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Research Article

Epileptic Encephalopathies in Adults and Childhood

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Epileptic encephalopathies are motor-mental retardations or cognitive disorders secondary to epileptic seizures or epileptiform activities. Encephalopaties due to brain damage, medications, or systemic diseases are generally not in the scope of this definition, but they may rarely accompany the condition. Appropriate differential diagnosis of epileptic seizures as well as subclinical electroencephalographic discharges are crucial for management of seizures and epileptiform discharges and relative regression of cognitive deterioration in long-term followup. Proper antiepileptic drug, hormonal treatment, or i.v. immunoglobulin choice play major role in prognosis. In this paper, we evaluated the current treatment approaches by reviewing clinical electrophysiological characteristics of epileptic encephalopathies.

1. Introduction

Epileptic encephalopathy is described as epilepsy with ictal and interictal epileptiform anomalies (clinical and EEG) and progressive cerebral dysfunction according to the classification and terminology criteria of International League against Epilepsy (ILAE) [1–3]. The following are syndromes meeting the criteria: Dravet syndrome, Doose syndrome, ESES (electrical status epilepticus of slow sleep) or CSWSS (continuous spike waves of slow sleep), Landau-Kleffner syndrome, Lennox-Gastaut syndrome, Ohtahara syndrome, and West syndrome [4]. Severe epilepsy with multiple independent spike foci is recently included in this group [2, 4].

Steroid-sensitive epileptic encephalopathies such as Hashimoto encephalopathy, progressive myoclonus epilepsies, and neonatal epileptic encephalopathies are not classified in this group but are worth mentioning [5–10].

2. Dravet Syndrome or Severe Myoclonic Epilepsy of Infancy

An important group of epileptic encephalopathies that are resistant to treatment, a severe myoclonic epilepsy of childhood, first described by Dravet in 1978, is characterized with recurrent febrile and/or afebrile, hemiclonic or generalized seizures, and status epilepticus. Child's development stops or retards after the onset of seizures [11–14]. Prevalence is unknown. The incidence is 0.5–1/40.000 and develops in 3–5% and 6.1–8.2% of all epilepsies in the first year and within the 3 years of life, respectively. Male-female ratio is 2 : 1. The most common cause is SCN1A mutations or deletions (35%) [11, 15–17]. Consequences in patients who reached adulthood and were observed for long term as well as neuropathology of the disease are unknown.

Patients with family history of febrile convulsion or epilepsy are reported to consist 25–71% in various patient series. Incidence is also significant in identical twins. GEFS is (+) in most of the cases. Ten percent of the cases are asymptomatic and SCN1A mutation is reported in their mildly affected family members. The possible genes involved are shown to be SCN1B, GABRG2, PCDH19, SCN2A, and 2q SCN [12, 18–26]. On the other hand, the association of SCN9A with febrile convulsions and Dravet's syndrome is also emphasized [27].

Common characteristics of Dravet's syndrome in animal models and patient groups are increased interictal epileptiform discharges or epileptic seizures due to sensitivity to increased body temperature and increased seizure frequency and severity due to aging [12, 13, 26, 28]. The abovementioned characteristics refer to juvenile form of Dravet's

syndrome and are based on solid evidence from several studies. Sufficient data about the adult form is not available [12, 29]. MRI findings are normal in most of the cases. Adult form of Dravet's syndrome may present with cerebral-cerebellar atrophy or cerebellar atrophy only [29].

Between ages of 1–5, myoclonic seizures may manifest with massive, generalized myoclonic jerks, and sudden falling attacks. Myoclonic jerks increase throughout the day and with emotional lability and disappear in sleep. Focal seizures may develop in 45–80% of the cases between 4 months and 4 years in simple partial motor or complex partial form, persisting as unilateral seizure or may develop into generalized seizure [11, 15, 30].

EEG is generally normal within the first 12 months. Generalized spike, spike and wave (5-6 sec) complexes may be observed in multiple foci localized in central regions and vertex photosensitivity is reported in 50% of the cases. Unexpected EEG findings have recently been reported [11, 28, 30].

