficit in central auditory processing. The anomalies have been reported in central auditory late latency components in children with language-based learning problems (LPs) [30]. Albeit displaying normal hearing sensitivity, these children had abnormalities in neurophysiological encoding marked by different patterns in amplitude or latency compared to their control peers. In fact, one normal category and three atypical categories based on cortical responses of children with LP were found. The atypical category 1 included children with a delayed P1 latency and no evidence of N1 or P2 component. The atypical category 2 was composed of children having normal P1 but delayed N1 and P2 responses. For the atypical category 3, children had generally low-amplitude responses [30]. Although N2 properties were not specifically examined in this study, observations from their results suggest that N2 amplitude and latency values were abnormal (low-amplitude and/or delayed latency) for children in the three atypical categories. These atypical responses might represent a general decrease in synchronous activity, indicating an immature development of the central auditory pathways or slower processing mechanisms [30].

4.5. Mismatch Responses. Similar patterns of results were obtained in the two groups of children with the negative mismatch response measured in the 150–200 ms window. These

results suggest that the auditory system can discriminate sounds, being the verbal or nonverbal, and that this pattern of discrimination can be found in children with hearing loss as well as in children with normal hearing. They further suggest that the amplification provided by the hearing aids could have contributed to get under way the maturational processes, allowing the children to develop adequate discriminative abilities.

A positive MMR was measured in the 200–300 ms window with the pair of 1 kHz pure tone and wide-band noise only. Results showed that the amplitude of this positive MMR was significantly smaller in children with hearing loss than that observed in children without hearing loss. This result may simply be related to the fact that children with hearing loss have, as stated above, a smaller N2 amplitude in response to the standard stimuli compared to normal hearing children.

The negative MMR was also found to differ according to stimulus type. When the stimuli were simple, (the pair 1 kHz and wide-band noise), the MMR had an earlier latency compared to more complex stimuli, such as the nonverbal and verbal /ba/-/da/. The effect of stimulus type on ERP results has also been reported by other studies [31, 32]. Those and the present results confirm that simple stimuli are more rapidly processed within the central auditory system in comparison to complex stimuli.

5. Conclusion and Clinical Implications

Although obtained in a limited number of children and in a restricted age range, these preliminary findings indicate that reduced auditory input early in life has an impact on the development of central auditory functions reflected by the specific patterns of CAEPs. The interaction and the combination of at least two factors, delay in maturation and deficit in the central auditory system, could contribute to the pattern of results obtained in children with hearing loss. The data further indicate that sensory hearing loss affects differently the earlier cortical component P1 compared to the later component N2. Moreover, the findings suggest that CAEPs can be more sensitive markers of the effects of sensory hearing loss than are mismatch responses in children with mild to moderately severe hearing loss. Measuring P1 and N2, as the neurophysiological markers in children with hearing loss, can provide an objective assessment of the maturation of their central auditory system. For well-trained audiologists with CAEPs, results can be easily interpreted. P1 and N2 amplitude measured before and after a given auditory training program may reflect the efficiency of the program and confirm the plasticity of the auditory pathways. Also, with these two neurophysiological components, audiologists may determine whether appropriate stimulation is being provided by a hearing aid or cochlear implant, and based on the findings, they may adjust the auditory training program. However, the CAEPs measures should be adapted before being implanted as an assessment tool in clinics and its cost effectiveness has to be assessed. In the near future, studies will take into account the clinical testing conditions by reducing the number of recording channels (limited to

frontal sites) in order to be suitable to clinical equipments and also by developing normative data.

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Review Article

Neonatal Stridor

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Neonatal stridor is an important condition, in many cases implying an impending disaster with a very compromised airway. It is a sign that has to be considered with the rest of the history and examination findings, and appropriate investigations should then be undertaken to confirm the source of the noise. Neonates with stridor should be managed in a multidisciplinary setting, by clinicians familiar with the intricate physiology of these children, and with access to the multitude of medical and surgical investigative and therapeutic options required to provide first-rate care.

1. Introduction

Neonatal life involves the readaptation of gas exchange from the intrauterine to extrauterine environment. Stridor in this period reflects a critical airway obstruction which may have been anticipated or wholly unexpected. With the advent of better investigations in utero, greater translation of established therapeutic practices to the neonatal setting, and technological advances that see more children coming to this world at an earlier gestational age, comes the challenge to be more cognizant of the needs of the neonate and to know when to intervene. In modern neonatal intensive care units (NICUs), infants weighing more than 1000 grams and born after 27 weeks of gestation have an approximately 90% chance of survival, and the majority have normal neurological development [1].

Stridor can be defined as a harsh, grating sound as a result of partial obstruction of the laryngotracheal airway. In Latin, originally in the 17th century, it meant “to creak.” Stridor in a neonate potentially implies an impending disaster with a very compromised airway. If seen with significant suprasternal tug and intercostal recession, stridor indicates an airway that may be less than a millimeter away from complete obstruction. Stridor is, however, a sign that has to be considered with the rest of the history and examination findings, and

appropriate investigations should then be undertaken to confirm the source of the noise. Its severity, as well as the severity of accompanying respiratory distress, determines the urgency with which investigations are required to proceed, ranging from the well neonate with mild stridor, no respiratory distress, and good feeding, to the one with severe airway compromise requiring immediate intervention.

2. Anatomical and Physiological Considerations

The newborn has a much narrower airway in dimensions compared to the infant, child, or adult. The average diameter of the subglottis is around 4.0 mm, and the impact of any form of swelling to an airway that size has been reiterated frequently by quoting the inverse relation of resistance of flow to the radius in a tubular structure (resistance $\propto 1/r^4$) [2].

The neonatal respiratory physiology and its impact on airway size highlight the adaptive requirements of the fetus to handle life outside uterus. Their pulmonary blood flow is relatively restricted in utero by relative fetal hypoxia, but this is radically changed when the establishment of respiration causes improved oxygen content and improved pulmonary blood flow. This can cause the development of unusual blood vessels that extrinsically impress on the airway, as is seen in patients with vascular rings.

The chest wall of the neonate stabilizes a very compliant ribcage, whilst the neonatal lung, especially in a premature child, accounts only for 10–15% of the total lung capacity. To increase the functional residual capacity of the neonatal lung, the child uses (1) expiratory braking—the use of active glottic narrowing during expiration, (2) ongoing active use of inspiratory muscles during expiration, and (3) rapid respiratory rates [3]. Lack of these reflexes, especially in a child with bilateral vocal cord impairment, produces biphasic stridor and rapid decompensation, hence the need for immediate intubation or possible continuous positive airway pressure (CPAP) to maintain a patent airway. However, in a neurologically functioning airway, this physiology also allows tubeless anaesthesia with spontaneous respiration, a common practice when most units perform microlaryngoscopy and bronchoscopy.

3. Evaluation of the Neonate

Stridor is but a symptom of an illness that requires a full history and examination. History should cover antenatal and perinatal events, breathing difficulties, feeding, and growth, and previous intubation or intensive care. This has to be complemented by looking for tachypnoea, grunting, inward retractions of the chest wall, nasal flaring, and central cyanosis.

Flexible laryngoscopy is now widely used in the assessment of neonatal stridor. The procedure is well tolerated and can be carried out either via the nose or via the mouth. It gives good view of the supraglottis and vocal cords, allowing one to make an assessment of the dynamic airway in an awake child. However, flexible laryngoscopy does not allow palpation, nor visualization of the subglottis and trachea. Therefore, most children with stridor other than simple mild laryngomalacia still require rigid laryngotracheobronchoscopy.

An additional investigation useful when assessing neonates with airway obstruction is polysomnography. Many babies with airway obstruction will suffer with sleep apnoea as the upper airway musculature relaxes during sleep. Polysomnography can therefore be a useful tool when investigating these neonates and deciding on operative management. It allows the calculation of certain variables such as the respiratory distress index (RDI), frequency and severity of oxygen desaturations (pO_2), and the retention of carbon dioxide (pCO_2). If a neonate has values such as RDI $>20/hr$, frequent pO_2 desaturations below 90%, or pCO_2 levels above 50 mmHg, this child may have impending respiratory failure.

The aetiology of stridor in neonates is usually congenital. In a study examining stridor in 219 patients, Holinger confirmed this, also noting that more than half of those children aged under 2.5 years had laryngeal abnormalities [4]. He also found that 45.2% of children with stridor had another associated abnormality involving the respiratory tract, prompting the statement that in evaluating stridor, one does not conclude with laryngoscopy but proceeds with an endoscopic examination of the entire tracheobronchial tree [4].

In a significant proportion of neonatal illnesses, stridor comes as a result of an underlying congenital abnormality

probably aggravated by an inflammatory component. It is also important to evaluate the response of stridor to more conservative treatment options. These include the response to adrenaline/epinephrine in croup or subglottic stenosis, the use of positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) for tracheomalacia, the use of inhaled and systemic steroids in inflammation, or the change in body positioning as in mandibular retrognathia.

Narrowing of the laryngotracheal pathway may be at the level of the supraglottis, glottis, subglottis, cervical trachea, or thoracic trachea. It may be a condition extrinsic to these areas, intrinsic to the structures that carry airflow to and from the lungs, or caused by a result of material within the lumen itself. Stridor implies an obstruction at the laryngotracheal airway and has to be distinguished from other airway noises; stertor is a pharyngeal-induced noise which is often worse when the child is asleep (typified by snoring), whilst wheezing is the result of bronchial narrowing. Stridor tends to be worse when the child is awake, feeding, or upset.

There have been many ways of describing the noise heard, including the quality of the sound, the site of obstruction, and the pathological diagnosis. However, the classical description of its relationship to breathing continues to hold firm. Stridor may be inspiratory, expiratory, or both. The length of the expiratory component often allows one to surmise where the site of maximal narrowing or where the closing pressure is most critical. If the sound is purely inspiratory, most otolaryngologists will assume the obstruction is likely supraglottic and the differential diagnosis will likely include laryngomalacia, or something causing the supraglottic structures to draw in as the child inspires. Stridor due to obstruction at the level of the vocal cords or subglottis is often biphasic. Obstruction in the trachea will cause predominantly expiratory stridor, with fixed obstructions (as opposed to dynamic ones) having biphasic stridor.

4. Supraglottic Airway Obstruction

Laryngomalacia is the commonest cause of neonatal stridor. It is typified by inspiratory stridor, which worsens with feeding, agitation, and supine positioning. Direct visualization of the larynx typically shows collapse of the supraglottis, tight aryepiglottic folds, an omega-shaped epiglottis, retroflexed epiglottis, and supra-arytenoid tissue prolapse. The condition is thought to be the result of neuromuscular alteration in laryngeal tone with subsequent collapse of the supraglottic structures [5]. Many children with laryngomalacia experience reflux [6]; whilst this may be the result of very negative intrathoracic pressure, reflux itself can contribute to oedema and thus airway compromise.

Laryngomalacia has also been associated with other congenital abnormalities such as neurological problems or Down's syndrome, and up to two thirds may have an associated second airway lesion.

For most children, laryngomalacia is mild and self-resolving [7], with the diagnosis confirmed on flexible laryngoscopy. However, in children with severe or atypical

features, rigid airway endoscopy is warranted, with surgical supraglottoplasty being used to relieve symptoms with good results in vast majority of cases.

In the neonatal practice, the other common cause of supraglottic obstruction is the mucus retention cyst in the vallecula. Our unit has seen many of these cases, and the condition is well described in the literature [8]. They often displace the epiglottis posteriorly causing stridor and apparent life-threatening episodes, which is readily corrected with a marsupialisation procedure of the cystic lesion.

5. Glottic Airway Obstruction

Glottic obstruction caused by vocal cord motion impairment (VCMI) is the second commonest cause of stridor in a neonate. Whilst bilateral VCMI tends to present with stridor and airway obstruction, patients with unilateral VCMI may also have stridor but additionally present with a weak cry or feeding difficulties due to aspiration. It is important to exclude correctable neural abnormalities resulting from the brainstem, such as the Arnold Chiari malformation, as correction of the pressure to the cerebellar tonsils often resolves a history of fluctuating stridor and airway obstruction. In practice, many cases of unilateral VCMI are iatrogenic, acquired following life-saving intrathoracic procedures such as in tracheoesophageal fistula repair or cardiothoracic procedures for cardiac abnormalities as a neonate. The damaged recurrent laryngeal nerve, often involving the left vocal cord, allows the cord to sit in a paramedian position, which draws in with inspiration. Occasionally, the arytenoid may rotate medially and the vocal cord may be midline and exertional stridor is heard. A variety of treatments are used in unilateral VCMI, including speech and language therapy, vocal cord medialisation, and laryngeal reinnervation [9].

The management of bilateral VCMI centers on achievement of a safe airway. Traditionally, this was achieved with a tracheostomy that may be required in approximately half of patients. However, more recently a variety of open and endoscopic procedures have been used to try and avoid tracheostomy [9]. Botulinum toxin to the cricothyroid muscle, excision of the cricothyroid muscle, vocal cord lateralisation, and endoscopic posterior cricoid split with costal cartilage graft have been proposed at the neonatal or early infancy period, whilst other modalities including vocal cord arytenoidectomy, cordotomy, or recurrent laryngeal nerve reinnervation are for older children with established tracheotomies needing decannulation. It is likely that in two-thirds of children movement in at least one vocal cord will recover in due course, so any aggressive early surgical interventions need to be balanced against the fact that the airway may improve spontaneously, especially as any surgical airway widening may be achieved at the expense of a good voice in the future.

