The relationship between the components of idiopathic focal epilepsy
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Abstract

The classification of epileptic syndromes in children is not a simple task; it requires a great clinical ability as well as some degree of experience. Until today there is no international consensus regarding the different diseases that are part of the Idiopathic Focal Epilepsies; however, these diseases are the most prevalent in children suffering from some type of epilepsy. For this reason, it is important to know more about these, their clinical characteristics, pathological findings in studies such as encephalogram, resonance, polysomnography, and others. In the same way, to explore the possible genetic origins of many of these pathologies, that have been little explored and become an important therapeutic goal. A description of the most relevant aspects of atypical benign partial epilepsy, Landau-Kleffner syndrome, benign epilepsy with centrotemporal spikes, and Panayiotopoulos syndrome is present in this review. Allowing physicians and family members of children suffering from these diseases to have a better understanding and establish in this way a better diagnosis and treatment in patients, as well as promote in the scientific community the interest to investigate more about these relevant pathologies in childhood.

Keywords: Idiopathic Focal Epilepsies, benign epilepsy, atypical benign partial epilepsy, Landau-Kleffner syndrome, Rolandic epilepsy, benign epilepsy with centrotemporal spikes, electrical status epileptics during sleep, Panayiotopoulos syndrome

Introduction

A way to classify the electro-clinical syndromes is arranged by typical age of onset (neonatal, infancy, childhood, adolescence-adult, familial onset). One of these is the childhood epilepsy, before named as “benign epilepsy”, now known as Idiopathic Focal Epilepsies (IFE). This group of epilepsies have some similarities between them, either because they share clinical symptoms, encephalographic patterns, alteration in the same gene and/or progress towards the same clinical deterioration. The main aim of this article is to correlate the commonalities between the Landau-Kleffner syndrome (LKS), electrical status epileptics during sleep (ESES), atypical benign partial epilepsy (ABPE) and Panayiotopoulos syndrome (PS). However, the correspondence between these syndromes have been already done, but with controversial findings. For this reason is that the present review presents the clinical, pathophysiological, genetic and complementary studies that help to better understand these syndromes their similarities and differences, to be able to make a better diagnostic approach and thus give a better treatment for affected children for these diseases. The search for information was made by consulting resources bibliographic databases, such as the Science Direct, Scielo, Medline and Pubmed databases, using different combinations of the following descriptors in English: benign epilepsy, Idiopathic Focal Epilepsies, Landau-Kleffner syndrome, electrical status epileptics during sleep, atypical benign partial epilepsy, benign epilepsy with centrotemporal spikes, Rolandic epilepsy, and Panayiotopoulos syndrome. All the articles that could be recovered were reviewed, published until 2017, and those considered relevant were selected.

The idiopathic focal epilepsies members

Landau-Kleffner syndrome

Historically: The original work made it for Landau and Kleffner and published in 1957 reports the cases of five children with epilepsy and acquired aphasia. The clinical findings of these patients were generalized, partial, myoclonic, or absence seizures, all developed aphasia for different periods of time. In the EEG was evident a paroxysmal disorder, usually bilateral, often more predominant in temporal localization with generalized spikes. After that in 1992, Paquier et al, publish the first review of the literature about it. In 1999 Rossi et al and in 2003 Mukhinet al describe the EEG findings and progression in patients with LKS. In 2001 Robinson et al, demonstrated that children with ESES have no presence of clinical alteration in language capacities in relation with LKS and in 2004 McVicar and Shinmar confirmed that clinically the syndrome present a limitation in the language...
The relationship between the components of idiopathic focal epilepsy

abilities compared with the clinical characteristics of other similar epileptic syndromes as ESES.

b. Clinical findings: The children with LKS have a pathological interaction between epilepsy and language, with the major symptom the acquired aphasia. The patients used to present different types of epileptic attacks such as atypical absences, secondary generalized, pharyngo-oral, tonic falls and hemiconvulsive, at age between the 2 and 10 years, presenting progressive alterations in the receptive and expressive language after the events, additionally have some symptoms as headache and confusion. When the LKS begins before the 4 years and the duration progress more than 1 year, it is possible to develop alterations in the cognitive and behavioral functions.

