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West Syndrome: from etiology to prognosis

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West Syndrome: from etiology to prognosis

Síndrome de West: da etiologia ao prognóstico

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ABSTRACT

The West syndrome is an epileptic encephalopathy in the child's first year of life, corresponding to 1.4% of the epileptic syndromes in pediatric age. It is characterized by the triad: 1) epileptic spasms, 2) hypsarrhythmic tracing on the electroencephalogram (EEG) and 3) neurodevelopment regression. It affects both sexes, with a higher incidence in males. The syndrome's etiology is diverse, including genetic, structural, metabolic, infectious, immunological and still unknown causes, which is why its diagnostic complexity is not negligible. Neonatal hypoxic-ischemic encephalopathy is one of the most frequent etiologies, but extensive genetic, structural and metabolic investigation is often necessary for a correct etiological diagnosis. The epileptic spasms accompanying this pathology are sometimes brief and subtle and are often confused with abdominal cramps or episodes of gastroesophageal reflux, which delays the recognition of this syndrome. At diagnosis, it is possible to document ictal and interictal epileptic activity on the EEG that occurs in an early period of brain maturation, which is why it is the cause of significant cognitive impairment. The prognosis is variable, according to the etiology, the age of onset, the age of diagnosis, the therapy instituted and the response to therapy.

In about two thirds of cases, the prognosis of West Syndrome is reserved, with progression to Lennox Gastaut syndrome and/or association with Autism Spectrum Disorder.

The identification of the etiology can play a crucial role, since it provides information that should be considered in the selection of the most effective antiepileptic therapy. Some etiologies respond better to specific medications and may show a worse response with others. The unfavorable prognostic impact of this encephalopathy will depend, among other factors, fundamentally on the etiology, on an early diagnosis of the encephalopathy and will certainly benefit from a therapeutic approach as directed as possible.

Keywords: Infantile Spasms; West syndrome; epileptic encephalopathy; etiology; therapeutics; prognosis.

RESUMO

O Síndrome de West é uma encefalopatia epilética do primeiro ano de vida da criança, correspondendo a 1,4% dos síndromes epiléticos, em idade pediátrica. Caracteriza-se pela tríada de espasmos epiléticos, traçado hipsarrítmico no eletroencefalograma (EEG) e paragem/regressão do neurodesenvolvimento. Atinge ambos os sexos, com maior incidência no sexo masculino. A etiologia do síndrome é diversa, incluindo causas genéticas, estruturais, metabólicas, infeciosas, imunológicas ou ainda desconhecida, pelo que lhe está associado uma complexidade diagnóstica não negligenciável. A encefalopatia hipóxico-isquémica neonatal é uma das etiologias mais frequentes, mas é muitas vezes necessária extensa investigação genética, estrutural e metabólica para um correto diagnóstico etiológico. Os espasmos infantis que acompanham esta patologia apresentam-se por vezes breves e subtis, sendo frequentemente confundidos com cólicas abdominais ou episódios de refluxo gastroesofágico, o que leva a algum atraso na identificação deste síndrome. Ao diagnóstico, é possível documentar atividade epilética ictal e interictal no EEG que ocorre num período precoce de maturação cerebral, sendo, por isso, causa de importante atraso no neurodesenvolvimento. O prognóstico é variável, de acordo com a etiologia, a idade de início e de diagnóstico, a terapêutica instituída e sua resposta. Em cerca de dois terços dos casos, o prognóstico do Síndrome de West é reservado, com evolução para síndrome Lennox Gastaut e/ou associação a perturbação do espectro do autismo. A identificação da etiologia pode desempenhar um papel crucial, uma vez que fornece informação que pode e deve ser considerada na seleção da terapêutica antiepilética mais eficaz. Algumas etiologias respondem melhor a medicações específicas e poderão mostrar pior resposta com outras. O impacto prognóstico desfavorável desta encefalopatia dependerá, entre outros factores, fundamentalmente da etiologia, do diagnóstico precoce da encefalopatia, beneficiando certamente de uma abordagem terapêutica o mais dirigida possível.

Palavras chave: Espasmos infantis; síndrome de West; encefalopatia epilética; etiologia; terapêutica; prognóstico.