An important diagnosis in VCMI is the differentiation between palsy/paralysis and fixation of the vocal cords due to posterior glottic stenosis. The latter is an acquired problem that has become more frequent in our practice with the increase in the number of extremely premature children

requiring ENT input. These children require neonatal intensive care, often having respiratory distress following meconium aspiration, and may require endotracheal intubation for a prolonged period of time. Unfortunately, the endotracheal tube may cause significant glottic irritation, and this in turn causes granulation of the posterior glottis. Acquired subglottic stenosis is rare as a result of better understanding of the pathophysiology of this condition, but this has been replaced to some extent by posterior glottic stenosis. Children born at 24–26 weeks of gestation, weighing less than 1000 g, are renowned for having chronic lung disease, and a small percentage of these neonates appear to react significantly to the presence of the endotracheal tube. It is only with trial extubation that the diagnosis of laryngeal granulomata is made, and these neonates may go on to develop interarytenoid adhesions and, unfortunately, posterior glottic stenosis.

Neurological dysfunction of the laryngeal airway can also come in the form of inflammation at the glottic aperture. The classical description of gastroesophageal reflux disease (GERD) involving the larynx is said to occur when the larynx is bathed in refluxate, and the sensitivity of the larynx is altered [5]. This can present with abnormal constriction of the larynx to stimuli causing intermittent spasmodic constriction of the neonatal larynx, or with lack of constriction allowing significant aspiration of the stomach contents leading to lower respiratory tract symptoms mimicking bronchiolitis or reactive airways disease. Bronchial aspiration confirming lipid-laden macrophages along with signs of the cobblestone tracheal mucosa may assist the pediatrician to consider prolonged antireflux therapy or in some cases fundoplication if maximal therapy fails to prevent ongoing respiratory issues.

Another uncommon cause of glottic obstruction is the laryngeal cleft [10]. This can be missed on routine fiberoptic nasendoscopy and even during laryngoscopy under anesthesia. The gold standard would be to perform a microlaryngoscopy with binocular vision and to spread the posterior laryngeal structures aside and examine the depth of the interarytenoid tissues. Excessive or exuberant tissues in this area can alert one to the possibility. In addition to aspiration, however, children with laryngeal cleft present with stridor when the tissues are more adducted than normal, and inspiration leads to mild indrawing of the vocal folds and the offending noise. Some have suggested that the incidence of laryngeal clefts is increasing, although this may simply reflect greater awareness amongst the clinicians. Small clefts can be repaired endoscopically, but longer ones with a significant cleft between the larynx/trachea and the esophagus require an external approach.

Congenital glottic webs can present as aphonia or a high-pitched cat-like cry along with stridor. Webs can be associated with a genetic alteration as seen with velocardiofacial syndrome [11]. Rarely the web is thin and confined to the larynx alone, and the web may end up being disrupted during intubation, or it can be divided with a sickle knife. More often the web is thick with subglottic extension that appears like a sail on a lateral radiograph. These cannot be treated with simple division, but may require tracheostomy,

open repair, keel placement (or the use of perichondrium to prevent web re-forming), and treatment of associated subglottic stenosis. Surgery was previously deemed possible when the child is older, but the improvement of neonatal anaesthesia and microscopic techniques has allowed the performance of this form of surgery at an earlier age, hence avoiding a tracheotomy [11].

Recurrent respiratory papillomatosis is rarely a cause of neonatal stridor, but it can present with normal breathing at birth and then progressive biphasic stridor and loss of voice either in infancy or as a toddler. It is hoped that the recent introduction of vaccines aimed at human papilloma virus (types 6 and 11) will reduce the incidence of this condition [12]. At present, the condition is most commonly treated with repeat debulking using a microdebrider, cold steel, or the CO₂ laser.

6. Subglottic Airway Obstruction

Subglottic stenosis (SGS) is nowadays seen relatively infrequently. If the stenosis is early and soft, a period of laryngeal rest may be used (2-week undisturbed intubation), whilst any granulation tissue can be removed, and any subglottic cysts forming due to obstruction of the mucous glands can be deroofed or removed (using cold steel techniques to minimize tissue damage). If recurrent granulations are a problem, mitomycin C may be of use. Balloon dilation is also useful, but if the oedema is severe or appears to be progressing, then cricoid split (endoscopic or open) can be used. Once the stenosis is firm and established, tracheostomy may be required, with the surgical options of laryngotracheal reconstruction (LTR) or cricotracheal resection (CTR).

To avoid tracheostomy, early surgery has recently been advocated for SGS; a study of patients aged less than 12 months undergoing single-stage LTR found that tracheostomy was avoided in 9 out of 10 neonates and infants [13]. Interestingly, earlier definitive surgical intervention to avoid tracheostomy has also been proposed in the Robin sequence, where distraction osteogenesis and glossopexy avoided tracheostomy in 6 infants that failed CPAP [14]. Similarly, early postnatal surgery has been advocated in children with masses causing airway obstruction. Whilst recent trends towards early surgery may be a tempting way to avoid tracheostomy, it is more technically difficult, with increased physiological risks including those due to blood loss.

Failed extubation is still a common scenario requiring ENT involvement in the neonatal or pediatric intensive care unit. Generally, extubation should be attempted when the child is relatively well, with a leak around the tube. Whilst it is important to ensure that there is no respiratory reason for failed extubation, from the ENT point one should look for both intubation-related and other ENT causes. Close co-operation between the different specialties is required.

Subglottic hemangioma is another condition that has seen its management evolve in the last three years. The child presents with a biphasic stridor, and in 50% of cases, there may be a cutaneous lesion as well. A plain X-ray of the tracheal column sees the classical asymmetrical air

column at the subglottis, and they respond fantastically to propranolol such that the operation of tracheotomy for this condition is a thing of the past. There is still controversy about the treatment duration, whether surgical intervention is still required in some cases, and whether simultaneous treatment with systemic steroids is required. However, there is consensus that following endoscopic confirmation of this diagnosis, the premature or low-birth-weight neonate should be closely monitored for hypoglycemic episodes whilst on the treatment with propranolol [15].

7. Obstruction in the Trachea

Tracheomalacia is caused by either weakness of the tracheal wall due to alterations in the ratio of cartilage to muscle, or due to hypotonia of trachealis muscle causing anterior prolapsed [16]. It can be primary or secondary to another lesion (such as tracheoesophageal fistula or vascular malformation). Tracheomalacia accompanying tracheal esophageal fistula in the neonate is usually expertly managed by the general pediatric surgeon in our institution. However, children with other associated midline cleft abnormalities such as VATER syndrome need more intensive scrutiny. There have been many case reports over the years where these children have developed tracheal diverticulum that continue to cause significant obstruction despite expert surgical care [17]. Surgical management of tracheomalacia varies depending on site, as the upper tracheomalacia is more amenable to an tracheopexy involving the sternum, whilst lower tracheomalacia involves attachment to the great vessels or possibly even a slide tracheoplasty with primary anastomosis.

Congenital tracheal stenosis with complete tracheal rings is often related to the presence of a pulmonary sling. This sling is a result of the development of a left pulmonary artery coming off the right pulmonary artery, wrapping itself around the trachea at a fetal stage of development. The failure of the development of trachealis or a C-shaped tracheal ring at birth leads to the condition, and if it involves a significant segment of the trachea, the neonate will go on to develop the washing-machine-type stridor characteristic of these cases. The surgical management of these cases often involves relocation of the left pulmonary artery to the pulmonary trunk away from the area of narrowing, whilst correction of the tracheal narrowing can be performed with either a slide tracheoplasty as championed by Grillo [18], or with a variety of other alternatives such as autograft tracheoplasty, pericardial patch tracheoplasty, or stent surgery.

The trachea can also be occluded by vascular abnormalities [19]. A variety of causes have been described. Common vascular rings, completely encircling the trachea, include a double aortic arch and a right-sided aortic arch with aberrant left subclavian artery. Common vascular slings, exerting noncircumferential pressure, are an aberrant innominate artery and a pulmonary artery sling produced by an anomalous left pulmonary artery. Surgical correction of underlying abnormality is often required, but secondary tracheomalacia is also a frequent complication.

8. CHAOS and EXIT

Clinical practice has changed much over the last few decades as advances in ultrasonography have facilitated accurate antenatal diagnosis of airway problems and thus appropriate perinatal management. Typical prenatal ultrasound features in congenital high airway obstruction syndrome (CHAOS) include polyhydramnios, dilated trachea and increased echogenicity of the lungs, flat or inverted diaphragm, and ascites [20]. The actual cause of airway obstruction may also be seen. In utero MRI is a useful imaging modality in addition to the ultrasound.

When airway obstruction at delivery is a concern, the procedure of ex utero intrapartum treatment (EXIT) has been used over the last few years to save lives of these children that would have died previously. In addition to EXIT, fetoscopic surgery has also been advocated [21]: creating a perforation in the obstructed larynx allows release of fluid from the obstructed lungs to aid lung development, and although EXIT is still required it is hoped that the long-term respiratory function will be better.

9. Conclusion

Stridor in the neonate implies a very severe airway obstruction which needs emergency management. The approach to management needs to be done by clinicians familiar with the intricate physiology of these children who may be still very immature in their development. There are medical and surgical options in the investigative armamentarium, and the use of these newer technological advances may be necessary to temporalize their condition until they grow out of their condition. Importantly, this is a multidisciplinary condition, and good communication among the professionals and carers is likely to achieve long-term successful outcomes for these very vulnerable members of our society.

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Review Article

Juvenile Angiofibroma: Evolution of Management

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Juvenile angiofibroma is a rare benign lesion originating from the pterygopalatine fossa with distinctive epidemiologic features and growth patterns. The typical patient is an adolescent male with a clinical history of recurrent epistaxis and nasal obstruction. Although the use of nonsurgical therapies is described in the literature, surgery is currently considered the ideal treatment for juvenile angiofibroma. Refinement in preoperative embolization has provided significant reduction of complications and intraoperative bleeding with minimal risk of residual disease. During the last decade, an endoscopic technique has been extensively adopted as a valid alternative to external approaches in the management of small-intermediate size juvenile angiofibromas. Herein, we review the evolution in the management of juvenile angiofibroma with particular reference to recent advances in diagnosis and treatment.

1. Epidemiology

Juvenile angiofibroma (JA) is a benign vascular neoplasm which affects young males between 9 and 19 years of age and accounts for 0.05% of all head and neck tumors [1]. In USA, this lesion represents the most frequent head and neck tumor of adolescence with one new case per 5000 to 50,000 patients referred to an otolaryngologist [2]. Glad and colleagues [3] reported an incidence of JA in Denmark of 0.4 cases per million inhabitants per year. In the Middle East and India, the incidence seems to be much higher than in Europe [4].

2. Histopathological Aspects and Pathogenesis

Histologically, JA is a pseudocapsulated lesion characterized by an irregular vascular component composed of numerous blood vessels of different calibers embedded in a fibrous stroma, rich in collagen and fibroblasts. Vessels are slit or dilated, organized in clusters, without elastic fibers in their wall, and the muscular lining is incomplete in large vessels, and totally absent in the smaller ones. Mitotic figures are rare [5, 6] (Figure 1).

Since the 19th century, there is considerable debate concerning the fibrous or vascular origin of JA. Because of its extensive vascularization, several authors have considered the hypothesis of vasoproliferative malformation: Sternberg

[7] and Hubbard [8] proposed JA as a specific type of hemangioma, while the theory of an ectopic proliferating vascular tissue was forwarded by Schiff in 1959 [9]. More recently, immunohistological and electron microscopic studies have suggested that this lesion may be considered a vascular malformation (or hamartoma) rather than a tumor [10]. These observations led Schick and colleagues [11] to postulate that JA might be due to incomplete regression of the first branchial artery, which arises in embryogenesis between days 22 and 24 and forms a temporary connection between the ventral and dorsal aorta. This artery commonly regresses and forms a vascular plexus that either involutes or may leave remnants, potentially leading to development of JA. This theory is supported by the finding that JA vessels express laminin alpha-2, which is considered to be a marker for early embryological angiogenesis [12]. Moreover, Gramann et al. [13] demonstrate prominent collagen-type VI expression in JAs, which is an extracellular matrix component that is attractive for neural crest cells and might be involved in the development of JA from plexus remnants of the first brachial artery.