c. Electroencephalographic findings: The EEG has a very important role in the diagnosis and evolution of the LKS; regional spikes were observed in all the patients, especially in the fronto-, centro-, or posterior-temporal areas (67 %) in contrast to CSWS the discharges have a frontal focus origin (71 %). Also in some LKS patients with behavior disorders have been found frontal lobe discharges (50 %).

d. Genetic characteristics: The genetic and molecular studies of the different types of seizures have been increase during the last 10 years, especially those related with the pathophysiology understanding of the IFE. In LKS have been establish a genetic/epigenic origin, related with the identification of copy number of variations (CNVs), single mutations and somatic mosaicism. Studies in LKS patients in a cohort of two discordant monoyzotic twin pairs and 11 isolated cases have been identified 16 genes with discordant CNVs. In relation to the presence of single mutations in childhood focal epilepsies with speech and language dysfunction the GRIN2A is the gene with most strong association. The somatic mosaicism related with rare variants identified in IFE genes are BSN, COL18A1, GALR1, L2H6DH and RELN.

Electrical status epilepticus during sleep: ESES has been defined as a syndrome that develops during childhood, and its main feature is the appearance on the EEG during non-eye-rapid-movement (Non-REM) sleep, continuous spike waves. The seizures vary in on it presentation, partial motor seizures are more prevalent during the night that appear after the ESES pattern is present, and absence seizures appear during the ESES phase. This electroencephalographic pattern and the seizures usually tend to cease during puberty, and this event usually is joint by the improvement some of the neuropsychological function, thou it has been noted that a full recovery after ESES disappears is very rare. It is important to bear in mind that ESES merely represents an electrophysiological pattern of ‘near-continuous’ spike-wave discharges observed in sleep; the accompanying clinical signs and symptoms may differ with different syndromes for example, ESES is seen in both Landau Kleffner syndrome and CSWS – which are two different entities.

History: CSWS was first described by Patry et al. in six children with epilepsy who had ‘subclinical electrical status epilepticus’ induced by sleep to designate an EEG finding with subclinical spikes waves (SW) occurring during slow sleep that could last from months to years. These children did not demonstrate overt clinical manifestations; thus, the condition was described as “subclinical” or “electrical.” It was initially described condition as a form of encephalopathy given cognitive impairment in all children, and as more patients were described with this condition, it became clear that neurocognitive deterioration occurred at the same time as the electrical status epilepticus during slow wave sleep developed. Subsequently, the International League Against Epilepsy (ILAE) opted to term the condition “continuous spike and waves during sleep” (CSWS) as a specific epilepsy syndrome characterized by continuous diffuse spike-waves occurring during slow-wave sleep, seen after the onset of seizures, that has a potentially poor outcome despite a noncatastrophic onset of seizures, related to the development of neurocognitive deficits (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). ESES is now the term typically used to describe solely the electrographic findings, while the CSWS syndrome remains a clinical diagnosis of the constellation of neurocognitive deterioration from baseline, affecting motor, language, cognitive, or behavioral development, and a significant proportion of non-REM sleep disrupted by spike-wave discharges.

Clinically: According to ILAE, ESES syndrome is an auto limited disorder that is widely involved with the children ages, its main features are the following (Ribera, 2010): epilepsy with focal crisis and apparently generalized, partial motor seizures, neuropsychological deterioration by causing global or selective cognitive regression, motor deterioration such as ataxia, dyspraxia, dystonia or unilateral deficit and in the EEG pattern of spike waves occurring in 85% of deep sleep and this pattern to persist on three o more EEG records for at least a month The first neurological symptoms usually appear at a medium age of 4.4 years old while the epilepsy starts at the age of 6.5 years old. On a 117 patients study it was found that the average time of the persistence of the ESES on the EEG was 10 months, with a range between 2 to 37 months. Patients that present this pattern have also shown behavioral alterations such as hyperactivity, aggressiveness, depression, hypersonia, and hemineglect, abnormalities regarding this behavior has been found in different studies. A recent finding has established a relation between cortical malformations, specifically polymicrogyria and the appearance of ESES, because these patients’ neural connections remain normal, however they became horizontal which permits the progression of the electrical impulse faster thus generating the convulsive episode. This condition has been found in numerous studies, such as Carballo et al, where they found that the appearance of ESES was due to some structural abnormality and the most common abnormality was polymicrogyria. Neonatal thalamic hemorrhage has been associated as a risk factor to develop ESES, since the thalamus along with the cortex participates in the generation of spike-waves, even though there is still a debate whether it’s relative importance and the need of and intact thalamus-cortical circuit to the generation of these discharges.