Treatment is resistant to several medications. Carbamazepine and lamotrigine are shown to exacerbate the seizures. Effects of other anticonvulsants vary. VAP, TPM, and LEV are the most promising agents used in USA. In Europe, more successful results are achieved by combining stiripentol, a cytochrome P450 inhibitor, with clobazam (CLB) and VPA, especially in prevention of status epilepticus [12, 31]. Recent studies indicate that addition of a voltage-gated calcium channel blocker, such as verapamil, to anticonvulsant therapy is beneficial. Ketogenic diet is another method for management or minimizing seizure frequency [31–37].

3. Myoclonic-Astatic Epilepsy or Doose Syndrome

Myoclonic-astatic epilepsy or Doose syndrome is a form of generalized epilepsy developing between 7 months and 6 years of life with myoclonic attacks, absence and tonic seizures [1, 38, 39]. Peak age is 1–5 and males are more prone than females. One-third of cases have history of febrile convulsion [1, 15]. EEG may show spike-wave, wave-multiple spike complexes in ictal period with 2–4 Hz frequency. It is initially normal in interictal period, 3 Hz wave-spike discharges may be observed in sleep in later periods [40–42]. Fifty-eight percent of the cases have normal intelligence, while 20% and 22% show mild and severe mental retardation, respectively. Cases with mental deterioration are usually resistant to treatment. Seizures may be managed after 3 years in a certain percentage of patients [22, 42, 43]. Neuroradiological findings are generally normal [41]. Genetical basis is not clear [22, 38, 39]. VPA and ethosuximide (ESM) are still the commonly preferred medications for management of myoclonic seizures [40, 42]. Although BDZ and clonazepam (CZP) are beneficial for management of generalized seizures, they are not preferred since they cause behavior changes [41]. Lamotrigine (LTG) can be used for generalized seizures [44, 45]. CBZ and vigabatrin (GVB) are not recommended [41].

Topiramate (TPM), levetiracetam (LEV), acetazolamide (AZD) and sulthiame (SLT) are common; however, the number of cases and studies is not sufficient [22, 41, 46–48]. Ketogenic diets are effective but difficult to maintain for long periods [40, 49]. Progressive myoclonic epilepsies, that is, MERRF syndrome (myoclonus epilepsy with ragged-red fibers) can be mistaken for with Unverricht-Lundborg disease, and late-infantile neuronal ceroid lipofuscinosis; however, neurological development in later stage, continuity and persistence of the disease facilitate differential diagnosis.

4. ESES or CSWSS

First defined in 1971 as a juvenile form of epileptic syndrome named subclinical status epilepticus, ESES (or CSWS) is characterized with neuropsychologic and behaviour changes and develops during sleep [3, 10, 50]. ESES and CSWS are synonyms; however, ESES indicates EEG findings while CSWS refers to electroclinical findings [10, 51]. Prevalence is not known, but incidence is reported to be 0.5%. Equal male-female incidence is defined in early studies; extended studies indicate higher incidence in males. Generalized tonic-clonic seizures, atypical absence, myoclonic and atonic seizures may be observed. Mental retardation, lower IQ secondary to deterioration, and motor loss such as aphasia, behaviour disorder, ataxia, and dyspraxia accompany the seizures. Clinical course is composed of 3 stages: (1) initial period with seizures and no mental retardation; (2) intermediate period composed of neuropsychologic regression, seizures and ESES, and (3) final period composed solely of neuropsychological deficit. Cases solely presenting with mental retardation or behaviour disorder with no seizures are also noted [10, 52–56]. In these cases, diagnosis is confirmed with night video-polysomnography (V-NPSG). In most cases, EEG anomalies and neuropsychologic losses continue in puberty meanwhile there may be regression in seizures, improvement in behaviour and motor findings, and normal EEG pattern may return. Although genetic factors are unknown, a study reported relation with familial seizures and monozygotic state, and 15% of cases is associated with febrile convulsions [56, 57]. MRI and CT studies indicated 33% anomaly with significant diffuse or unilateral cerebral atrophy [58]. LTG, LEV, VPA, steroids, and BDZ are among treatments, the best outcomes are observed with diazepam (DZP) [6, 59]. Corticosteroids are beneficial in some resistant cases [60–62].