The observation that JA typically arises in adolescent males and that the lesion frequently regresses only after full development of secondary sex characteristics provided the evidence of hormonal influence on JA growth [14, 15]. In spite of reports of hormonal disorders in patients with JA and

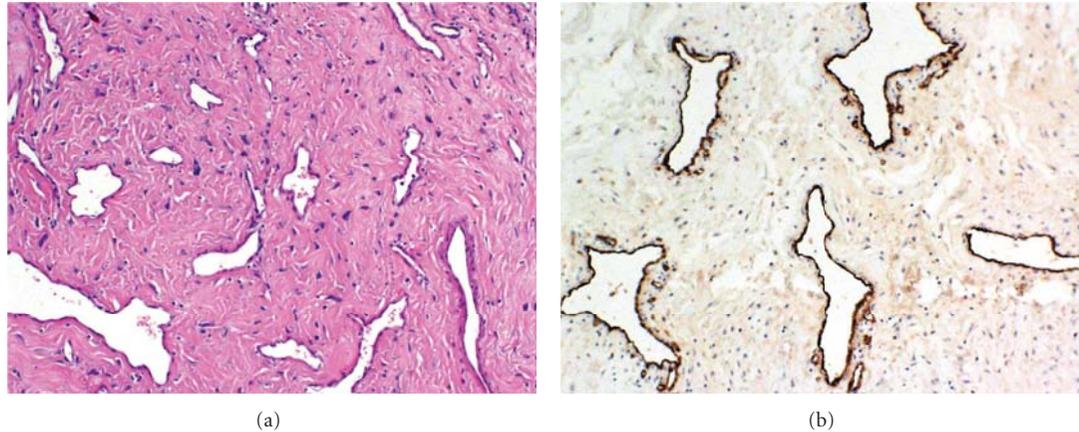


FIGURE 1: Microscopic appearance of JA (hematoxylin-eosin staining (a) and immunohistochemistry for factor VIII (b)). Vessel caliber is extremely variable, the muscular layer of vessels is frequently absent, and stromal cells have usually a spindle-shaped appearance.

the presence of androgen and/or estrogen receptors and their role in the tumor development or regression, a hormonal pathogenesis of this lesion is still a matter of debate [14–19].

Many studies have demonstrated numerous chromosomal alterations in patients affected by JA. Gains at chromosomes 4, 6, 8, and X and losses on chromosomes 17, 22, and Y are the most frequent chromosomal abnormalities detected [11, 20–23]. Moreover, Schick [21] described the gene *AURKA* (20q13.2), a centrosome-associated serine/threonine kinase, with a possible role in chromosomal and genetic instability in JA. These data provide important information regarding the possible location of tumor suppressor genes and oncogenes potentially involved in the pathogenesis of JA.

The observation of an increased prevalence of JA in patients with familial adenomatous polyposis (FAP) suggested a possible association between these two pathologies [24]. Although evidence of adenomatous polyposis coli (APC) gene mutations was not found [25], activating β -catenin gene alterations are frequently detected in JA [26]. The APC proteins regulate the level of β -catenin, which play a role in cell-cell adhesion and in the Wnt signaling pathway as a transcriptional activator. Nuclear accumulation of mutated β -catenin suggested that APC/ β -catenin pathway might be involved in JA pathogenesis. Moreover, β -catenin can act as coactivator of androgen receptors and consequently increase tumor androgen sensitivity, which might explain why JA develops in adolescent males [21].

Schick et al. [27] and Nagai et al. [28] observed losses of the tumor suppressor gene p53 in 5 of 7 cases and increased expression of p53 mRNA in 32% of patients affected by JA, respectively. Nagai et al. also described increased expression of the oncogene *c-fos* in 14% of cases. However, further studies are necessary to better understand if the tumor suppressor p53 and oncogenes of the *fos* family play a role in JA growth.

Renkonen and colleagues [29] investigated the expression of growth factor receptor C-KIT, protooncogene C-MYC, and polycomb protein and oncogene BMI-1 in JA. They

observed C-MYC and BMI-1 expression only in stromal cells, whereas C-KIT immunorexpression was shown in both stromal and endothelial cells suggesting that both the stromal and the vascular component may be involved in the neoplastic growth of JA.

The oncogenes Ki-ras, Ha-ras, and Her-2/neu have been investigated with no detection of mutations [27, 30].

3. Site of Origin and Patterns of Spread

JA is considered to arise in the area of the sphenopalatine foramen; based on the results on CT or MR imaging, some authors consider that the lesion originates in the pterygopalatine fossa at the level of vidian canal aperture [31]. The growth of the lesion has the peculiar tendency to follow a submucosal plane, growing in the adjacent anatomical sites that offer less resistance and invade the cancellous bone of the basisphenoid. Because of the constant site of origin and the knowledge of tumor behavior in relation to surrounding tissues, spreading patterns of JA are highly predictable [32, 33]. From the pterygopalatine fossa, the tumor grows medially into the nasopharynx, nasal fossa, and eventually towards the contralateral side. Laterally it can extend into the sphenopalatine and infratemporal fossae, via an enlarged pterygo-maxillary fissure with typical anterior displacement of the posterior maxillary wall, until it comes in contact with masticatory muscles and soft tissues of the cheek (Figure 2). Posterior growth may find several points of minor resistance through which JA may reach critical anatomic structures such as the internal carotid artery (ICA) through the vidian canal, cavernous sinus through the foramen rotundum medially to the maxillary nerve, and the orbital apex through the inferior orbital fissure (Figure 3). Bone involvement occurs via two main mechanisms: (1) resorption by direct pressure of preexisting bony structures with osteoclastic activation or (2) direct spread along perforating arteries into the cancellous root of the pterygoid process. Subsequent extension posteriorly towards the upper-middle of the clivus and laterally within



FIGURE 2: Axial contrast enhanced MRI: extensive JA with a typical pattern of spread into the cancellous bone of the basisphenoid along the vidian canal (white dotted line); on the contralateral side, black arrows indicate the right vidian nerve. Moreover, the lesion spreads deeply into the pterygomaxillary fossa toward the masticatory muscles, with anterior displacement of the posterior maxillary wall (white arrowheads). Asterisks indicate the foramen ovale bilaterally. TM: temporalis muscle; MM: masseter muscle.

the greater wing of the sphenoid, usually with late erosion of the inner table of the middle cranial fossa, may be detected in advanced cases [34]. Intracranial extension along a canal or resulting from spreading through bone destruction cannot be considered a rare event, especially in large JA, while infiltration of the dura is very rare [35].

4. Clinical and Radiologic Findings

Typical symptoms for JA are progressive unilateral nasal obstruction (80–90%) with rhinorrhea and recurrent unilateral epistaxis (45–60%), and thus these complaints in a male adolescent should immediately generate suspicion. Headache (25%) and facial pain may arise secondarily to the blockage of paranasal sinuses, or impairment of Eustachian tube function with unilateral secretory otitis media, respectively. Tumor extension into the sinonasal cavity can cause chronic rhinosinusitis. Proptosis and alteration of the vision clearly indicate an involvement of the orbit. Swelling of the cheek, neurologic deficits, alteration in olfaction, rhinolalia clausa, and otalgia are also possible [1].

Given the presenting symptoms, the patient should be examined by nasal endoscopy which usually shows a large, lobulated mass behind the middle turbinate filling the choana with a smooth surface and clear signs of hypervascularization (Figure 4).

Since epidemiologic and endoscopic findings are typical, biopsy is absolutely contraindicated because of a considerable and undue risk of massive hemorrhage [1].

Imaging techniques after contrast enhancement (MSCT and/or MR) are crucial to confirm the clinical suspicion pattern of vascularization and to assess the extension of the lesion. The diagnosis on imaging is based on three factors: the site of origin, hypervascularization after contrast enhancement, and patterns of growth [31, 32]. The evidence

that up to 96% of JA caused enlargement or erosion of the anterior part of the vidian canal supports the hypothesis of its typical location in the pterygopalatine fossa at the exit of this canal [32]. After administration of contrast agent, a strong and homogeneous enhancement on MSCT or MR is visible, with several signal voids within the lesion in both MR T1 and T2 sequences, indicating major intralesional vessels [31]. Moreover, enlargement of the internal maxillary artery can be detected by MSCT or MR, as well as signs of bone remodeling whereby thinning and anterior displacement of the posterior maxillary wall, with bone erosion typically at the level of the pterygoid root. Without doubt, MR better depicts cancellous bone invasion and, in lesions invading the middle cranial fossa, the relationship of the lesion with cavernous sinus and dura. Differential diagnosis includes other hypervascularized lesions such as hemangiopericytoma, lobular capillary hemangioma, and paraganglioma which have a different gender/age distribution and pattern of growth.

Preoperative identification of blood supply is a crucial finding to select the most appropriate surgical strategy. Although angio-MR may help in the vascular assessment, the complete map of all feeders requires digital subtraction angiography. Typically the JA receives vascular supply via the external carotid system and particularly from internal maxillary, ascending pharyngeal, and vidian arteries [1]. Vascular components from branches of ICA, such as the inferomedial trunk or inferior hypophyseal artery, may be frequently detected in large lesions involving the skull base and in contact with ICA. Because of the frequent detection of bilateral vascular supply, around 36% by Wu et al. [36] in a recent literature review, both carotid systems require angiographic evaluation.

Preoperative embolization is recommended by most authors [37–40] as a standard procedure to reduce blood loss during surgical resection. Some reports [33, 41] have stated that this procedure did not affect perioperative bleeding, although some years later Glad et al. [3] observed that embolization provides a 60–70% reduction in intraoperative bleeding, and the need for blood transfusion is required. Although the modification within the lesion induced by the embolization has been indicated as a contributory cause of incomplete excision [42], refinements in the technique and the introduction of new materials have minimized the risk of leaving residual disease. During the last decade, the availability of small particles and microcatheters has made it possible to reach collateral and terminal branches of external carotid artery to avoid the risk of neurologic sequelae following the inadvertent embolization of small vessels supplied by the ICA. Polyvinyl-alcohol particles are the most frequently used material for this procedure, which must be planned 24–48 hours before surgery to avoid the risk of revascularization [1]. As suggested by Hackman et al. [43], when vessels from both external carotid systems vascularize the lesion, bilateral embolization of internal maxillary artery is recommended. To control bleeding arising from vessels supplied by the ICA in lesions with extensive skull base involvement, Tranbahuy et al. [44] introduced a technique of direct embolization through a transnasal or lateral

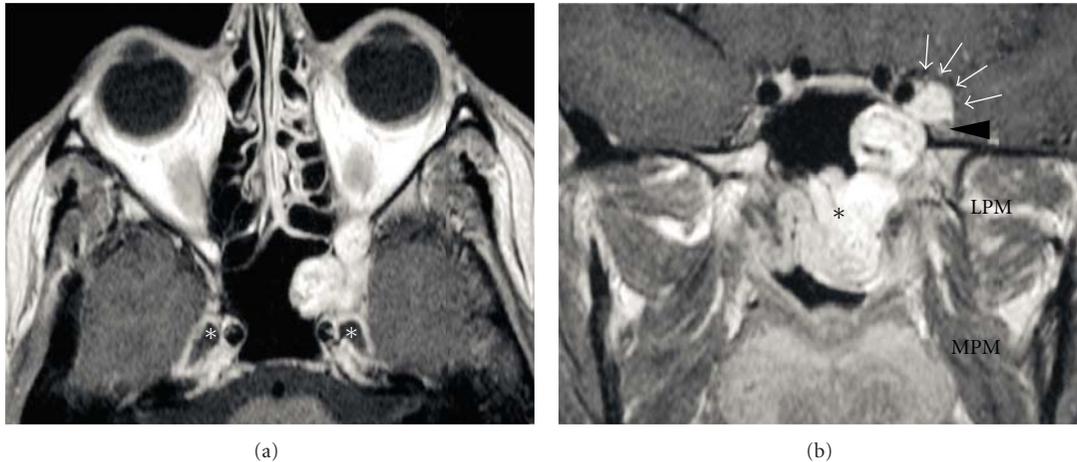


FIGURE 3: Axial (a) and coronal (b) contrast-enhanced MRI. JA with its epicenter into the root of the left pterygoid process. The nasopharyngeal component with submucosal spread is clearly evident (black asterisk). The lesion reaches the intracranial extradural compartment through the inferior and superior orbital fissures (white arrows), inferolaterally displacing the maxillary nerve (black arrowhead). The white asterisk indicates Meckel's cave. LPM: lateral pterygoid muscle; MPM: medial pterygoid muscle.

transcutaneous access with a mixture of cyanoacrylate, Lipiodol, and tungsten powder. In view of the possible occurrence of severe neurologic complications, this technique has not gained much popularity [45]. However, some recent reports on limited numbers of patients treated with a new embolic material, Onyx, with properties that seem to prevent its migration, have revived interest in this procedure [46, 47]. In the rare instance of huge lesions with ICA encasement, balloon occlusion test and sacrifice of this vessel may be considered [45].

5. Staging Systems

Different staging systems based on tumor extension have been proposed to stratify patients with the intent of easing comparison between different series. Over the years, several authors have modified and adapted staging systems based on advances in diagnostic and treatment techniques. Since 1981, when the first staging system was introduced by Sessions et al. [48], many other systems have been used. [2, 49–51] Only those proposed by Andrews et al. [52] and Radkowski et al. [53] have been quite extensively adopted. More recently, the staging systems proposed by Önerci et al. [54], Carrillo et al. [55], and Snyderman et al. [56] attempted to give indications concerning treatment planning by identifying lesions amenable to endoscopic surgery and those resectable by an external or combined approach. Additionally, Snyderman et al. [56] introduced a new parameter useful in preoperative evaluation represented by residual vascularity after embolization. Table 1 summarizes the most common classifications used in clinical practice.