Electroencephalographic findings: The electrical discharges in patients with ESES were predominant on the frontal region, which would explain the behavioral problems and also discharges in the perysilvian region which are associated with the language impairment. Slow waves during sleep on patients with ESES didn’t decrease from the beginning of the sleep until no REM sleep. This finding was predominant of the hemisphere on which the spike-wave activity was induced. Despite of this, the decrease of the contra lateral hemisphere was not statistically significant. The mode of the deficit responds to the site of the brain on which the decrease of the slope of the slow waves didn’t occur. The thicker the spike wave was, the more obstruct the decrease of the slope was. Spike waves discharge during the night and its propagation were associated to hyper metabolism, and some areas with hipo metabolism, probably

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associated with inhibitory functions. Hyper metabolism in ESES has been found in the central region and in the posterior parietal cortex and ind Landau-Kleffner Syndrome on the centroparietal superior gyrus.\(^{39}\)

**Molecular**: The dysfunction of the gen NHE6 (SCL9A6), which transcripts for an endosomal exchanger of Na\(^+\)/H\(^+\) it has been related with the predisposition to develop ESES, since this causes alkalosis in the cortex, hence promoting the neural excitability.\(^{37}\) Also bio molecular associations regarding CSWS and LKS have been linked with genes that also play an important role in autism such as genetic alterations in regions links ATP13A, CDH9, CDH13, CTNNA3, DIAPH3, MDGA2, SHANK3, which constitute regions that are related with rolandic epilepsy, and/or with impairment in language, and speech and most of those alterations related to autism disorders.\(^{38}\)

Also number variations in CHRNA7 and PCYT1B was found in patient with ESES however with different clinical characteristics, both related to the cholinergic pathway and the last one associated with the regulation on neuronal sprouting and branching.\(^{39}\)

**Forecast**: Just one third of the children with ESES have a long lasting favorable outcome without permanent cognitive impairment.\(^{30,42}\) The cognitive impairment has been directly associated with the period of duration of ESES.\(^{41}\)

**A typical benign partial epilepsy**

**Definition and clinical features**

ABPE is a special type of epileptic syndrome first described by Aicardi & Chevrie\(^{38}\) studied in the group of IFE, characterized by occurrence of generalized minor, simple focal, generalized tonic-clonic se, and rarely myoclonic seizures. That present a typical EEG with focal sharp waves that are identical to those of BECTS.\(^{43}\)

Because the clinical spectrum exhibits similarities to the Lennox-Gastaut Syndrome, the term pseudo-Lennox Syndrome was proposed by Doose et al.\(^{44}\) Also, according to the EEG findings the ABPE is considered an atypical variant of BECTS.\(^{44}\) The onset of seizures occurs between 2 and 6.5 years of age.\(^{44}\) Initially a period of typical rolandic seizures is followed by frequent atonic seizures, epileptic negative myoclonus (ENM), partial or generalized motor seizures as well as atypical absence seizures also occur, there is absence of developmental and neurological deficits prior to onset, focal epileptic EEG, abnormity during wakefulness and generalized continuous slow spike-waves during sleep, and favorable seizure and intellectual prognoses.\(^{47,48}\) Hahn et al reported ABPE patients with a delay in language development prior to the onset of epilepsy as well as on patients attending school for mentally handicapped children after remission of seizures.\(^{48}\) The ENM includes a brief postural lapse of one or both arms, dropping objects, instability during standing, and inclining of the body or falling down. Relative to the ENM, Akiko et al, found in their study that, performance intelligence quotients, decrease permanently if the period of active negative motor seizures is prolonged, whereas intelligence quotients are maintained if the period of active negative motor seizures is shorter.\(^{46}\) Typically the patient with ABEP has therapy resistance that has been associated to the involvement of the frontal cortex in EEG findings.\(^{47}\)

