Main Electroclinic Syndromes of The Infant: A Literature Review

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Main Electroclinical Syndromes of The Infant: A Literature Review

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Abstract
An electroclinic syndrome (also known as epileptic syndrome) consists of a set of characteristics that associate with seizures, characteristics of electroencephalography and imaging that tend to occur together. Among them is a group that affects infants, usually having a genetic etiology. Objective: to carry out a literature review on the most common types of infant electroclinical syndromes, describing their main characteristics.

Methodology: This is a narrative review of the literature of articles published between 2005 and 2020, in Portuguese and English. The research was carried out in December 2020. The following descriptors were used to search for the articles: Electroclinical syndromes. Epilepsy. Infant.

Results: Through the research carried out, 12 scientific articles were selected, nine of them in English and three in Portuguese.

Conclusion: The study identified 7 common electroclinical syndromes in infants and made it possible to conclude that knowledge of the clinical profile, types of crises and characteristics of the electroencephalography of the disease phenotype associated with the specific mutation can help improve the accuracy and management of the diagnosis of electroclinical syndromes.

Keywords: Epileptic Syndromes; Epilepsy; Infant.

1. Introduction
An epileptic syndrome (or electroclinical syndrome) refers to a set of features that incorporate types of seizures, electroencephalography (EEG) and imaging characteristics that tend to occur together. It often has age-dependent characteristics. It may also have distinct comorbidities, such as intellectual and psychiatric dysfunction, along with specific findings in EEG and imaging studies. It may have associated etiological, prognostic and treatment implications, but it is important to note that epilepsy syndrome does not have an individual correlation with an etiological diagnosis and serves a different purpose, such as guiding treatment (Gürsoy and Erçal, 2016; Scheffer et al., 2017).

An epileptic seizure (EC) can be described as the clinical expression of an abnormal, excessive, in chronic discharge into neurons that are basically located in the cerebral cortex. This paroxysmal activity is intermittent and usually self-limited, lasting from seconds to a few minutes (Da Silva et al., 2013). When prolonged or recurrent it is characterized as a state of epileptic disease (E) (Fisher et al., 2014). Epilepsy (or convulsion) means the repetition of two or more unprovoked ECs. The term "unprovoked" indicates that EC was not caused by fever, head trauma, hydroelectrolytic alteration, toxic disorders, or concomitant disease. Seizures caused are those that occur in the presence of a specific circumstance, using only if the acute cause remains, not characterizing epilepsy (Da Silva et al., 2013).

In other words, epileptic syndromes are a generalized term and means a chronic disease is already installed.
Its main clinical feature is recurrent epileptic seizures. That is, epileptic seizures are the most common clinical manifestations of epileptic syndromes. In addition, epileptic syndromes are classified considering the topographic axis (related to location, which may be generalized or focal) and the etiological axis (idiopathic, symptomatic and cryptogenic) (Brazil, 2018).

Early-onset electroclinical syndromes represent a significant diagnostic challenge and a large proportion of cases still remain unexplained (Allen et al., 2016). Understanding the implications of a specific syndrome diagnosis helps support families who are often burdened by the diagnosis of epilepsy in their children (Carney et al., 2005).

A number of epilepsy syndromes develop in childhood, and accurate identification of the type of seizure and correlation with EEG findings provide important prognostic and management information for families with a child with epilepsy. Many childhood epilepsy syndromes are promptly treated and have an excellent prognosis. Therefore, the knowledge of the main electrolyte syndromes in the infant as well as the clinical characteristics of these syndromes, together with an accurate and early diagnosis can improve the psychosocial impact of these disorders on children and their families (Carney et al., 2005).

In view of the above, the aim of this study was to conduct a literature review on the most common types of electroclinical syndromes of the infant, describing their main characteristics.

2. Methodology

The study was developed through a narrative bibliographic review of the literature, whose data were researched in scientific articles, which were selected from the Databases PubMed, Virtual Health Library and Google Scholar, and selected articles published between the years 2005 and 2020, in the Portuguese and English languages.

3. Results and Discussion

In the research conducted, 12 scientific articles were selected, nine of them in The English language and three in the Portuguese.

Table 1 presents a synthesis of the most common electroclinical syndromes of the infant and their main characteristics, based on data extracted from the study by Plouin (2017).