INTRODUCTION

The West syndrome (WS) is a subgroup of a broader clinical entity called Infantile Spasms (IS). [1] It is important to distinguish West Syndrome from IS. IS are a form of severe epilepsy, age dependent, which arises primarily during the first year of life. [2] They are characterized by epileptic spasms, often accompanied by psychomotor development regression and hypsarrhythmia on the EEG. The term West Syndrome is used when these three characteristics are presented simultaneously.[3)] [4]

IS are a clinical entity that include a type of pathognomonic seizure - spasms (in clusters or isolated), presenting interictal epileptiform activity on the EEG (not necessarily hypsarrhythmic). IS can occur with or without interictal hypsarrhythmia and with or without regressing psychomotor development. West syndrome is characterized by a classic triad: infantile spasms that appear in clusters, presenting hypsarrhythmia on the EEG and concomitant or subsequent psychomotor regression or delay. Infantile spasms syndrome is often referred to as West syndrome. According to the international West Delphi consensus, the presence of hypsarrhythmia is not essential for the diagnosis of IS, which emphasizes the role of the ictal event as an electrodecrement on EEG, in a child under two years old.[5] [6]

The clinical diagnosis and the determination of the prognosis of seizure disorders that present in the first year of life is complex. Indeed, the occurrence of epileptic phenomena is relatively common during childhood, translating abnormal and excessive neuronal electrical activity, with consequent motor and/or sensory alterations. The prenatal, neonatal and first year of life are critical periods of brain development, crucial in the processes of dendritic arborization, axonal myelination and establishment of neuronal synapses. Seizures that occur during this critical period can have undesirable consequences on brain development, which can lead to psychomotor developmental delay. There are seizures in the first year of life, such as Self-limited Neonatal Familial Epilepsy, Simple Febrile Seizures or Acute Symptomatic Seizures, which have a benign course and usually have a good prognosis.[7] However, there are also seizures in the first year of life that have a poor prognosis, showing resistance to therapy and causing impairment of brain development. These are the so-called epileptic encephalopathies that constitute, according to the International League Against Epilepsy (ILAE) definition: “a group of disorders based on the notion that epileptic activity *per se* can contribute to a serious neuro-cognitive and behavioral dysfunction, above and beyond what it would be expected only from the underlying pathology.” [7][8][9] West Syndrome and Infantile Spasms constitute epileptic encephalopathies, once they fulfill the criteria by which epilepsy *per se* determines neurodevelopmental delay and intellectual disability.

WS/IS have a gloomy prognosis: varying with the underlying etiology, which is not always identified.[8] They are refractory to conventional antiepileptic drugs. Still, there is evidence that children with WS have a better prognosis if both the diagnosis and the treatment response are precocious. [7][2] This syndrome is characterized by the onset of epileptic spasms between 3 months and 12 months of age. A later onset may occur, although it is rare after 18 months of age. Epileptic spasms, the type of seizure characteristic of this clinical entity, occur more frequently on awakening and in the early stages of sleep. Its occurrence does not usually appear in response to common triggering factors in other forms of epilepsy, such as food, light stimulus or loud noise. Children may have no clinical history or, on the contrary, may show antecedents of a basic pathology, such as trisomy 21, neurocutaneous syndromes such as tuberous sclerosis or acquired brain changes, such as hypoxic ischemic encephalopathy (HIE), one of the most frequent acquired etiologies. Family history is rare, occurring in 3 to 6% of cases.[4] In some cases, children with Ohtahara's syndrome and other epilepsies with an even earlier onset (usually focal epilepsies) may progress electroclinically to WS at 3 to 4 months of age. In about two thirds of the cases, the West Syndrome prognosis is reserved, with evolution to Lennox Gastaut Syndrome[10] and/or association with Autism Spectrum Disorder (ASD), with future intellectual or motor deficits.

The present work provides information about this encephalopathy, aiming to gather the evidence from the last years, documented in guidelines and consensus on clinical therapeutic protocols considered effective and recommended. At the same time, it seeks to collect research on the numerous underlying pathologies expressing Infantile Spasms throughout its natural history. New therapeutic approaches depending on the underlying etiology must be explored, in order to improve the unfavorable prognosis of this encephalopathy.