**Electroencephalographic studies**

The electroencephalogram of these patients shows typical bilateral rolandic spikes and spike-wave activity during drowsiness and sleep. Epileptic negative myoclonus is one of the characteristic seizure pattern in ABPE,\(^{46}\) this is defined as an interruption (lasting 50-400 ms) of tonic muscular activity, time-locked to a spike or to a sharp wave in the area of the contralateral centroparietal cortex on EEG without evidence of a previous myoclonus.\(^{52}\) Javadini et al found in a retrospective study that 61% of patients showed frontal sharp wave foci, that are typical of ABPE.\(^{51}\) Also is characteristic the tendency toward generalization while awake or asleep and possibly an extremely irregular pattern similar to that of hypsarrhythmia.\(^{41}\)

**Bio molecular**

Hereditary impairment of brain maturation represents the common basic mechanism shared by BECTS, ABPE, Landau-Kleffner syndrome and EECSWS.\(^{43}\) Lemke and collaborators found mutations in gene GRIN2A that encodes the a2 subunit of the N-methyl-D-aspartate (NMDA)-selective glutamate receptor that affected patients with the whole spectrum of IFE including ABPE.\(^{51}\) Specifically, a missense alteration p. Ala243Val demonstrated impaired reduction of receptor by low concentrations of Zn\(^{2+}\), suggesting increased activation of the NR1-NR2 Aheteromer due to reduced high-affinity Zn\(^{2+}\) -mediated inhibition in vivo. This results in a higher susceptibility to repeated activation and enhanced Ca\(^{2+}\) influx.\(^{55}\)

**Benign epilepsy with centrotemporal spikes**

**Definition**

BECTS or Rolandic epilepsy is the most common epileptic syndrome during childhood (children aged 3-13 years). It resolves spontaneously before 15 years of life. “Rolandic” refers to the rolandic area of the brain, which is the part that controls movements. This type of idiopathic and focal epilepsy disappears during adolescence without leave consequences and that is the reason of the term “Benign”. Children with BECTS have normal IQ. There is a 1:5 male predominance, prevalence is around 15% in children aged 1–15 years with non-febrile seizures and incidence is 10–20/100,000 children aged 0–15 years. There is an incidence around 14-24% of newly diagnosed epilepsy in children before 15 years of life. It always begins after 2 years of age (with a peak incidence at age 8 and disappears before 16 years of age).

**History**

People believe that Rolandic epilepsy is named due to the anatomical region of the brain, but the real name came from Martinus Rulandus, who gave the first known details of the condition in 1597 based on studies of an abnormal disease in a boy that nobody would classify as a rolandic seizure. In 1941 the electroencephalograph was invented and it was used to identify people with epilepsy. Then, Gastaut noticed the spikes in the pre-rolandic area in children; this information was taken by Nayrac y Beaussart and they established that there was a relation between the seizures described by Rulandus and the spikes in the rolandic area during these electroencephalograph, this allowed appearing the name of “Rolandic Epilepsy”. Until the 1990s, the principal characteristic of this disease was the electroencephalograph pattern, then Ute Staden (pediatrician, Germany), studied 20 children with BECTS and he noticed that all of them shared a similar way to speak and language.\(^{1}\)

**Clinical**

In rolandic epilepsy seizures are usually brief and occur during sleep or while the child waking up in the morning, are described as
hemi facial sensor motor manifestations and pharyngeal accompanied by hemi body motor seizures. The children have tonic deviation of the angle lips, clonic contraction of one side of the mouth and increased salivation with gurgling noises. The episodes last between 1-2 minutes and consciousness and memory of the episode is preserved in 50% of cases. In more than 50% of patients seizures occur during sleep and these patients do not present any disability or neuronal injury explaining that they are not usually diagnosed.