5. Landau-Kleffner Syndrome

William Landau and Frank Kleffner reported epileptic encephalopathy for the first time in 1957 in six children who underwent various types of seizures and developed acquired aphasia [6, 63]. LKS first appears between ages of 3 and 7 in children with normal motor-mental-linguistic development [64]. Range may be 2–14 in rare cases. Male-female ratio is 2 : 1. Family history is incidentally (+). The main criterion is determined as normal development in premorbid period; however, preexisting language anomaly is reported in 13% of

the cases. Aphasia is progressive and usually develops gradually. Total speech loss develops approximately in 1 year and acute-onset aphasia is rare. Various types of aphasia may be observed during the whole course. Hearing is usually normal, but patients may develop mutism and unresponsiveness to all verbal and nonverbal stimuli. Hyperactivity, aggressiveness, impulsiveness and attention deficit are extremely common [65–69]. EEG shows spikes or spike-waves prominent in temporal or centrotemporal sleep. Methohexital suppression test, intraoperative electrocorticography, and magnetoencephalography results are localized in superior temporal gyrus, intra- and peri-Sylvian cortex. EEG is rarely normal in sleep. ESES can be observed rarely. In pathogenesis, frequent EEG discharges are estimated to interrupt central pathways of speech development. This relation is explained for similar syndromes like Benign childhood epilepsy with centrotemporal spikes (BECTS) [59, 70–74]. MRI findings are normal. SPECT studies reveal temporal hypo- or hypermetabolism. Hypermetabolism are associated with active epileptic discharges [68].

LKS prognosis is poor depending on the earlier date of onset (prelinguistic). However, some cases show significant improvement in communication in second and third decades of life [75]. Seizure management is usually successful with appropriate drug choice. CBZ may deteriorate the seizures, monotherapy with VPA or its combination with BDZ seem to be the best choice. Higher and long-term use of adrenocorticotropic hormone (ACTH) and steroids is strongly recommended due to beneficial results. CLB, nitrazepam (NZP), VPA, ESM, and flunitrazepam are used, and PB, CBZ, and PHT are not used. IV immunoglobulins are as successful as steroids [60–62, 74–76].

6. Lennox-Gastaut Syndrome

LGS is a rare form of epileptic encephalopathy, first described in 1969 by Lennox and Gastaut [77]. Classical triad includes early onset with multiple and various types of seizures, mental deterioration, and generalized slow spikes waves in EEG [76–79]. First seizure occurs at 1–8 years, peaking between 3 and 4, and is etiologically divided into symptomatic and cryptogenic. Major division includes cryptogenic cases. Symptomatic cases are secondary to hypoxic-ischemic encephalopathy, vascular damage, tuberous sclerosis, Down's syndrome, trauma, brain tumor, and perinatal meningoencephalitis. WS is reported in history of 10–25% of the cases [44, 80–82] (Figure 1).

Tonic seizures are the most common seizures of LGS (74–90%) and occurrence in the initial period is not mandatory for diagnosis. The second most frequent symptom is atypical absences, followed by atonic seizures and myoclonic seizures. Nonconvulsive status epilepticus is observed in 54–97% of the cases [81, 82]. EEG findings are characteristic: generalized slow spike-waves (2–2.5 c/s) and burst in awake state, burst or fast wave and slow polyspikes and generalized fast activity at about 10 c/s during sleep [80].