PURPOSES AND METHODS

The main objective of this review is the presentation of a disorder belonging to the clinical spectrum of epilepsies in the first year of life, which constitutes an epileptic encephalopathy: West Syndrome. We address epidemiology, clinical presentation, treatment and prognosis, with emphasis on the importance of etiological diagnosis in its early therapeutic approach. It is known that etiology is one of the main determinants of this syndrome's prognosis, nevertheless the pathophysiological mechanisms involved in this epileptic encephalopathy are still far from being fully understood. Is it, as it has been proposed, a mechanism in which all the etiologies converge, or, alternatively, are the mechanisms plural?

This epileptic syndrome does not respond to traditional anticonvulsant drugs. Currently, hormonal therapy with adrenocorticotropic hormone (ACTH), corticosteroids, vigabatrin and ketogenic diet are recommended. Still, about 30%[(2)]of cases do not respond to these therapies.

This review aims to analyze etiology and report studies on the etiologic classification. Besides, we emphasized the importance of animal models that mimic the various underlying etiologies so that more knowledge on this topic would emerge. We also intended to incorporate the evidence published in the last ten years. We conducted an online search in the Pubmed database on 28th February 2020. We used MeSH term “infantile spams” and added the subheadings “epileptic encephalopathy”, “etiology”,” therapeutics” and “prognosis”.

In the initial search for Infantile spasms, we obtained n = 4492 articles. Applying the criteria publications with summary and publication between 01/01/2010 and 01/02/2020, in English, Spanish, French and Portuguese, we obtained an n = 1445 articles. Afterwards, we restricted our search to publications applying the evidence pyramid and using the article filter and we obtained n = 50 articles, explicitly 8 meta-analyzes, 20 systematic reviews and 22 RCTs (Randomized Controlled Trials). We carefully analyzed all articles by title and abstract reading and we excluded 23 articles, which were non-relevant for our study. From the 27 articles included, screening of bibliography was considered and, subsequently, we decided to include 24 other articles, to complete our review, in a total of 51 articles. (Figure 1)