The seizure may also involve the throat, which may cause the child’s speech to be unclear and therefore difficult to understand. The child may make strange throaty or gurgling noises, and it is often this which alerts parents that something may be wrong. The child often knows what they want to say but cannot speak properly. The seizure can have tonic movements or clonic movements of one side of the face, and then those movements spread to the arm or to the leg, usually on the same side as the movements in the face. Many children lose consciousness, becomes stiff, this is called a tonic-clonic seizure, that is generalized affecting both sides of the brain. After the seizure, many children return to sleep.2

Electroencephalographic findings

The spikes are localized in the C3 and C4 or C5 and C5 suprasylvian electrodes and not in the temporal electrodes. Centrtemporal spikes are bilateral and activated by slow sleep (non-REM). Centrtemporal spikes are diagnostic markers of BRECTS only when there is a clinical presentation. It is important to know that the frequency, location and persistence do not guide the clinical manifestation, frequency and severity of the seizures. Centrtemporal spikes are not specific of BRECTS as the 2-3% of normal school-aged children giant somatosensory evoked spikes. Occur in many types of organic brains disease, for example: cerebral tumours, Rett syndrome, fragile X syndrome, focal cortical dysplasia and others. It is well establish that somatosensory stimulation is one of the factors of activation of centrtemporal spikes and evokes giant somatosensory evoked spikes. The GABA ergic stimulation produces an slow activity on the EEG (10-20%), so during severe stages of BECTS, cortical inhibition is powerful enough to start the epileptic activity.54

Molecular basis

It's known a genetic susceptibility that tries to explain the etiology, however this genetic susceptibility can’t explain all the factors and causes of the syndrome. The gene locus is located on chromosome 15q14 and it is in charge of encoded for the KCN3 Cl-K- co transporter, essential for the neuronal excitability regulation. In Rolandic epilepsy, this gene is altered causing an extra cellular K+ accumulation and subsequent GAB Aergic inhibition decreasing the inhibitory factor of these cells on the central nervous system.55

Panayiotopoulos syndrome

PS is childhood epilepsy that has a characteristic autonomic symptoms and the crisis occur usually during sleep, that is why often is misdiagnosed with another epileptic syndromes or pathologies or simply remain without a diagnosis. Affects otherwise normal children, the onset is usually at 4 years old, the EEG shows occipital spike-wave paroxysms. The prognosis is excellent; it is self-limited and often does not required antiepileptic drugs.26,57

Epidemiology

Represents the 13% of all epilepsies in children between 3 and 6 years old, and the 6% in 1 to 15 years old.58-61 The patients may have or not family history of convulsive disorder or febrile convulsions.60 Approximately 87% of the cases, the symptoms begins before the age of 8,61 and 76% starting between 3 and 6 years.62 Is thought that at least 2 to 3 in 1000 children may be affected, and whether cases that are nowadays considered to have atypical features are included, these numbers could be higher.63,64 It’s considered the most common specific cause of non-febrile, non-convulsive status epilepticus in childhood.65

History

The first approach to this syndrome was in 1988-1989 when C. Panayiotopoulos described a new type of epilepsy that he named as “Benign Nocturnal Childhood Occipital Epilepsy”, it’s main characteristics was define as a ictal triad of nocturnal seizures, tonic deviation of the eyes, and vomiting.66,67 But this wasn’t the first description of occipital epilepsies, previously in 1982, Gastaut described seizures with visual symptoms mainly or companied by hemiclonic movements, automatisms or headache; the EEG showed high-amplitude spike waves in the occipitoposterotemporal part meanwhile the eyes were closed and in a interictal period; later, the ILAE classified as “Gastaut type of childhood occipital epilepsy”.68 Panayiotopoulos initially described 24 children with ictal vomiting, 12 of that children had an EEG that showed occipital spikes and another 9 had extraoccipital spike or normal EEG (the other 3 patients had brain damage).66,67 Posteriorly ILAE proposed the descriptive term “early onset benign childhood occipital epilepsy”, but most authors decided use the eponym “Panayiotopoulos syndrome”.68 In the ILAE Revised Terminology for Organization of Seizures and Epilepsies 2011 – 2013 was decided eliminated the term “benign”.69