6. Surgical Treatment

Although several nonsurgical methods have been proposed, surgery is unanimously considered the treatment of choice

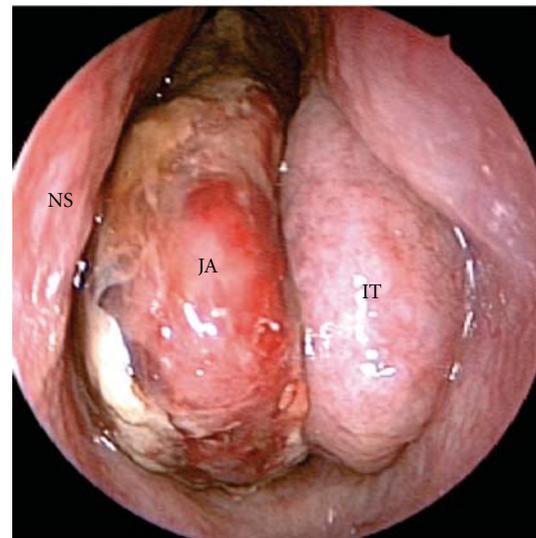


FIGURE 4: Endoscopic appearance of JA showing a lobulated hypervascularized mass with a smooth surface partially covered by fibrin growing into the left nasal fossa. NS: nasal septum; IT: inferior turbinate; JA: juvenile angiofibroma.

for JA. In the last two decades, the surgical approach to the lesion has considerably evolved mainly in relation to the indication of endoscopic techniques. Transpalatal, transpharyngeal, transfacial through lateral rhinotomy, mid-facial degloving, and Le Fort I osteotomy, other than infratemporal and subtemporal lateral approaches [39, 57, 58] were once the traditional surgical methods commonly performed to remove JA. Advances in radiological imaging and improvements of embolization techniques have significantly contributed to better preoperative management and treatment planning. Moreover, increasing experience in endoscopic surgery together with better understanding

TABLE 1

Andrews et al. [52]	
(I)	Limited to the nasopharynx and nasal cavity. Bone destruction negligible or limited to the sphenopalatine foramen
(II)	Invading the pterygopalatine fossa or the maxillary, ethmoid, or sphenoid sinus with bone destruction
(III)	(a) Invading the infratemporal fossa or orbital region without intracranial involvement (b) Invading the infratemporal fossa or orbit with intracranial extradural (parasellar) involvement
(IV)	(a) Intracranial intradural without infiltration of the cavernous sinus, pituitary fossa or optic chiasm (b) Intracranial intradural with infiltration of the cavernous sinus, pituitary fossa or optic chiasm
Radkowski et al. [53]	
(I)	(A) Limited to posterior nares and/or nasopharyngeal vault (B) Involving the posterior nares and/or nasopharyngeal vault with involvement of at least one paranasal sinus
(II)	(A) Minimal lateral extension into the pterygopalatine fossa (B) Full occupation of pterygopalatine fossa with or without superior erosion orbital bones (C) Extension into the infratemporal fossa or extension posterior to the pterygoid plates
(III)	(A) Erosion of skull base (middle cranial fossa/base of pterygoids)—minimal intracranial extension (B) Extensive intracranial extension with or without extension into the cavernous sinus
Önerci et al. [54]	
(I)	Nose, nasopharyngeal vault, ethmoidal-sphenoidal sinuses, or minimal extension to PMF
(II)	Maxillary sinus, full occupation of PMF, extension to the anterior cranial fossa, and limited extension to the infratemporal fossa (ITF)
(III)	Deep extension into the cancellous bone at the base of the pterygoid or the body and the greater wing of sphenoid, significant lateral extension to the ITF or to the pterygoid plates posteriorly or orbital region, cavernous sinus obliteration
(IV)	Intracranial extension between the pituitary gland and internal carotid artery, tumor localization lateral to ICA, middle fossa extension, and extensive intracranial extension
Snyderman et al. [56]	
(I)	No significant extension beyond the site of origin and remaining medial to the midpoint of the pterygopalatine space
(II)	Extension to the paranasal sinuses and lateral to the midpoint of the pterygopalatine space
(III)	Locally advanced with skull base erosion or extension to additional extracranial spaces, including orbit and infratemporal fossa, no residual vascularity following embolisation
(IV)	Skull base erosion, orbit, infratemporal fossa Residual vascularity
(V)	Intracranial extension, residual vascularity M: medial extension L: lateral extension

of complex sinonasal anatomy, the possibility to safely reach adjacent sites through the nose such as the orbit, infratemporal fossa, masticatory space, parasellar region, the availability of navigation systems, and the well-known morbidity associated with external procedures have made an endoscopic approach a viable alternative. Due to the fact that one of the most challenging aspects in JA surgery is control of intraoperative bleeding, the cooperation of an anesthesiologist with endoscopic skull base experience, the availability of a cell salvage machine and any material (absorbable gelatin powder, sponge oxidized regenerated cellulose, microfibrillar collagen, fibrin, or synthetic sealants) [59] that helps the surgeon to control bleeding are mandatory.

In the 1990s, several authors reported their first experience of transnasal endoscopic resections for early stage JA, demonstrating the feasibility of this procedure and recurrence rates similar to that observed with external approaches, in addition to lower risk and morbidity [37, 57, 60–66]. Nicolai et al. [67] in 2003 reported that lesions extending

to the nasopharynx, nasal cavities, sphenoid sinus, ethmoid sinus, maxillary sinus, and/or pterygopalatine fossa could be managed successfully through endoscopic surgery [67]. There is no doubt about the role of the surgeon's experience and "learning curve" in JA management with consequent widening of indications for an endoscopic approach, from early stage to lesions staged IIC and IIIA, according to the classifications of Radkowski and Andrews, respectively, [67–75]. More recently, Mohammadi Ardehali et al. [76] asserted that endoscopic resection of JA is strongly recommended as a first surgical step for tumors with stages (I) to (III-A) of Radkowski's staging system because of its significant lower intraoperative blood loss, hospitalization, and recurrence rate in comparison to traditional approaches. Furthermore, several series suggested that this technique can be performed even in JAs that extend to the infratemporal fossa, orbit, and/or parasellar region, compatible with the capabilities and experience of the surgeon [39, 44, 76, 77]. A crucial issue is represented by those lesions with large infiltration of skull

base, extensive vascular supply from ICA, or encasement of the artery itself: an anterior or lateral combined external approach according to the relationship of the tumor with ICA, and the surgeon's preference should be planned. Moreover, endoscopic surgery is contraindicated in residual tumors involving critical areas (ICA, optic nerve, cavernous sinus, dura), whereas adhesions due to scar tissue increase the risk of severe uncontrolled complications during dissection of the lesion [77].

The first surgical step when the surgeon approaches a JA endoscopically is to expose the tumor as extensively as possible through a middle turbinectomy, ethmoidectomy, wide antrostomy and sphenoidotomy, and resection of the posterior third of the nasal septum, which enhances the exposure of the nasopharyngeal portion of the lesion. The posterior wall of the maxillary sinus has to be resected as far lateral as dictated by the lateral extension of the lesion into the pterygopalatine and/or infratemporal fossae. For JA largely involving the infratemporal fossa, the surgeon can improve lateral exposure through a so-called Sturmann-Canfield maxillectomy, which provides resection of the anteromedial corner of the maxillary sinus [77]. An endoscopically assisted antral window approach through the anterior wall of the maxillary sinus, as proposed by Pasquini et al. [72], may be considered a possible alternative. Another important principle in the resection of large-volume lesions is the fragmentation technique ("piece-meal" resection) that helps to completely assess the extension without an increased risk of recurrence [69]. During dissection, to maintain a proper cleavage plain between the tumor and adjacent tissues, a four-handed technique is highly recommended [77]. The procedure is completed by accurate subperiosteal dissection of the tumor attachment and subsequent extensive drilling of the basisphenoid and other bone area where the JA is adhered to remove residual disease, which may not be immediately evident, and prevent its regrowth [78].

Because of its high degree of vascularization, bleeding during surgery is a crucial topic. Some studies compared the blood loss between endoscopic and external approaches, showing a lower loss in endoscopic surgery [78, 79]. However, the reliability of these data requires confirmation since JAs treated by an open approach usually have a higher stage than those resected endoscopically. Another question widely discussed in literature is the reduction of intraoperative bleeding, thanks to preoperative embolization. Some authors have correlated the amount of blood loss with the quality of embolization and with tumor extension [67, 71]. Glad et al. [3] showed a statistically significant decrease in bleeding between the nonembolized (650 mL) and the embolized group (1200 mL).

To better control bleeding during the procedure, several authors have proposed the use of diode laser, KTP laser, or ultrasonic scalpel [70, 77, 80–82].

7. Postoperative Surveillance

Based on the experience by Kania et al. [83], Lund et al. [1], and Nicolai et al. [77] recommended postoperative MR imaging after removal of the nasal packing and until 72 hours

for early identification of any suspicious residual disease. The reason for this is the presence of minor inflammatory changes, typically observed 3–4 months after treatment, which frequently challenge differentiation between residual JA and active scar tissue. Although this surveillance policy has to be validated by longer follow-up periods, Nicolai et al. [77] observed that patients with no signs of persistence do not develop any lesion even at subsequent MR examination. Endoscopic examination has limited value in the identification of residual/recurrence disease because of the submucosal growing pattern of JA, which is detected with more precision by enhanced MR or MSCT. Whatever technique is selected, the examination should be performed every 6–8 months for at least 3 years after surgery. Moreover, depending on suspicious enhancement, incomplete resection and age of onset, angio-MR imaging may be scheduled [1]. Closer radiologic survey may be required to better evaluate the growth and plan treatment for persistent JA.

8. Outcome

Although comparison between external approaches and endoscopic techniques is biased by the different staging systems and follow-up strategy adopted, recently Wang et al. [84] observed no significant difference in the rate of recurrence between 11 patients treated endoscopically and 13 who underwent transpalatal excision, all staged (I) and (II) according to Chandler classification. Series with a consistent number of patients treated with external approaches have shown a reduction over time in terms of recurrence rate ranging from 36–40% [34, 85] reported in the 1990s, to the excellent results of Danesi et al. [35] in 2008 with 13.5% and 18.2% of residual disease in lesions with extracranial and intracranial extension, respectively. At present, endoscopic resection in small/intermediate JA is widely recommended because of the low risk of recurrence demonstrated in several studies during the last decade [34, 71, 73, 85–89].

Currently, the results of the two major series (Table 2) of JA resected through an endoscopic approach corroborate the principle that this modality of treatment can encompass all lesions from stage (I) to (IIIA) or (IIIB) according to Radkowsky and Andrews staging systems, respectively [76, 77]. An overall recurrence/residual rate of 8.6% [77] and 19.1% [76], respectively, was reported. As previously highlighted by Howard et al. [78], Nicolai et al. [77] in their study on 46 patients treated with an exclusive endoscopic procedure observed that all the residual lesions detected in 4 patients by MR within 24 months after treatment were located at the level of the basisphenoid bone, thus emphasizing the need to extend drilling well beyond the apparent margin of tumor infiltration.

In a recent study on 95 JA, Sun et al. [90] identified three predictive factors that may increase the recurrence rate: patient age at diagnosis (under 18 years), tumor size (>4 cm), and stage according to Radkowsky classification.

The management of residual disease, especially when located intracranially or with a relationship with critical structures such the ICA, cavernous sinus, and the optic nerve, remains a source of discussion. Certainly, close survey

TABLE 2

	Mohammadi Ardehali et al. [76]	Nicolai et al. [77]
Number of patients	47	46
Mean age (years)	17.1 (7–37)	17 (10–35)
Previous treatment	16 (IA) 5 (IB) 10	5 (IA) 3 (IB) 1
Stage (Radkowski classification)	(IIA) 3 (IIB) 3 (IIC) 22 (IIIA) 3 (IIIB) 1	(IIA) 5 (IIB) 10 (IIC) 19 (IIIA) 7 (IIIB) 1
Preoperative embolization	5	40
Mean blood loss (mL)	1336.2 (300–8500)	580 (250–1300)
Mean hospitalization time (days)	3.1	5
Mean followup (months)	33.1	73
Persistence rate (%)	19.1	8.6

with enhanced MR or MSCT is strongly indicated to evaluate the growth rate, and consequently, the need for surgical revision. Önerci et al. [54] prefer an observational strategy to infratemporal craniofacial resection for intracranial residual disease. Moreover, some reports [91–93] described the possibility, in at least a minority of cases, of spontaneous involution or reduction in size because of hormonally dependent JA pathogenesis.

9. Nonsurgical Treatments

The use of radiation therapy (RT) in JA is still debated for the reported risk of sarcomatoid transformation [94] or radio-induced neoplasms in the following decades. Some authors recommended RT as adjuvant treatment in unresectable tumors, in failure of complete tumor removal, or for extensive intracranial extension [53, 95, 96]. Nicolai et al. [77] suggested that RT may be indicated for residual lesions in critical areas that have been demonstrated to increase in size. Lee et al. [97] reported on 27 patients affected by advanced JA treated primarily with RT (30–55 Gy): the recurrence rate was 15%, and long-term complications observed in 4 patients included growth retardation, panhypopituitarism, temporal lobe necrosis, cataracts, and radiation keratopathy. More recently, McAfee et al. [98] treated 22 patients affected by high staged JA with RT (30–36 Gy): in 10 cases as primary treatment, and in 12 for recurrence. Local control was obtained in 90% of patients, with 2 cases of local persistence. Late complications, which occurred in 7 (32%) cases, included cataracts, transient central nervous system syndrome, and cutaneous basal cell carcinoma. The use of intensity-modulated RT for the treatment of 3 patients with

extensive or persistent JA showed no recurrences and a late toxicity with epistaxis and chronic rhinitis in 2 cases [99]. Although a small number of cases of JA have been treated by Gamma-Knife radiosurgery [100, 101], the insignificant morbidity documented may be reasonably correlated to the optimized irradiation of the target volume by sparing uninvolved structures.