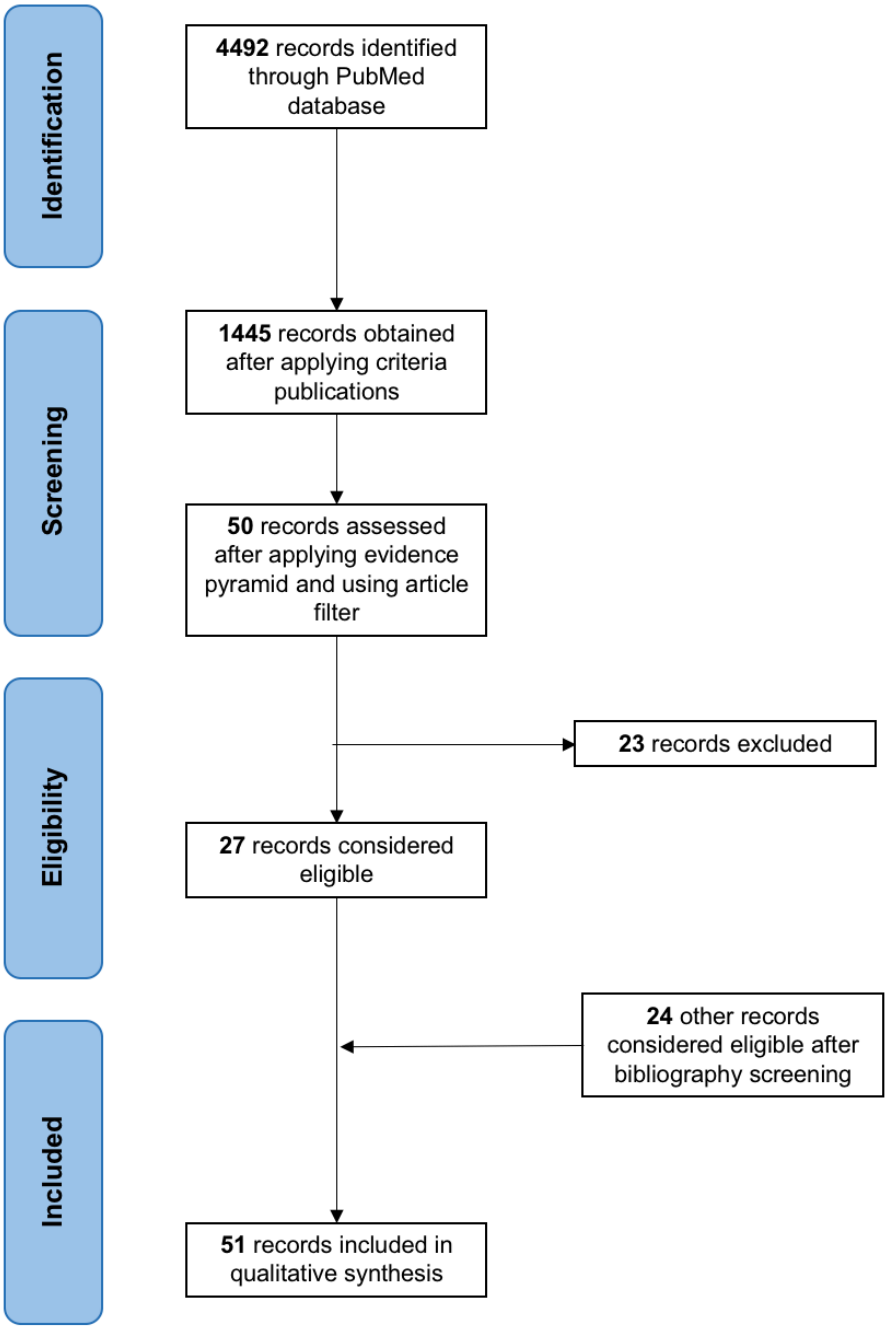

FIGURE 1. Flowchart of the methodology used in record selection: identification, screening, eligibility, included.

RESULTS

HISTORY

The first historical reference to infantile spasms occurs in 1841. The English doctor James West published a clinical case in the scientific journal “The Lancet”, in which his son James Edwin West was the patient. In this publication, this doctor asked for advice from medical professionals who may have had experienced similar cases. He described his son as apparently healthy until 4 months of age, reporting he started with “light head-swings forward”, having seizures with increasing frequency and intensity over the days and months, not remitting with any therapy. The child still presented motor development arrest / regression: "His hearing and vision are good, yet he is unable to stand or use his limbs like a child his age".

A century later, in 1952, Gibs et Gibs described the association between infantile spasms and a typical electroencephalographic pattern, which showed a chaotic and disorganized cerebral electrical activity, with slow waves of great amplitude, where electric waves of greater intensity stood out in multifocal points, distributed in a diffuse way, a pattern they called hypsarrhythmia.[9] [8]

In 1958, Dusancy-Baulony, based on a study of 21 clinical cases, communicated to the world the “spectacular effect” of the ACTH, in the control of infantile spasms. At the ninth Colloquium in Marseille, in 1960, despite several proposals of designations for this clinical presentation, the EMHI (infantile myoclonic encephalopathy with hypsarrhythmia) was proposed to be called West Syndrome, in honor of its eponym to describe the triad infantile spasms, hypsarrhythmia and psychomotor development arrest / regression. Over the years, research has continued and there has been great progress, specifically in terms of diagnosis and therapy. Later studies have shown the effectiveness of ACTH, corticosteroids and vigabatrin. However, the etiology and pathophysiology of IS are not yet fully understood.

EPIDEMIOLOGY

The incidence of IS is 2 to 3.5 per 10,000 newborns.[3][7] The prevalence is about 1-2 / 10,000 children aged 10 years [11]. It is one of the most frequent forms of early infantile epilepsy, if we exclude neonatal seizures and febrile seizures. Studies in developed countries report a higher incidence (0.05 - 0.6 / 1000) in areas of greater geographic latitude such as Sweden, Finland and Denmark, reporting a lower incidence in the north region of USA, Great Britain and South Korea. However, it has not been clarified whether this differential incidence is due to environmental factors or specific genetic predisposition.[12]

About 90% of cases appear during the first year of life, with a peak incidence between the third and seventh month.[7][13] The onset of this phenotype is rare after 18 months, although it has been reported some few cases starting later, until the 14th year of life. It affects children of both genders, regardless of their ethnicity. [14] The male gender seems to be more affected than the female, in a proportion of 60:40, [13] although some studies point to a lack of consistency in this predominance of male incidence.