Clinical presentation

The beginning occurs usually in the early childhood (3 to 6 years) in the 76% of the cases.67,68 Usually these patients have not a relevant previous familiar or personal history. 17% have typical febrile seizures. Both sexes are affected in the same way, no ethnic preference.70 In the 66% of the cases the crisis are during sleep, the main symptoms is vomiting (80%), and another autonomic manifestations like pallor (28%), incontinence of urine (19%) and faeces (3%), hyper salivation (10%), cyanosis (12%), mydriasis (7%), miosis (2%), coughing, abnormalities of intestinal motility (3%), breathing and cardiac abnormalities could be higher than reported. Cardio respiratory arrest has been reported (0,4%-0,5%).73 The consciousness is usually preserved at the beginning of the crisis but lose it posterior.71,74 The symptoms can last 5 to 10 minutes, but in the 50% of the patients reach an autonomic status epileptics (30 minutes or more).75 The autonomic symptoms are the main characteristics of the syndrome but not the only ones. There are ictal behavioral changes (agitation, terror, quietness), and non-autonomic symptoms (deviation of the eyes or eyes opening, hemi facial convulsions, visual hallucinations, generalized convulsions, Jacksonian marching) that can occur in combination with other autonomic manifestations. Pure autonomic seizures and pure autonomic status epilepticus is relatively rare, occur in approximately 10% of patients. They start and terminate usually only with autonomic symptoms.57,58

Differential diagnosis

PS’S differential diagnosis have to be made with another pathologies or epileptic syndromes that can be presented with similar symptoms. These are acute encephalitis, migraine, syncope or gastroenteritis and
structural origins focal epilepsy.  Childhood occipital epilepsy of Gastaut and PS are wide different in their symptoms but there are still some physicians that can confound them. Is more common the overlapping with rolandic epilepsy than with other epileptic syndrome. Like with other syndromes, could exist atypical cases that may be difficult to diagnose.

Prognosis

The prognosis is excellent, the remission occurs after 1 or 2 years. Most of patients present 1 or less than 5 crises until remission. Only 25% of the cases have very frequent and prolonged seizures. 20% can develop Rolandic epilepsy or age-related epilepsy that remit. Atypical evolution is rare. The risk for adult epilepsy is the same for the general population. Antiepileptic drugs are usually not need in a unique crisis, but could be necessary in cases of multiple crises.

Electroencephalographic findings

The EEG pattern of the PS is usually describe with occipital spikes but the 80% of the patients have multifocal spikes (parieto-occipital, calcarine, central sulci or frontal lobes) but with occipital predominance that can shift from one region to another in the same child. Isolated routine EEG is normal in 10% of the patients, frequently is necessary a continuous sleep recording to detect the abnormalities. Sleeps increase the spikes aberrations. The prognosis of the seizures seems to be a favorable despite of EEG pattern.

Genetic characteristics

Currently there is not a clear etiology of the syndrome, but genetic cause is suspected. Several studies had been tried to find a specific gene related with PS, but without succeed. One of the suitable genes is SCN1 gene (encodes for alpha1 subunit of neuronal sodium channel, it has been associated with Dravet Syndrome and generalized epilepsy with febrile seizures plus). But like Martin del Valle et al suspect that this gene could be not the origin of PS but can be related with its severity. It’s necessary more research in this field (Figure 1). It is important to highlight that these different epileptic syndromes develop in childhood in a different way, and it is essential to determine early the appearance of the symptoms, the importance of a characteristic electroencephalographic tracing and the degree of clinical deterioration that the patient may have. Figure 1 presents a summary of the previous information, showing how the evolution and follow-up of the affected child depends on their clinical evolution, the degree of deterioration in their cognitive functions, as well as the time, allowing to understand which of these syndromes can be more aggressive (despite being called benign) and which of them even have similar genetic origins.

Conflict of interest

As the author of this article I declare that I do not have any financial interest or any conflict of interest.

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