The use of chemotherapy in treatment of JA is supported by only a few reports [102–104]. In the 1980s, Goepfert et al. [102] described successful results with two different chemotherapy schedules, including doxorubicin and dacarbazine, or vincristine, dactinomycin, and cyclophosphamide.

Several studies on hormone pathogenesis have extensively demonstrated the hormonal dependence of this tumor, suggesting a promising role of estrogen or androgen receptor blockers in its treatment [9, 15–19]. Gates et al. administered flutamide, a potent nonsteroidal androgen receptor blocker, in 5 patients affected by JA and detected an average tumor regression of 44% in four cases [105]. However, in a report on 7 patients, Labra et al. observed no significant differences between tumor dimensions before or after flutamide administration, questioning its use in JA [106]. Very recently, flutamide-induced regression in a series of 20 advanced staged JA was demonstrated only in postpubertal patients [107].

10. Conclusions

Juvenile angiofibroma is a pathology that should be included in the differential diagnosis of unilateral nasal obstruction, associated or not with epistaxis, especially in young adolescent males. The finding at nasal endoscopy, which is the first step in the diagnostic algorithm, of a hypervascularized lesion occupying the posterior half of the nasal fossa should immediately raise suspicion. Morphologic imaging confirms the diagnosis. Endoscopic surgery after embolization has been demonstrated to be a viable alternative to external techniques for the management of small-intermediate size JA. Resorting to external anterior or lateral approaches is still recommended in JAs encasing the ICA or with a massive feeder contribution from it, or in the rare instances of intradural spread.

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Research Article

Surgical and Pathological Characteristics of Papillary Thyroid Cancer in Children and Adolescents

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Background. Thyroid carcinoma is a relatively rare pediatric pathology, comprising around 3% of all childhood tumors. We investigated parameters of tumor aggressiveness, multicentricity, and locoregional metastatic spread patterns in patients up to 18 years of age and made comparison with the older group. All patients were operated upon with total thyroidectomy, with or without lymph-node neck dissection. *Results.* Patients with papillary carcinoma present with more advanced stage, larger primary tumor, and more commonly present with palpable thyroid and/or neck node. Overall, papillary cancer demonstrated pathological aggressiveness as defined by our criteria in 60%, multicentricity in 40%, and locoregional metastatic foci in 77% of cases. Multicentric tumor foci in both thyroid lobes and tumor aggressiveness were identified as a risk factor for metastatic development. *Conclusion.* By observing clinicopathological parameters, we demonstrated that papillary thyroid cancer behaves more aggressively in the younger group. We recommend total thyroidectomy with careful intraoperative exploration of thyroid bed and lateral neck in search for possible metastatic spread. In case of positive findings, it is obligatory to perform a standard neck dissection, keeping in mind that neck lymphonodes are primary site of locoregional recurrence. With meticulous attention to technical aspects of operation, perioperative morbidity should be minimal.

1. Introduction

It is generally accepted that papillary thyroid carcinoma in children and adolescent population has a different clinical presentation and course than in adults [1]. Initial diagnostic presentation in pediatric patients tends to be in more advanced stage, namely, the larger primary tumor, the higher incidence of primary tumor multicentricity and higher incidence of locoregional metastatic spread. More specifically, palpable neck lymphonodes are most commonly presenting sites in children (up to 90%). In addition, significant primary tumor aggressiveness has been demonstrated in young age [1]. It is already demonstrated that primary thyroid tumor aggressiveness (as measured by nuclear atypia, tumor necrosis, and lymphovascular invasion) correlates with metastatic disease, independently from tumor size [2]. Consequently, histological grade should be set as prognostically important component and included in any classification system of differentiated thyroid cancer [3].

Despite these aggressive characteristics, specific prognosis in pediatric age is better than in adults. As a consequence, several recommendations have been made that propose less aggressive therapeutic approach (less than total thyroidectomy and no neck dissection). On the contrary, some researchers advise more aggressive therapy, including total thyroidectomy, neck lymphonode dissection, and post-operative radioiodine ablation [4–6]. However, recurrent disease and locoregional spread still present major clinical concern regarding optimal extent of the initial surgical therapy, in pediatric population specifically. Several major studies attempted to evaluate influence of patient and tumor characteristics, as well as treatment factors, but without clear recommendations regarding possible risk factors for developing recurrent disease [7–11].

In this paper, we show our retrospective clinical material in 16 patients up to 18 years of age, who underwent surgical therapy at our institution for diagnosis of thyroid papillary carcinoma. The aim of the presentation is to give insight into

clinical and selected pathological characteristics (tumor size and aggressiveness, multicentricity, and locoregional spread) of the disease in pediatric age, assess their role in cancer risk, and identify possible critical parameters for developing metastatic disease.

2. Material and Methods

This study is a retrospective analysis of data from 16 pediatric patients with papillary thyroid cancer, ages from 10–18. All patients were operated upon at the Department of ENT—Head and Neck Surgery, University Hospital “Sisters of Charity”, Zagreb, Croatia during the 28-year period (1980–2008). Patients’ data are summarized in Table 1.

All patients underwent total thyroidectomy with or without neck dissection (paratracheal or some type of lateral neck dissection). We used Robbins et al.’s neck dissection classification data from Consensus Statement on the Classification and Terminology of Neck Dissection [12]. Medical data were collected from patient documentation (intraoperative reports, recurrences, FNAB results, and additional thyroid diagnosis) and final pathology reports, as well as from the Hospital Registry for Thyroid Diseases were reviewed. Postoperatively, we followed *Diagnostic and Therapeutic Guidelines for Differentiated Thyroid Cancer*, issued by Croatian Thyroid Society; postoperative diagnostic scintigraphy was performed with 1–3 mCi ¹³¹I. High-risk patients were put to 100–200 mCi ¹³¹I ablation without L-T4. Posttherapeutic whole body scintigraphy was performed 5–8 days after ¹³¹I. Six to twelve months later, the patients were followed up with the exploration of neck ultrasound, FT4, TSH, Tg, and TgA (without L-T4) measurements and afterwards yearly.

All patients were assigned to groups for variables of age (≤ 18 and comparison group >18 years), gender, size (diameter) and pathological parameters of primary tumor aggressiveness, multicentricity, type of neck dissection performed, and presence of locoregional metastatic foci in neck. Grading of pathological aggressiveness, multicentricity, and locoregional spread is demonstrated in Table 2. We applied statistical analysis of differences with χ^2 test and model of multivariate logistic regression for risk factors for metastatic locoregional spread. Statistical significance level was set at $P \leq 0.05$.

3. Results

From the total of 699 cases with papillary thyroid cancers of all ages, 16 patients (2.3%) with age up to 18 years fulfilled inclusion criteria, 13 females, and 3 males. The average age at the moment of diagnosis was 16, with a range of 10 to 18 years. Mean tumor size was 2.2 cm. Majority of patients presented with palpable thyroid mass, 12/16 or 75%, and palpable neck node in 8/16, or 50%. There were only 4 microcarcinoma cases (25%), which is in sharp contrast to older population (45% microcarcinoma). Distribution of parameters of pathological aggressiveness, multicentricity, neck dissection, and metastatic spread and

comparison by age group (≤ 18 and >18 years) are shown in Table 3. Results showed that 60% of pediatric tumors were aggressive, according to our chosen criteria. Forty percent of tumors were multicentric, with foci in both lobes twice as often as in the single lobe (13% versus 27%). Total thyroidectomy was the operation of choice in all cases. Neck dissection was performed in 76.5% patients (35% paratracheal, 41% lateral). There were 77% positive metastatic tumors: paratracheal metastases in 23% and lateral neck metastases in 54%. Bilateral metastatic neck involvement was demonstrated in 50% of cases.

Overall, no age differences were found for pathological aggressiveness ($P = 0.19$) and multicentricity ($P = 0.89$) even though younger group had significantly wider aggressiveness (34% versus 16%). Younger patients had significantly more neck dissections performed ($P = 0.005$) and more metastatic spread as well ($P = 0.000$). There were no cases of postoperative recurrent nerve paralysis on postoperative indirect laryngoscopy. We had two cases of temporary early postoperative hypocalcaemia, which were successfully controlled by calcium carbonate and Rocaltrol p. o. There was one case of permanent hypocalcaemia (recurrent case).

There were two cases of disease recurrence, both locoregional: one patient with single neck recurrence (lateral neck metastatic foci after initial TT and paratracheal ND) and one patient with two recurrences (both in lateral neck regions after initial TT and paratracheal ND). Both recurrences were detected on follow up by neck palpation and ultrasonography with cytology, and pathologic Tg; both cases were amenable to surgical therapy and were put to further radioiodine treatment. No patients with N0 neck developed recurrence. In all patients, postoperative and postablative average follow up was at least 5 years, and they were alive and free of disease. Multivariate analysis revealed the presence of multicentric foci in *contralateral lobe* and higher tumor aggressiveness (group III) to be an independent risk factor for regional metastatic spread (OR 3.119 and 2.591, resp.). Male gender was identified as an additional risk factor (OR 1.919), while older age was associated with lower risk for metastatic development (OR 0.537). Lymphomatous goiter bears lower risk (OR 0.633) (Table 4).

4. Discussion

Different potential prognostic factors of papillary thyroid cancer have been revealed so far, most importantly patient age, tumor grade, and extension (extrathyroid invasion, distant metastasis, and less frequently regional). Papillary cancer characteristics and behavior in children and adolescent population is subject of several controversies, mainly about the most appropriate surgical therapy, the use of postoperative iodine ablation and TSH suppression, as well as follow-up modalities [1, 13]. It is well demonstrated that clinical course of this disease in children and adolescent population is significantly different: the worse initial clinical presentation in children and, paradoxically, the better disease prognosis than in adult population [14, 15]. Children tend

TABLE 1: Epidemiologic, clinical, and pathological data of 16 children with papillary thyroid carcinoma, operated upon with total thyroidectomy w/o neck dissection.

Case no.	Gender	Age (years)	Tm size (cm)	Thyroid gland multicentricity	Aggressiveness ¹	Neck dissection ²	Metastatic spread ³	Recurrence no.	Additional dx
(1)	F	10	2,7	Contralateral lobe	1	2	2	0	—
(2)	F	13	0,9	—	0	1	0	0	—
(3)	F	13	5	Contralateral lobe	2	2	2	1	—
(4)	F	15	1,1	—	0	0	0	0	—
(5)	F	15	2,8	—	0	1	1	2	—
(6)	F	15	1,2	—	1	1	0	0	—
(7)	M	16	1,9	Contralateral lobe	1	2	2	0	—
(8)	F	16	2,3	—	2	2	2	0	—
(9)	F	17	0,4	—	0	1	0	0	Lymphomatous goiter
(10)	F	18	2,1	—	1	1	1	0	—
(11)	F	18	0,5	—	0	1	1	0	Lymphomatous goiter
(12)	F	18	1	Ipsilateral lobe	0	0	0	0	Lymphomatous goiter
(13)	M	18	5,5	Contralateral lobe	1	2	2	0	—
(14)	M	18	2	Contralateral lobe	2	2	2	0	—
(15)	F	18	2,6	Ipsilateral lobe	2	2	2	0	—
(16)	F	18	3	—	2	0	0	0	—

¹Aggressivity: (1) Sharply demarcated; encapsulated tumor; (2) No clear tumor border; tumor capsule invasion; (3) Thyroid capsule invasion, perivascular, perineural spread, penetration of adjacent soft tissues, fat tissue, muscle or cartilage invasion.

²Neck dissection (ND): (1) Not done; (2) Paratracheal ND; (3) Paratracheal and lateral ND.

³Metastatic spread: (1) No metastatic spread; (2) Paratracheal region involved; (3) Paratracheal and lateral regions involved.

TABLE 2: Study variables: gradation by severity of pathohistological features of tumor aggressiveness, intraglandular dissemination, and locoregional metastatic spread.

Gradation	Variables			
	Pathological aggressiveness of primary tumor	Intraglandular dissemination (multicentricity)	Neck dissection*	Locoregional metastatic spread
Grade I	Sharply demarcated; encapsulated	No multicentric foci	Not done	No metastatic spread
Grade II	No clear tumor border; tumor capsule invasion	Ipsilateral lobe spread	Paratracheal	Paratracheal
Grade III	Perivascular, perineural spread; penetration of adjacent soft tissues; fat tissue, muscle, cartilage invasion	Bilateral/Contralateral lobe spread	Paratracheal and Lateral	Paratracheal and Lateral

* Neck dissection classification from: Robbins et al. [12].

to present with larger primary tumors, greater incidence of neck lymphonode metastasis, and distant metastasis as well [16]. This presentation/prognosis discrepancy is not yet fully understood. Possible explanations are more common occurrence of well-differentiated forms of tumor and more effective response to postoperative TSH suppression with thyroid hormone [1].