<table>
<thead>
<tr>
<th>INFANT ELECTROCLINICAL SYNDROMES</th>
<th>SPECIFIC CLINICAL CHARACTERISTICS AND MANIFESTATIONS</th>
</tr>
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<tbody>
<tr>
<td>Benign family epilepsy of the infant</td>
<td>Its clinical manifestation consists of epileptic spasms, myoclonic seizures, focal crises, generalized tonic crises, generalized tonic-clonic seizures (TCGs) and absences. Epileptic spasms consist of axial contractions that may occur in flexion, extension, or both, and may be symmetrical or asymmetrical.</td>
</tr>
</tbody>
</table>
**Main Electroclinic Syndromes of The Infant: A Literature Review**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
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<tbody>
<tr>
<td>Asymmetry</td>
<td>Asymmetry may involve the limbs, head, and videoelectroencephalography (VEEG) is usually required for detailed analysis. Contractions are brief and occur in clusters (together) and last about 1 to 2 seconds, reaching their maximum more slowly than the myoclonic crisis and faster than the tonic crisis.</td>
</tr>
<tr>
<td>Myoclonic epilepsy of the infant (EML)</td>
<td>Involuntary, rapid, arrhythmic and abrupt movements. The muscles that usually move are those of the cervical region, arms and shoulders and can cause extension or flexion. They may manifest slightly or intensely, symmetrically or not, involving the whole body or regionally or localized. There may be a change in consciousness. Crisis tonics or absences are never observed. Myoclonus represents the only type of crisis, except for the presence of febrile crises or rare TCG crises in adolescence.</td>
</tr>
<tr>
<td>Benign epilepsy of the infant</td>
<td>The main clinical signs are seizures of eye clonias, eyelids, head and eye deviation, unilateral clonias, body movements, behavioral parade, and unilateral or bilateral hypertonia.</td>
</tr>
<tr>
<td>West syndrome</td>
<td>It presents the following triad: infantile spasms, hypsarrhythmia and developmental stop or regression. It is characterized by an interictal electrographic pattern composed of slow waves and spicules of anarchic projection and high voltage, extremely variable duration and location, practically continuous and, in most cases, present in both wakefulness and sleep. Spasms with focal EEG abnormalities may occur, evolving with partial epilepsy with or without hypsarrhythmia.</td>
</tr>
<tr>
<td>Epilepsy of infants with migratory focal attacks</td>
<td>They occur between 24 days and 10 months (average approximately 4.5 months), being almost continuous, evolving with clinical deterioration and alternating with crisis-free periods. There is good electroclinical correlation according to the topography of discharges and a complex combination of simultaneous focal crises, which may affect a single hemisphere for several months, and without VEEG, seizures are often unnoticed. During the period from 1995 to 2005, 27 cases were reported; in most recent cases, the prognosis has been less severe, although seizures are intractable over the</td>
</tr>
</tbody>
</table>
Myoclonic encephalopathy in non-progressive disorders:

Subtype of EML. Occurs during the first or second years of life in a normal child, who often has a family history of epilepsy or seizures. Seizures are characterized by being frequent, brief, usually symmetrical, isolated or grouped into clusters, involving the axial muscles of the body and limbs, exacerbated by drowsiness.

Dravet syndrome:

Dravet syndrome or severe myoclonic epilepsy of the infant occurs in a previously normal child, who may have presented febrile, unit or bilateral crisis before 1 year of age. Massive myoclonus occurs during the second and third year of life, progressive mental deterioration, often evolving to a state of epileptic disease and refractory epilepsy. Myoclonus occurs preferably upon awakening, or preceding a GCT crisis, are usually grouped, predominantly axial, and can cause fall to the ground and throw to the ground of objects of the hands. There may be distal erratic myoclonus at rest, which are exacerbated by.

In 1983, in Marseille, France, an international convention was held to discuss and classify electroclinical (epileptic) seizures and syndromes. Before that, still in the 1970s, there were already reports of some electroclinical syndromes of the infant, including early myoclonic epilepsy (EMP), early epileptic encephalopathy of the infant (EPL) and Ohtahara syndrome (neonatal onset). At the time, there were some important aspects in this field, because it was unusual to perform videoelectroencephalography (VEEG) and, also, there was no use of muscle electrodes. Thus, there was no way to differentiate or classify epileptic seizures by tracing, and there were no imaging tests available for this, such as computed tomography of the skull and/or magnetic resonance imaging (Plouin, 2017).

Thus, the only way to characterize epileptic seizures was anamnesis. To classify an electroclinical syndrome, it is necessary to detail its semiology, because only in this way is the patient's disease better understood. Once, it was common for parents to describe only the most exuberant characteristics related to crises, which led the clinician to classify their majority as generalized, however, when the evaluation was made through VEEG, it was found that in fact, the majority was a focal crisis (Plouin, 2017).