Antiepileptic drugs, ketogenic diet, hormonal therapies, and surgical and rehabilitation methods are used in

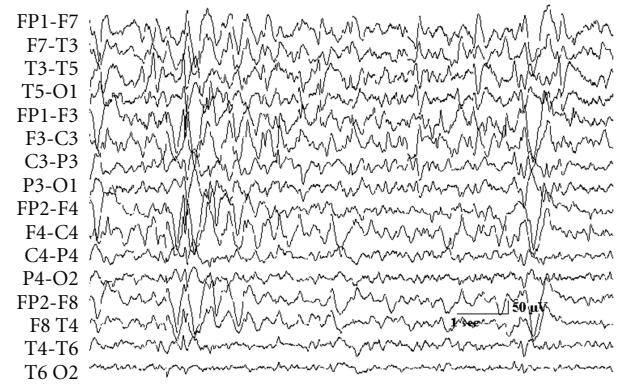

Figure 1: Slow electroencephalographic spike and wave discharges in Lennox-Gastaut syndrome.

treatment. Monotherapy or combined therapy with old-generation antiepileptic medications did not give significant benefit; however, benzodiazepines are still utilized. The most promising choices seem to be LTG and rufinamide (RUF). Carisbamate (CBM), fluorofelbamate (FFBM), ganaxolone (GNX), and remacemide (RMC) are among the antiepileptic medications of the future. Ketogenic diet is as effective as in all types of intractable epilepsies. Difficulty in continuation and complications of some medications (kidney stones) are of concern. Initiation of ACTH and corticosteroids short time after disease onset, especially in cryptogenic cases, is known to be effective, but they are not used frequently due to increased rate of relapse. Other choices are amantadine, imipramine, IV immunoglobulin, and TRH analogs. Surgical treatment options include callosotomy and VNS (vagal nerve stimulation). Nonmedical treatment methods are composed of specific education and rehabilitation [45, 83–90] (Figure 2).

Prognosis is extremely poor. Most of the cases continue to live dependently [80].

7. Ohtahara Syndrome or Early-Infantile Epileptic Encephalopathy

Ohtahara Syndrome, first described in 1976 by Ohtahara et al., characterized with tonic seizures and burst suppression pattern in EEG, develops earlier than other forms of epileptic encephalopathies, is resistant to treatment, and has one of the poorest prognosis among other types [6, 91–93]. Cause is unknown but it generally accompanied structural brain anomalies such as Aicardi syndrome, migrational disorders, porencephaly, and hemimegalencephaly; male-female prevalence is equal. First seizure may occur in the first day of life, but general onset is within 1–3 months [7, 94–101].

Single or clusters of tonic spasms occur in awake state or during sleep. Other seizure types are rare. It accounts for 0.2–4% of all juvenile epilepsies. Seventy-five percent of cases turn into West Syndrome within 3 to 6 months, and some of these turn into Lennox-Gastaut syndrome.

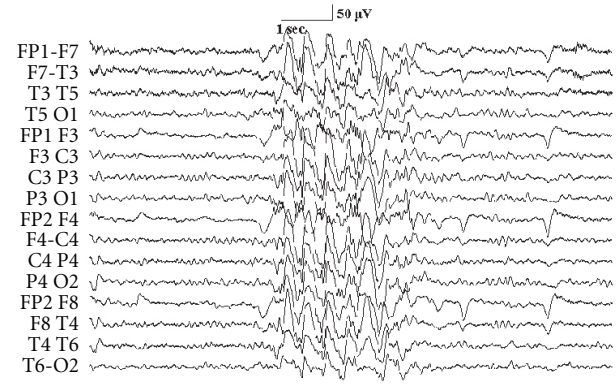

Figure 2: Polyspike and wave discharged been recorded in atypical absence seizures (Lennox-Gastaut syndrome).