In our series, we demonstrated aggressive characteristics of papillary cancer in 60% of cases. Most aggressive cases came in the form of a wider tumor aggressiveness, that is, thyroid capsule invasion, penetration of adjacent thyroid tissues, and/or perivascular/perineural spread. Additionally, mean tumor size in younger age group was significantly larger than in adult population. The role of tumor size

was commented recently in the review of Sherman, who emphasized that smaller size of thyroid gland in children can lead to earlier thyroid and extrathyroid spread of disease [17].

Papillary thyroid cancer multicentricity is a well-described feature of this tumor, with estimated frequency range from 22% to 49% [1]. There are major disagreements about the importance of papillary cancer multicentricity; its etiology and clinical significance are not yet fully understood [6, 18–20]. As a consequence, many authors propose total thyroidectomy as an adequate surgical approach, claiming that more extensive operation decreases the likelihood of recurrence [21]. There are other different reports as well. Our study revealed that 40% of papillary carcinomas developed multicentric foci, with most of them appearing

TABLE 3: Comparison of chosen pathological parameters by age groups (≤ 18 years, ≥ 18 years).

Characteristic	Age ≤ 18 y, $n = 16$ (2,3%)	Age ≥ 18 y, $n = 683$ (97,7%)	<i>P</i>
Pathologic aggressiveness	9/15 (60%)	302/651 (46,4%)	<i>P</i> = 0,19
Capsule invasion/no clear border	4 (26%)	198 (30,4%)	
Wider aggression	5 (34%)	104 (16%)	
Multicentricity	6/15 (40%)	222/645 (34,4%)	<i>P</i> = 0,89
Ipsilateral lobe	2 (13%)	81 (12,5%)	
Bilateral/contralateral lobe	4 (27%)	141 (21,9%)	
Neck dissection	13/17 (76,5%)	300/674 (44,5%)	<i>P</i> = 0,005
Paratracheal	6 (35,3%)	200 (29,7%)	
Paratracheal and lateral	7 (41,2%)	100 (14,8%)	
Metastatic spread	10/13 (77%)	180/671 (26,8%)	<i>P</i> = 0,0000
Paratracheal	3 (23%)	92 (13,7%)	
Paratracheal and lateral	7 (54%)	88 (13,1%)	

TABLE 4: Risk factors for regional metastatic spread, a logistic regression model.

	OR	95% CL		<i>P</i>
		Upper	Lower	
Gender				
Male	1,919	1,30	2,84	0,012
Female	0,591	0,35	0,77	0,012
Older Age	0,537	0,38	0,75	0,0003
Multicentricity				
Ipsilateral	1,062	0,63	1,78	0,8187
Bilateral/contralateral	3,119	2,12	4,59	0,0000
Expansive tm growth				
No expansion	0,540	0,38	0,77	0,0007
Capsule invasion/no clear border	1,022	0,71	1,47	0,9056
Wider aggression	2,591	1,69	3,97	0,0000
Additional diagnosis				
Lymphomatous goiter	0,633	0,40	1,00	0,0485

synchronously in both thyroid lobes. Thus, multicentricity, when it occurred, was bilateral in more than two-thirds of multicentric cases. Further, on multivariate analysis multicentricity was found to be the most important risk factor for development of metastatic spread (OR 3.119). Interpretations of these findings strongly signify the need for an implementation of more aggressive surgery of the primary tumor, incorporating complete removal of the contralateral thyroid lobe in the same act as thyroidectomy.

Positive neck lymphonodes are a frequent presenting sign in children/adolescent population. Locoregional metastatic spread is identified as one of the most important risk factors preceding distant dissemination. Neck metastases occur in 15%–60% and with meticulous search can be found in up to 90% of cases [22, 23]. However, even for distant spread, chances of long-term survival are significant, particularly in younger age group [24]. Half of all our cases had palpable neck node on presentation. On final pathology, there were 77% positive metastatic tumors: paratracheal metastases in 23%, and lateral neck metastases in 54%. Bilateral metastatic

neck involvement was demonstrated in 50% of cases. It has been demonstrated that metastatic disease, locoregional and distant, seems to be most important prognostic factor for the good response to therapy [25]. Data from present study clearly demonstrate the significance of detailed preoperative neck examination and careful intraoperative exploration, with special emphasis on lateral neck regions.

Presently, total or less commonly subtotal thyroidectomy is considered optimal surgical therapy for papillary thyroid cancer in all preoperatively diagnosed cases [18, 26]. Conducted studies showed that more extensive operation (total thyroidectomy) usually leads to significant reduction of recurrence [9, 13, 27]. A more conservative surgical approach (lobectomy) is advocated by some authors as well, emphasizing less risk of surgical and postoperative morbidity (temporary or permanent hypoparathyroidism and recurrent laryngeal nerve injury) [11, 28, 29].

Thyroid cancer recurrence is more common in extremes of age, most notably in patients less than 20 years of age, as well as older than 60 [4, 30]. Generally, studies performed

on all age populations revealed higher chances for recurrence in procedures including less than total thyroidectomy. This higher aggressiveness of thyroid cancer demonstrated in younger population does not necessarily bear higher risk for fatal outcome, which is more common in older population [14, 15]. Our both recurrence cases had a large primary tumor in the thyroid gland; one had aggressive characteristics (thyroid capsule invasion and perivascular, perilymphatic spread), and both had initially neck metastatic disease.

Regarding intraoperative and early postoperative complications rate, in our material, we have not found significant differences in perioperative complication rates in children versus older patients, with extent of surgery being the same as for adults. We had two cases of temporary and one case of permanent hypocalcaemia. In recurrent cases, reoperative surgery, which consisted of lateral neck dissection, was performed without any complications. However, in this cohort of patients, we advise that strong emphasis should be put on minimizing morbidity related issues, bearing in mind excellent long-term disease prognosis.

In conclusion, in this study, we investigated parameters of papillary thyroid cancer aggressiveness, multicentricity, and locoregional metastatic spread in children/adolescent population. Overall, papillary thyroid cancer demonstrated aggressiveness in 60%, intraglandular dissemination in 40%, and metastasized locoregionally in 77% of cases. By observing clinicopathological parameters and their distribution across selected groups, we demonstrated that papillary cancer behaves more aggressively in younger age group. Multicentric foci in both thyroid lobes and wider tumor aggressiveness were identified as a risk factor for metastatic development. We support the need for total thyroidectomy and meticulous intraoperative exploration of the thyroid bed and lateral neck, with surgical extirpation of all potential microscopic disease foci. For positive regional metastatic disease, standard paratracheal and/or modified radical neck dissection is obligatory part of surgery, in the same act as total thyroidectomy, keeping in mind that neck lymphonodes are primary sites of locoregional recurrence. With meticulous attention to technical aspects of surgery, perioperative morbidity of parathyroid glands and recurrent laryngeal nerve should be minimal.

Conflict of Interests

The author declares that he has no conflict of interests.

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Review Article

Chronic Rhinosinusitis in Children

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Rhinosinusitis is a very common disease worldwide and specifically in the US population. It is a common disease in children but may be underdiagnosed. Several reasons may account to the disease being missed in children. The symptoms in children are limited and can be very similar to the common cold or allergic symptoms. Cough and nasal discharge may be the only symptoms present in children. A high index of suspicion is necessary to make the diagnosis of rhinosinusitis in these children. The majority of those children are treated medically. Only a few number will require surgical intervention when medical treatment fails. Complications of rhinosinusitis, even though rare, can carry a high morbidity and mortality rate.

1. Introduction

Rhinosinusitis (RS) is a common disease in children that is sometimes overlooked. Children average 6–8 upper respiratory viral illness with 0.5–5% of these progressing to acute rhinosinusitis (ARS). An undefined number of these children will progress to have chronic rhinosinusitis (CRS) [1]. The disease has great impact on the health care system and the national economy as a whole [2].

The clinical symptoms of ARS in children include nasal stuffiness, colored nasal discharge, and cough with resultant sleep disturbance. Facial pain/headache can be present in older children. ARS is defined as symptoms lasting up to 4 weeks, subacute is when symptoms are between 4 weeks and 12 weeks, and CRS is when symptoms have been present for more than 12 weeks [3].

Rhinosinusitis is defined as a symptomatic inflammatory condition of mucosa of the nasal cavity and paranasal sinuses, the fluids within these sinuses, and/or the underlying bone [4]. The term “sinusitis” has been supplanted by “rhinosinusitis” due to evidence that the nasal mucosa is almost universally involved in the disease process [5].

2. Etiology and Pathogenesis

The etiology of CRS is a subject of much debate and ongoing research. The current hypothesis is that of a multifactorial

pathogenesis. The paranasal sinuses are a group of paired, aerated cavities that drain into the nasal cavity via the sinus ostia. Several ostia drain in the middle meatus leading to the “osteomeatal complex” (OMC) as the focus of pathology [6]. Though the true anatomic role of the paranasal sinuses is uncertain, their ability to clear normal mucous secretions depends on three major factors: ostial patency, ciliary function, and mucous consistency [4, 7]. Any variety of inciting factors may irritate the sinus mucosa leading to inflammation, edema, bacterial proliferation, outflow obstruction, and mucociliary dysfunction.

The association between CRS and allergic conditions, specifically rhinitis, has been well studied. Studies have shown that patients with persistent or seasonal allergic rhinitis had more significant radiographic findings of sinus disease [8, 9]. Further, CRS patients with concomitant allergic rhinitis have a significantly decreased rate of long-term success following surgical treatment [10].

Microbes have a controversial role in CRS. Though viral infections are known to precede episodes of viral rhinosinusitis [11], viral infections are not usually targeted as a part of CRS treatment. The use of antibacterial agents, however, has remained a first-line treatment for many practitioners despite the questionable role of bacteria. The paranasal sinuses, normally considered sterile, house a characteristic set of bacteria in CRS. A recent study showed that greater than half of CRS patients studied produced

polymicrobial flora. The most common pathogens were those found in ARS. *Staphylococcus aureus* and coagulase-negative staphylococci were noted in those cultures from children with chronic disease. Anaerobes have been shown to be present in higher percentage in children with CRS [12]. The literature is replete with studies showing favorable patient response to treatment with antibiotics targeting these species, suggesting that there is some role for bacteria in CRS etiology [13].

The role of inflammatory mediators in the pathogenesis of CRS in children is still vague. In adults, emphasis is made on inflammatory response to the presence of bacteria rather than the action of microbes themselves. The finding of a sinus mucosal infiltrate of eosinophils, plasma cells, and lymphocytes suggests a process of “bacterial allergy.” In reality, there is likely a spectrum of illness ranging from an infectious etiology to a purely noninfectious inflammation [14].

Systemic factors can predispose to the development of CRS. Cystic fibrosis patients develop chronic mucosal inflammation and nasal polyps causing mechanical obstruction of sinus ostia [15]. Primary ciliary dyskinesia, though uncommon, is an example of CRS caused by a defect in a specific element of mucociliary clearance [16]. When clinically suspected, testing for the presence of allergy or any of the other above conditions will assist in tailoring a treatment regimen.

3. Case Study

3.1. Chief Complaint. A 5-year-old girl presents to her primary care physician complaining of nasal stuffiness, colored nasal discharge, and cough for the past few weeks.

3.2. History. The patient has been stuffy and has been having a cough mainly at night that is keeping parents and child awake. This has been going on for some time over the past year. She does get treated with antibiotics; she seems to get better but then it starts again. Parents have been frustrated because of that. She was diagnosed with asthma and has been on inhalers and medications but with frequent exacerbations. She was tested for allergies, and she does not seem to have any, despite that she has been on nasal steroid sprays as well as oral antihistamines over the past several months. This current episode started a couple of weeks ago and has not resolved despite the oral antihistamines, nasal steroid sprays, and cold medicine.

Her past medical history is negative. The child snores when sick, but no history of sore throats or ear infections. There is also no prior history of surgery. Grandparents do smoke but not near her.

3.3. Physical Examination. The patient is a healthy-appearing girl, very cooperative with normal vital signs. Heart and lung sounds are normal. Examination of the head and neck reveals a nasal septum deviated to the right. Anterior rhinoscopy shows bilateral hypertrophy of the inferior turbinates with mucopurulent discharge. Ears are clear with mobile tympanic membranes. Oral cavity is clear

with no enlargement of the tonsils. No submucous cleft is noted.

4. Diagnosis

CRS in children is a clinical diagnosis. It is based on clinical presentation as well as duration of symptoms. In the first 7–10 days it is usually a viral one except if symptoms worsen and a complication develops. If symptoms persist and are not improving by 10 days, then acute rhinosinusitis needs to be entertained [17]. CRS is when symptoms persist beyond 12 weeks. Sometimes acute exacerbations of these symptoms can occur. Allergic rhinitis can present with a similar clinical picture and must be distinguished based on timing of symptoms, as well as presence or absence of purulence.

The physical examination of a patient suspected to have CRS involves direct visualization of the nasal cavity and associated structures. Anterior rhinoscopy with an otoscope is easy in children and should be a part of the initial evaluation. Attention is given to the nasal septum, all visible turbinates, and the presence of colored discharge. Nasal endoscopy in the older or more cooperative child may be very helpful.

Some authors have reported on the use of laboratory tests, including sedimentation rate, white blood cell counts, and C-reactive protein levels, to help diagnose acute sinusitis. These tests appear to add little to the predictive value of clinical findings in the diagnosis [18].