Researchers performed an analysis of 90 neonates who were evaluated by VEEG for three hours, and it was observed that the period in which there is a higher risk of developing the first crisis is in their first week of life, and it was verified that 76 children belonging to this studied group presented crises. With this, it is believed that crises in this period of life occur as a result of the transition that is made of the gabaergic system (from excitatory to inhibiting), although it is not yet known exactly when this occurs (Plouin, 2017). In this population of the aforementioned study, cases with the Ohtahara syndrome (7 cases), EMP (5 cases) and 2
cases of neonatal seizures benign familial seizures (CNFBs), 2 benign non-familial neonatal seizures (CNNFBs) and 2 of epilepsy with migratory partial seizures of the infant (Plouin, 2017).

The etiology of epilepsies is divided into six subgroups, selected because of their potential therapeutic consequences. A new terminology has been introduced, such as epileptic and developmental encephalopathy. The term benign was replaced by the terms self-limited and responsive to medications, for use where appropriate (Scheffer et al., 2017).

Regarding this classification of electroclinical syndromes, Scheffer et al. (2017) describe the six types of etiologies: 1) Structural: that is when a structural abnormality has a substantially increased risk of being associated with epilepsy (e.g., visible abnormalities in structural neuroimaging); 2) Genetics: results directly from a genetic mutation, in which seizures are a central symptom of the disorder; 3) Infectious: when epilepsy occurs as a result of an infection (e.g., meningitis or encephalitis); 4) Metabolic: results directly from a known or presumed metabolic disorder in which seizures are a central symptom of the disorder (e.g., portileia, uremia, amino acid-acidopathies, or pyridoxine-dependent seizures); 5) Immune: when seizures are derived from inflammation of the central nervous system mediated by autoimmunity; 6) Unknown: when the cause of epilepsy is not yet known. In this category, it is not possible to make a specific diagnosis beyond basic electroclinical semiology, such as frontal lobe epilepsy. Furthermore, the extent to which a cause can be found depends on the extent of the evaluation available to the patient.

The most common electroclinical syndromes that may affect children in the neonatal period are: 1) Benign familial neonatal epilepsy; 2) Ohtahara syndrome; 3) Early myoclonic encephalopathy. In the infant phase: 1) Benign family epilepsy of the infant; 2) Benign epilepsy of the infant; 3) Myoclonic epilepsy of the infant; 4) West syndrome; 5) Epilepsy of infants with migratory focal attacks; 6) Myoclonic encephalopathy in non-progressive disorders; 7) Dravet syndrome. In childhood: 1) Panayiotopoulos syndrome; 2) Febrile crises plus (but these may begin in the infant); 3) Epilepsy with atonic (previously astatic) myoclonic seizures; 4) Occipital epilepsy of late-onset childhood (Gastaut type); 5) Nocturnal autosomal-dominant epilepsy of the frontal lobe; 6) Benign epilepsy with centrotemporal discharges; 7) Epilepsy with myoclonic absences; 8) Landau-Kleffner syndrome; 9) Epileptic encephalopathy with continuous spicule-wave during sleep; 10) Lennox-Gastaut syndrome; 11) Epilepsy absence of childhood (Guilhoto, 2011).

Accurate diagnosis is often difficult, and most patients go through many investigations, including brain imaging and neurophysiological, blood, cerebrospinal fluid and urine tests, and sometimes more invasive tests such as liver and muscle biopsies (Chemaly et al., 2018; Gürsoy and Erçal, 2016; McTague et al., 2016). Some may have even faced epilepsy surgery with varying benefits and later received a genetic diagnosis, which, if already known before, could have affected the decision to proceed with the surgery. Finding a cause can save the family from further distress and the child from ongoing investigations. With a diagnosis, the family can start to learn about the disease, its comorbidities and prognostic implications, which allows planning the long-term care of their children and early access to services and therapies (McTague et al., 2016).

The classifications of epileptic seizures and epilepsies began to be documented by the International League Against Epilepsy (ILAE) in the 1960s, which generated the Classifications that were most used until a few
years ago, which are the 1981 and 1989 Classifications. According to these classifications, seizures were divided into focal or generalized, according to their form of onset, or in a specific region in the brain or bilateral. The etiology of epilepsies was then considered idiopathic, symptomatic or cryptogenic (Guilhoto, 2011). Thus, electroclinical syndromes could be classified according to their location (i.e., focal or generalized), their etiology (such as idiopathic or non-idiopathic) and age of onset. However, symptomatic or cryptogenic focal epilepsies, such as those caused by cortical dysplasias, can appear at any age without knowing why. Those patients in the group of focal epilepsies present only focal crises, while those in the generalized group may present both focal and generalized seizures (Plouin, 2017).