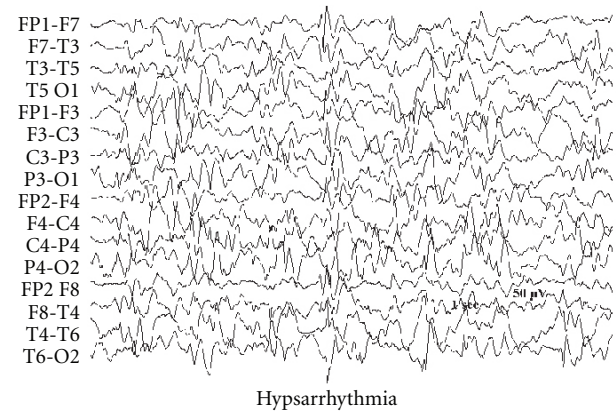

Figure 3: Hypsarrhythmia electroencephalogram in infantile spasms shows chaotic high-amplitude background (West syndrome).

ARX gene mutation, Stxbp 1 (MUNC 18-1) mutations are reported in some cases [102–104].

ACTH, VGB, and zonisamide offer some benefits; however, no treatment showed significant improvement in long-term. Severe morbidity and high mortality are inevitable [105–112].

8. West Syndrome or Infantile Spasms or Salaam Spasms/Tics

West Syndrome, a well-known form of epileptic encephalopathy first described in 1841 by James West, has a 0.16–0.42 incidence in thousand births [6]. Triad includes epileptic seizures, hypsarrhythmia in EEG and psychomotor retardation [113]. It usually starts within the first year of life peaking at 5 months. Seizures appear in various types and are usually in the form of sudden, bilateral, and symmetrical flexor, extensor or mixed-type spasms of the neck, body, and extremities. These spasms usually have 20–100 clusters [64, 114–117].

Early diagnosis and treatment prevent poorer prognosis and development of Lennox-Gastaut syndrome. There are three forms: symptomatic, idiopathic, and cryptogenic [118] (Figure 3).

EEG shows random high-amplitude slow wave and spike complexes and is first described by Gastaut in 1950, and named hypsarrhythmia by Gibbs. It may gain multifocal character in time or may rarely turn into generalized spike discharges [112–116] (Figure 4).

Preferred agents are ACTH and VGB [115–130].

9. Severe Epilepsy with Multiple Independent Spike Foci (SE-MISF)

Ohtahara et al. described the clinical symptoms, also previously described by Noriega-Sanchez and Markand, characterized by high-frequency seizures and MISF in EEG, which generally involves both hemispheres and develops secondary to cerebral pathologies in children between 4–7 years [41, 101].

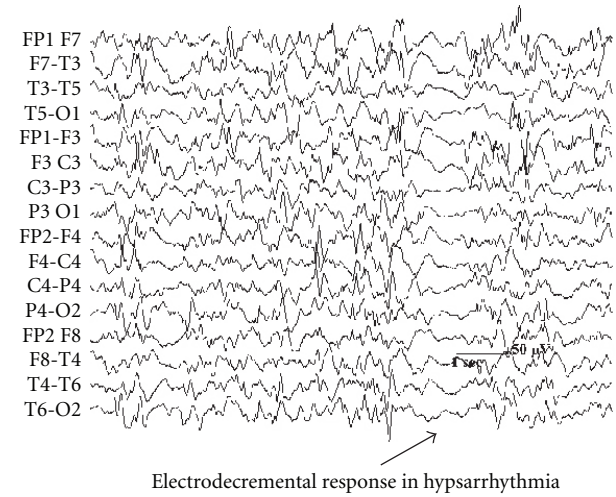

Figure 4: Electroencephalogram response in hypsarrhythmia was associated and recorded in infantile spasms (West syndrome).

Various types of frequent generalized minor seizures usually manifest along with mental retardation. Condition develops secondary to pre-, peri-, and post-natal factors (degenerative disorders, neurocutaneous diseases, infections, hypoxic-ischemic encephalopathy, hydrocephaly, and cerebral malformations), and patients develop WS and LGS, continuing their lives with severe seizures and mental retardation [59, 131–133].

VPA, BDZ, VGB, PTH, and ZNS combinations are used for treatment. Neurosurgical intervention is not an option [59, 133, 134].

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