Imaging studies are not necessary when the probability of sinusitis is either high or low but may be useful when the diagnosis is in doubt, based upon a thorough history and physical examination. Plain sinus radiographs may demonstrate mucosal thickening, air-fluid levels, and sinus opacification. A CT scan is necessary when a complication is suspected, in children with polyps, or in those children who failed medical therapy and are considered for surgery (Figure 1) [1].

5. Treatment

The case presented meets the diagnostic criteria for CRS based on her complaints of nasal stuffiness, colored nasal discharge, and cough with acute exacerbations for greater than 12 weeks, as well as a finding of colored discharge on anterior rhinoscopy.

The goal of treatment in rhinosinusitis is to reduce the mucosal inflammation thus relieving the blockage of the ostia and impairment of mucociliary flow that is the hallmark of the disease.

Empiric treatment with a course of orally administered antibiotics has been a mainstay of treatment. For ARS a 10–14 days course of oral amoxicillin is first line of treatment. If the patient does not get better in 48–72 hours, then antibiotic should be changed to amoxicillin with clavulanic acid. Three to four weeks of amoxicillin with clavulanic acid is a first-line choice for CRS or those children with acute exacerbation of CRS because of adequate penetration of the sinus mucosa and efficacy against *S. aureus* and anaerobes [19]. Antibiotic choice is largely guided by patient tolerance.

However, in adult cases of treatment failure, culture and sensitivity from sinus secretions can guide antibiotic choice [20]. Since this cannot be performed in children in the office, performing those cultures in the operating room can be an option. Obtaining cultures is not the standard of care for initial therapy, however. There is a lack of evidence comparing randomized head-to-head efficacy of the various antibiotic classes or demonstrating a benefit of multiantibiotic regimens.

Initial medical management also includes a regimen of topically applied corticosteroids. Fluticasone, beclomethasone, budesonide, and mometasone are popular choices. Topical corticosteroids have been shown to downregulate the inflammatory cytokine profile of sinus mucosa and improve subjective patient symptoms [21–23]. Though uncommon, patients should be aware of local side effects of mucosal drying and bleeding. Often, the choice of agent simply depends on local practice patterns. Duration of therapy is up to 3 months, and patient response is unlikely before 2 weeks of use. Systemic absorption of topical agents is minimal, but there is evidence that using metered-dose inhalers, rather than spray bottles, prevents accidental overdose and subsequent adrenal suppression [21]. Systemic steroids in burst or taper are generally avoided due to side effects. They do have a role in patients with significant polyposis, as this may physically prevent the delivery of topical agents to the site of action. Saline nasal irrigation with a 2-3% solution has been found to be helpful. Daily irrigation has been shown to significantly decrease symptoms and improve QOL scores [24, 25]. Relief is likely due to improved mucous outflow and a decrease in secretions and load of inflammatory mediators.

Some clinicians prescribe the use of nasal decongestants for symptomatic use. These agents, however, should not be used for longer than 3-4 days because they are relatively short acting and can cause rebound congestion with chronic use. There is also ongoing research into the use of antileukotrienes. Although they are theoretically effective in situations of eosinophilic inflammation, substantial evidence is lacking [16]. Future directives in medical management include the use of immunotherapy to decrease inflammation, especially in patients with recalcitrant disease and those with concurrent allergic disease.

6. Treatment Failures

In cases of treatment failure, a referral to an otolaryngologist can be helpful for further treatment and possibly surgical intervention. Other indications for referral include the presence of severe signs including bleeding, orbital symptoms, facial swelling, uncertainty regarding diagnosis, or the presence of nasal polyposis.

Nasal endoscopy in a cooperative child and the older child in the office can be very informative. Anatomical abnormalities, nasal polyps, and adenoid hypertrophy are findings that will help with further management of the child (Figure 2).

Based on the exam findings, a CT scan can be obtained. It is important that the scan is obtained after at least

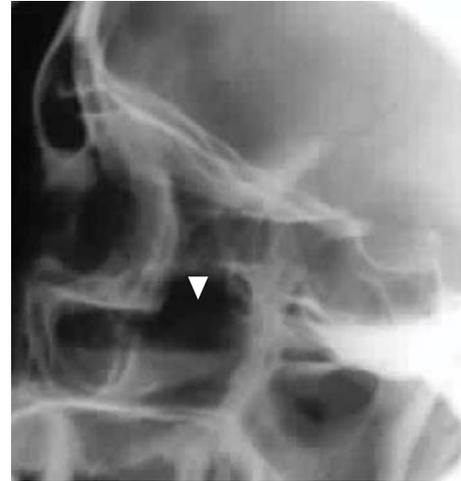


FIGURE 1: Lateral plain X-ray showing air-fluid level in the maxillary sinus.

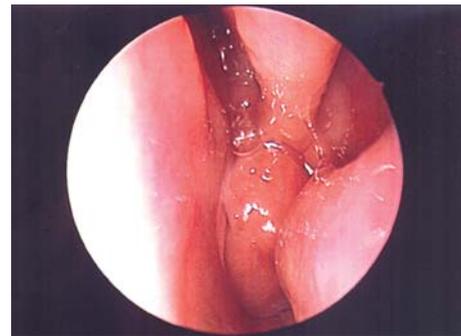


FIGURE 2: An endoscopic view using a 2.7 mm zero-degree rigid scope showing enlarged adenoids.

3-week course of antibiotics. Plain films of the sinuses are not helpful because of low sensitivity and specificity. MRI does have a place in the evaluation of complications, soft tissue involvement, and suspected neoplasia.

After referral for further evaluation, our patient had mucopurulence bilaterally. After treatment with 20 days of antibiotics and topical nasal steroids with nasal saline washes, a CT scan was obtained, and it showed blockage of her osteomeatal complex area with mucosal thickening in both maxillary sinuses (Figure 3).

7. Surgical Management

Surgical management for CRS that failed medical therapy in adults is ESS [26]. In children, however, we have several surgical options to consider prior to ESS. Most advocate an adenoidectomy as an initial step in the surgical management of those children. The success rate however is in the 50–60% [27, 28] range which is less than the 87% success rate with ESS [29]. Interestingly, a recent study comparing biofilm presence of adenoid samples from children with CRS found an incidence of 95% biofilm present in those samples compared to only 2% in adenoid samples of children with

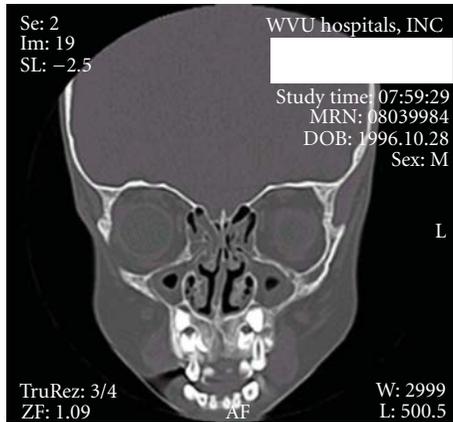


FIGURE 3: Coronal CT scan of the sinuses demonstrating significant disease in both ethmoids and maxillary sinuses with blockage of the OMC.

sleep apnea. This may partially explain the importance of removing the adenoids in those children with CRS [30]. Otolaryngologists are reluctant to proceed with ESS as a 1st line of treatment because of the fear of facial growth retardation [31]. Despite the fact that one study showed no difference in facial growth 10 years after ESS in children compared to a comparative group of children who had no surgery, that concern is still there [32]. Because of the average success rate with adenoidectomy alone, a sinus wash at the time of adenoidectomy has been advocated. The procedure will flush the sinuses, and at the same time a culture for antibiotic guidance would be obtained. Success rate with this procedure was 88% [33].

After a detailed review of those children who failed adenoidectomy was reviewed, it was noted that children with asthma or severe sinus disease as noted by their CT scan score had the worst outcome. Based on that information, subsequent studies have noted that children with asthma and a more severe disease had a much improved outcome if a sinus wash or sinus surgery was performed at the time of adenoidectomy [34].

Functional endoscopic sinus surgery (FESS) is a term for minimally invasive procedures designed to restore the natural drainage pathways of the paranasal sinuses [26]. FESS is performed under general anesthesia, typically as a same-day procedure. The nasal cavity is directly visualized, and various specialized tools are used to relieve obstructive lesions of sinus outflow including polyps and diseased mucosa. The affected sinus air cells are opened in a manner that augments natural mucociliary outflow. The procedure is usually a conservative one in those children [35].

FESS is indicated in patients with CRS who fail medical therapy or demonstrate complications of disease. Surgical complications are rare and are usually related to damage to adjacent structures including the orbital contents and the skull base. Regular postoperative followup is essential. Medical management with antibiotics and intranasal steroids may continue postoperatively, specifically if the children have allergic rhinitis.

8. Outcomes and Summary

Our patient had an adenoidectomy with a sinus wash of her maxillary sinuses, since she had severe asthma and severe disease based on her CT scan. There were no operative complications. Postoperatively she was given culture-directed oral antibiotics for 14 days. At-six-month followup, there was no reported sinus infections and her symptoms were much improved. She continues to use her topical nasal steroids. Her asthma was much improved that her parents reported discontinuation of all of her asthma medications.

9. Conclusions

CRS is a common disease in children which was shown to have significant impact on the quality of life of these children. In the majority of cases medical treatment is very successful; however, in a small percentage surgical treatment may need to be entertained specifically in those children with asthma. Proper patient selection, counseling, and followup are essential for a favorable surgical outcome.

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Clinical Study

Troublesome Tinnitus in Children: Epidemiology, Audiological Profile, and Preliminary Results of Treatment

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Introduction. Although tinnitus often has a significant impact on individual's life, there are still few reports relating to tinnitus in children. In our tinnitus clinic, children with distressing tinnitus constitute about 0,5% of all our patients. *Objectives.* The aim of this study was to analyse children with troublesome tinnitus as regards epidemiology, audiological profile, and preliminary effects of the therapy. *Methods.* A retrospective study was carried out involving the cases of 143 children consulted in our Tinnitus Clinic in 2009. The selected group with troublesome tinnitus was evaluated and classified for proper category of Tinnitus Retraining Therapy (TRT). *Results.* The study showed that 41.3% of the children suffered from bothersome tinnitus. In this group 44.1% of the patients demonstrated normal hearing. The success of the therapy after 6 months was estimated on 81.4% of significant improvement. *Conclusions.* It is recommended that a questionnaire include an inquiry about the presence of tinnitus during hearing screening tests.

1. Introduction

Tinnitus is perception of sound like buzzing, ringing, roaring, clicking, pulsations, and other noises in the ear, ears, or in the head occurring without an outside acoustic stimulus. Tinnitus is a symptom, not a disease, and as such can arise as a result of inappropriate activity at any point in the auditory pathway. The neural plasticity, responsible for tinnitus, appears as an adaptation or compensation, at a central nervous system level, following peripheral damage. Tinnitus may be caused by a variety of pathologies, illnesses, medications, allergies, dietary changes, stresses, or traumatic events. It is often caused by pathologies related to the ear, head, and neck area like: head trauma or whiplash. One of the most common causes of tinnitus involves noise exposure. It can be both: long term and produced by brief loud sound. Long-term exposure to noise or acoustic trauma can produce substantial and often irreparable damage to the delicate structures of the inner ear—especially outer hair cells. In the majority of cases, tinnitus is clearly related to some changes in the inner ear. At the same time tinnitus is not necessarily associated with hearing loss. About 40% of tinnitus patients

have also the symptoms of decreased loudness tolerance called hyperacusis [1].

The prevalence of tinnitus increases with age. In older people, tinnitus occurs most often in conjunction with the hearing problems connected with ageing or it can be associated with general diseases. About 5% of adult Poles suffer from constant tinnitus [2]. Research into the prevalence of tinnitus in a pediatric population in Poland on large scale has been continued by the Institute of Physiology and Pathology of Hearing for last years. The initial results show that 12.8% of seven-year-old children have tinnitus in our country [3]. There are few epidemiological studies on the prevalence of tinnitus in children in the literature. In a group of children with normal hearing, the prevalence of tinnitus has been reported to be between 6% and 36%. In a study by Nodar [4], there was 15% of those patients. Other researchers, Mills et al. [5] estimated that 29% of normally hearing children complain about tinnitus, and only 9,6% reported the troublesome tinnitus [5]. The latest paper by Holgers [6] highlights about 13% of pediatric patients with normal hearing and tinnitus [6]. In children with hearing loss, the prevalence of tinnitus is reported to be as high as 55% [7].

TABLE 1: Categories of TRT mixing point-level close to the place where the sound from the instrument blends with the tinnitus.

Category	0	I	II	III	IV
Tinnitus	Small problem	Serious problem	Serious problem	Present/absent	Present/absent
Hyperacusis	Absent	Absent	Absent	Present	Present/absent
Noise exposure	No prolonged Effect	No prolonged effect	No prolonged effect	No prolonged effect	Prolonged effect
Subjective HL	Absent	Absent	Significant	Irrelevant/significant	Irrelevant/significant
Main problem	Tinnitus	Tinnitus	HL	Hyperacusis	Tinnitus or hyperacusis
Treatment	Avoid silence recommendation	Noise generators set at mixing point	Hearing aids with/without noise generators set below mixing point	Noise generator firstly set at hearing threshold then gradually increased to mixing point	Noise generators firstly set at hearing threshold then gradually increased to mixing point

Graham and Butler [8] found the prevalence to be twice as high (66%) in children with mild to moderate hearing impairment than in those with severe to profound hearing loss (29%) [8]. Mills and Cherry [9] estimated 43,9% of children with conductive hearing loss and tinnitus compared to 29,5% of those with sensorineural hearing impairment [9].