Over the years and due to the technological advances, that have emerged, such as veeg, which allowed a better knowledge of the ictal manifestations (i.e., the manifestations of seizures), new classification proposals began to be disseminated by ILAE at the beginning of the 19th century. XXI, culminating in innovations in knowledge in the areas of imaging and molecular genetics. Since the publication of this document, numerous nosological aspects have been discussed by the scientific community in relation to this area of epilepsy (Guilhoto, 2011).

A study conducted by McTague et al. (2016, p.1) concluded that “With the molecular revolution, the number of known monogenic determinants underlying epileptic encephalopathies grew rapidly. New dominant mutations are often identified; Somatic mosaicism and recessive disorders are also seen. Several genes can cause an electroclinical syndrome and, conversely, a gene may be associated with phenotypic pleiotropy. Several genetic causes and molecular pathways have been implicated, involving ion channels and proteins necessary for the synthesis, regulation, and development functions. The discovery of the gene provides the basis for neurobiological perceptions, often showing the convergence of mechanistic pathways. These findings underpin the development of targeted therapies, which are essential to improve the outcome of these devastating diseases.”

As a course, the ILAE Classification of Epilepsies has been updated to reflect the gain in the understanding of epilepsies and their underlying mechanisms, following the main scientific advances that have occurred since the last classification ratified in 1989. As a critical tool for the practicing clinician, the classification of epilepsy should be relevant and dynamic according to the changes of scientific thinking, besides being robust and translatable for all areas of the planet. The main objective of the tool is patient diagnosis, disease research, the development of antiepileptic therapies and worldwide communication (Scheffer et al., 2017).

The new classification stems from a draft document submitted for public comment in 2013, which was revised to incorporate broad feedback from the international epilepsy community into several rounds of consultation. It has three levels, starting with the type of seizure (focal, generalized, combined and unknown epilepsy group), in which it assumes that the patient is having epileptic seizures, as defined by the new ILAE Seizure Classification of 2017. After diagnosis of the type of seizure, the next step is the diagnosis of the type of epilepsy, including focal epilepsy, generalized epilepsy, combined generalized and focal epilepsy, and also an unknown group of epilepsy (Scheffer et al., 2017).

The third level is that of electroclinical syndrome, where a specific syndrome diagnosis can be made. The new classification incorporates etiology throughout each stage, emphasizing the need to consider the etiology at
each stage of diagnosis, as it often has significant implications for treatment (Scheffer et al., 2017).
There is a group of childhood electroclinical syndromes that are called epileptic encephalopathies, characterized by recurrent clinical crises and prominent interictal epileptiform discharges, seen during the initial infant period, being associated with impaired cognitive, sensory and motor development. Approximately 40% of seizures occur during the first 3 years of life. Although epileptic encephalopathies are mainly associated with structural defects in the brain and inherited metabolic disorders, pathogenic genetic mutations may also be involved in the development of this disease, even when there are no clear patterns of genetic inheritance or consanguinity (Gürsoy and Erçal, 2016).

The most common epileptic encephalopathies are Ohtahara syndrome, early myoclonic encephalopathy, childhood epilepsy with migratory focal seizures, West syndrome, and Dravet syndrome, which generally do not respond to the traditional antiepileptic drug. Many diagnoses describe the phenotype of these electroclinical syndromes, but not the underlying causes. To date, approximately 265 genes have been defined in epilepsy and several genes, including STXBP1, ARX, SLC25A22, KCNQ2, CDKL5, SCN1A and PCDH19, have been associated with early epileptic encephalopathies, and many of these genes are potentially involved in brain development and function (Gürsoy and Erçal, 2016).

4. Conclusion
This study allowed the authors to delineate the most common Electroclinical Syndromes in infants as well as to describe their main clinical characteristics. When researching the electroclinical syndromes of the infant, it is verified that they are a condition that causes great dismay and concern for parents, being fundamental the knowledge of the characteristics of the Syndromes combined with an accurate and early diagnosis. Currently, data on the etiopathogenesis and genetic basis of some of these syndromes have been progressively improved and expanded, and the detection of the genes responsible translates into importance in the treatment of the disorder and in the selection of therapy. In addition, the prognosis of diseases can be better estimated and help identify families who may benefit from referral for genetic counseling.

Knowledge of the clinical profile, types of seizures, and EEG characteristics of the disease phenotype associated with the specific mutation can help improve diagnostic accuracy and management. In cases where electroclinical findings are obscure, genetic panels directed to epilepsy would be an economical alternative to the sequencing of individual genes for the genetic diagnosis of the syndrome.

After all, gene discovery provides the basis for neurobiological insights, usually showing convergence of mechanistic pathways, and these findings support the development of targeted therapies, essential to improve the outcome of these devastating disorders.

5. References

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