However, tinnitus is a common disorder in childhood, and only 3% to 6.5% of young patients spontaneously complain about it [7, 10]. In a survey showing the children with that symptom presented to audiologists, Martin and Snashall reported that 83% of children suffered from bothersome tinnitus [11]. Overall, children with normal hearing found tinnitus more troublesome and presented higher levels of anxiety than those with hearing loss [12]. Tinnitus primarily produces psychological distress. Even if a child does not report the existence of tinnitus, it may cause serious consequences such as difficulties in concentration, stress, fatigue, irritation, sleep disturbances, deterioration in learning, poor attentiveness, and emotional distress. In older children, complaints relating to sleep disturbance, auditory interference, and emotional distress have been consistently found in subsequent studies [13]. On the basis of our experience, even though some children really suffer from tinnitus, they usually do not need an additional psychological help.

A treatment derived from the neurophysiological model of tinnitus applied on time for young patient is a good and effective therapeutic tool. It is a specific form of sound therapy and counseling [1] called Tinnitus Retraining Therapy (TRT) [1]. This management facilitates habituation to tinnitus by suppressing negative reactions and associations caused by tinnitus as well as suppressing or even associations its perception. On the basis of the interview and some of the audiological tests, the patients are divided into five categories of treatment. The factors that determine ration to appropriate category are the impact of tinnitus on the patient's life, presence or absence of hyperacusis, subjective hearing loss, the presence of prolonged worsening of tinnitus, and/or hyperacusis after exposure to loud sound (Table 1).

The therapy needs at least 18 months of training to have stable effects. A positive result of the therapy is achieved by about 80% of adult patients and approximately 90% of children after 18 months of treatment [14, 15].

2. Materials and Methods

This study considered 143 children with tinnitus aged under eighteen who were consulted in our clinic in 2009. All of them were accompanied by at least one parent for the initial assessment, where detailed information about a child's life, tinnitus onset, and its influence upon life was gathered.

The children underwent the following protocol: case history, filling in the initial contact questionnaire, audiological evaluation, medical evaluation, diagnosis, and selection for the treatment category. The hearing screening tests were performed using: pure tone audiometry with air conduction in the range of frequency 0,25–8 kHz and impedance audiometry with acoustic reflexes. Children with the abnormal tympanometry test and those whose the only problem was hyperacusis were excluded. The degree of hearing loss, when presented, was classified according to BIAP (20–40 dB: mild, 40–70 dB: moderate, 70–90 dB: severe, >90 dB: profound).

To report tinnitus as troublesome, there were three parameters displayed on the visual scale from 0 to 10 with 10 being the worst. The children with parents help subjectively evaluated on this scale the degree of annoyance caused by tinnitus, the impact on their activities, and the intensity of tinnitus. Only those who indicated five or more were included in our study.

All the children with troublesome tinnitus took part in the TRT. There were no other preselection criteria except the requirements for children to be treated for at least 6 months and each of them had to be actively present at all follow-up visits. They underwent directive counseling, selection of the treatment category, fitting of the most suitable hearing aids or noise generators, follow-up counseling according to the individual needs of the patient, and an established timetable.

Treatment effects were estimated after a 6-month therapy involving filling a special questionnaire and using the visual analog scale from 0 to 10 with 10 being the worst. It

TABLE 2: The questionnaire that was used to estimate results of treatment.

Measure the following parameters using visual analog scale (VAS):	VAS (10 means the worst)
(1) The impact of tinnitus with/without hyperacusis on various everyday activities	0-1-2-3-4-5-6-7-8-9-10
(2) Percentage of time of being aware of tinnitus	0-1-2-3-4-5-6-7-8-9-10
(3) The degree of annoyance	0-1-2-3-4-5-6-7-8-9-10
(4) The impact of tinnitus on your life	0-1-2-3-4-5-6-7-8-9-10
(5) The intensity of tinnitus	0-1-2-3-4-5-6-7-8-9-10
(6) The level of distress caused by tinnitus	0-1-2-3-4-5-6-7-8-9-10

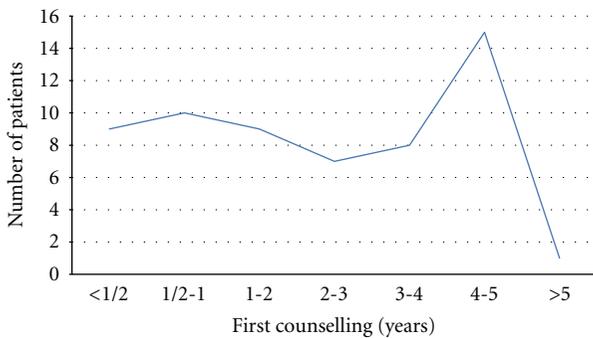


FIGURE 1: Time from the onset of tinnitus to first counseling.

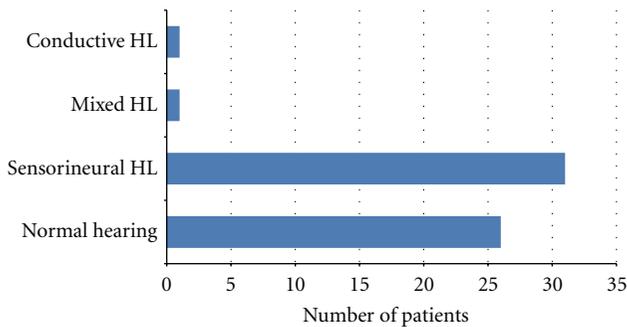


FIGURE 2: Hearing level in the study group. Hearing loss (HL).

comprised the parameters, which were presented in the form of questions to be answered by the child before, during, and after 6 months (Table 2).

The data acquired from the questionnaire results of the therapy were evaluated by means of two criteria: significant improvement and no improvement or deterioration. The criterion of significant improvement was the decrease of at least three of the above-mentioned parameters by a minimum of 20% and the liberation of at least one of the everyday life activities previously impaired by tinnitus.

3. Results

Troublesome tinnitus was present in 59 children (41,3%), 31 girls (52,5%) and 28 boys (47,5%), at the average age of 14,4 (min. 7, max. 17). Some of them complained about hyperacusis ($n = 22$, 37,3%). There were significantly more girls with this symptom ($n = 14$, 63,6%) than boys ($n = 8$,

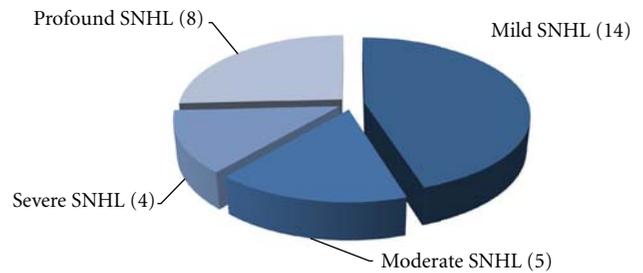


FIGURE 3: Number of children with tinnitus and different degrees of severity of sensorineural hearing loss (SNHL).

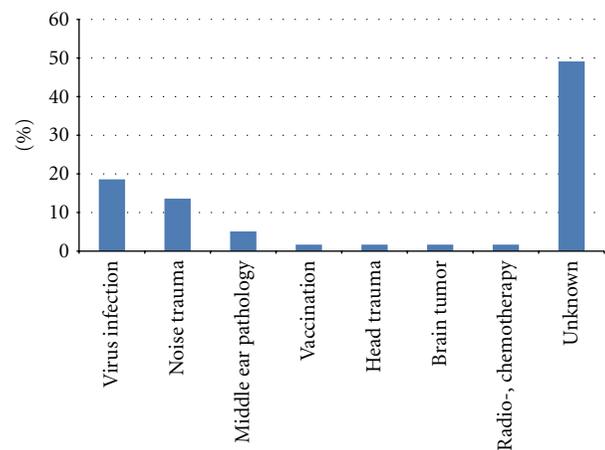


FIGURE 4: The suspected etiology of tinnitus in the study group.

36,4%). Despite bothersome tinnitus, only 19 children (32,3%) had first audiological counseling within a year after the onset of tinnitus (Figure 1). In all, 44,1% of children ($n = 26$) demonstrated normal hearing while 55,9% ($n = 33$) had hearing impairment (Figures 2 and 3). According to the suspected etiology of tinnitus, the most common one was a clinical history of a virus infection (18,6%), and in 49,1% of cases etiology was unknown. In Figure 4, there is a detailed summary of the causes percentage distribution.

As far as the specific characteristics of tinnitus were concerned, 56 children described their tinnitus as continuous in 20 cases (33,9%), as intermittent in 36 cases (61%). There were 3 children that did not specify duration of tinnitus. The pitch of tinnitus was low (<2 kHz) in 14 children (23,7%), high (>4 kHz) in 40 children (67,8%), pulsating in 1 case (1,7%), and undefined in 3 cases (5,1%).

TABLE 3: The number of children in each category of TRT who used recommended devices.

Category of TRT	Number of children	Devices used
I	14	13 bed-side noise generators
II	32	12 hearing aids, 4 bed-side noise generators
III	13	3 noise generators behind ears, 7 bed-side noise generators.

TABLE 4: The result of TRT in the subsequent categories.

Category of TRT	Significant improvement	No improvement	Undefined result
I (14 children)	12	1	1
II (32 children)	28	4	0
III (13 children)	8	4	1

Tinnitus was declared as bilateral in 29 cases (49,1%), unilateral in 28 cases (47,5%), and in the head in 2 cases (3,4%). The patients with sensorineural HL declared that unilateral tinnitus is the most common (Figure 5). It was observed that in a group of children with bilateral tinnitus, more than half had normal hearing ($n = 18, 62, 1\%$).

All children with troublesome tinnitus fell into appropriate categories of the TRT: 14 children with tinnitus and normal hearing fell into category I, 32 children with tinnitus and HL belonged in category II. In category III, there were 13 children classified with tinnitus and hyperacusis as a main problem; 12 of them had normal hearing.

Enriched environmental sounds and silence avoidance were recommended to all patients. The children in category I were advised to use noise generators, in category II to use hearing aid and in category III to use noise generators behind ears. The children with conductive and mixed HL underwent myringotomy with tube insertion additionally. However, less than half of the patients (47,5%) strictly observed the orders. Table 3 shows how many children in each category used recommended devices.

The preliminary results were evaluated after 6 months of therapy. Management success: significant improvement was observed in 48 cases (81,4%). There was no change in perception of tinnitus in 9 cases (15,2%). In 2 cases (3,4%), the effect of the therapy was undefined. Results of the TRT in subsequent categories are presented in Table 4.

The TRT has been continued by about 30% of children. Characteristics of this group after 1 year of treatment will be shown in the next study.

4. Discussion

This small-scale preliminary study showed, in contrast with the data by Martin and Snashall, that less than half of the the patients with tinnitus reported that the ailment was bothering them [11]. Over 50% of children with tinnitus seen in our clinic had hearing impairment. Similar results have been presented by Holgers [16] who estimated a prevalence of tinnitus in children between 23 and 64% [16].

A past medical history of middle-ear pathology in a pediatric group with tinnitus was performed in 35,6% of cases

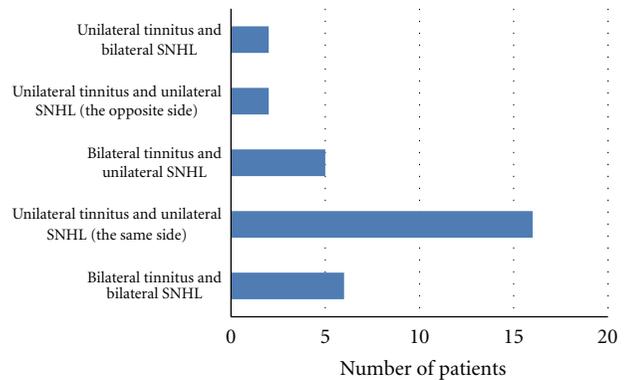


FIGURE 5: Number of children with sensorineural hearing loss (SNHL) divided into 5 groups according to laterality of tinnitus and SNHL.

and did not seem to be a significant factor in the pathogenesis of children's tinnitus. Similar results were presented by Mills and Cherry, Martin and Snashall, and Viani [9, 11, 17]. Those researchers found no statistical difference between the group without middle ear pathology and the group who had positive history of middle ear disorder.

Although tinnitus seems to be a serious problem for over 40% of children, causing many disturbances in their lives, only about one-third of them decides to get audiological help.

After just 6 months of treatment, most of the children with troublesome tinnitus gained benefits from the therapy. What is more, for over 80% of pediatric population, the TRT is limited to sound and noise generators.

About half of the children in our study had normal hearing. It indicated the greater significance of other factors than hearing impairment. Similar results were obtained by Graham and Butler [8].

5. Conclusions

Troublesome tinnitus is a quite frequent complaint among children and concerns both normal hearing children as well as those with some degree of hearing loss. This problem still

needs careful attention and research. Until we gain more knowledge on the development of bothersome tinnitus in pediatric population, audiologists have to rely on the reports based on adults. It is recommended that an inquiry about the presence of tinnitus during hearing screening tests at school should be included in the questionnaire. Treatment strategies should be applied individually and involve both the parents and children.

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