CLINICAL PRESENTATION

IS/WS is characterized by the occurrence, of epileptic spasms, usually symmetrical, bilateral, with contraction of the axial musculature. In the electromyographic record, during a spasm, a phasic contraction is observed for a period of less than two seconds, usually followed by a less intense tonic contraction of longer duration (up to ten seconds). In some children, the tonic phase may not be present, appearing only in the initial phase contraction.[2] Therefore, Epileptic spasms are longer duration than a myoclonic contraction and shorter than a tonic contraction.

Phenotypically, spasms can have different aspects, depending on the muscle group involved, the intensity of the contraction and the child's position during the seizure, whether the children is sitting or lying down, portraying, in order of frequency, the following three variants: mixed flexion-extension spasms, flexion spasms and extension spasms. In flexion spasm, it can normally be observed flexion of the neck, trunk with adduction of the lower limbs, if involved, while upper limbs present adduction or abduction. Spasms can vary in intensity: from a subtle shake of the head, liable to be unnoticed, to perfectly evident rhythmic balancing movements. Extension spasms are expressed as sudden extension of the same muscle group.

On the other hand, mixed spasms, in flexion-extension, usually present themselves with flexion of the neck, trunk and upper limbs and lower limbs extension. Most children who have epileptic spasms have more than one type. The type of spasm, whether it occurs in flexion, extension or mixed, is not associated with the etiology nor predicts the prognosis. Spasms usually occur in clusters, at intervals of five to thirty seconds. Within the cluster, they usually increase in intensity until reaching a peak, followed by a decline. They can vary in frequency and be scarce, occurring, only a few times a day or reaching hundreds of daily episodes. [15] They appear predominantly on awakening and are rare during the child's sleep. However, this does not mean that its occurrence is greater during the day than at night, as its frequency is similar. What happens is that these children have frequent awakenings. Sometimes, after the seizure, a behavior arrest can be observed, lasting up to 90 seconds,

which is not observed without association with the occurrence of spasms. Usually, an episode of brief crying follows the spasm, masking the pathology that can be disregarded by parents and doctors and be mistakenly perceived as colic or gastroesophageal reflux. Phenomena associated with epileptic spasm may also occur, such as ocular deviation, nystagmus, yawning. Changes in respiratory rhythm are frequent, while changes in heart rhythm are rare.[13][16]

INTERICTAL AND ICTAL PATTERN ON EEG

In the interictal period, on EEG, a specific feature of IS is the presence of a typical electroencephalographic pattern called hypsarrhythmia. This typical pattern of electrical brain activity occurs outside seizures, though at first, right after the semiological identification of IS still in the course of the diagnostic process, the electroencephalographic recording may be normal. The hypsarrhythmic pattern is most often documented upon waking up and during phases 2 and 3 of non-rapid eye movement (N-REM) sleep, decreasing or being absent during rapid eye movement (REM) sleep. The electroencephalographic record shows a background of slow waves of low frequency and of great amplitude interrupted by sharp waves of greater amplitude, multifocal, without apparent rhythmicity. This classic hypsarrhythmia pattern is most common in children under the age of one year old. There are variants of the classic hypsarrhythmia, a pattern called modified hypsarrhythmia. This occurs in two thirds of the cases. Cases of Tuberous Sclerosis Complex (TSC), Aicardi Syndrome and Lissencephaly reveal modified hypsarrhythmia that present interhemispheric synchronization, unilateral or asymmetric hypsarrhythmia, focal aspects and suppression of the basal rhythm.[2]

During the ictal period, the EEG records slow waves or sharp waves of high voltage followed by sudden attenuation. When spasms occur in the context of another form of epilepsy, they can emerge concurrently in the middle of a cerebral electrical pattern of focal seizure. (Figure 2)

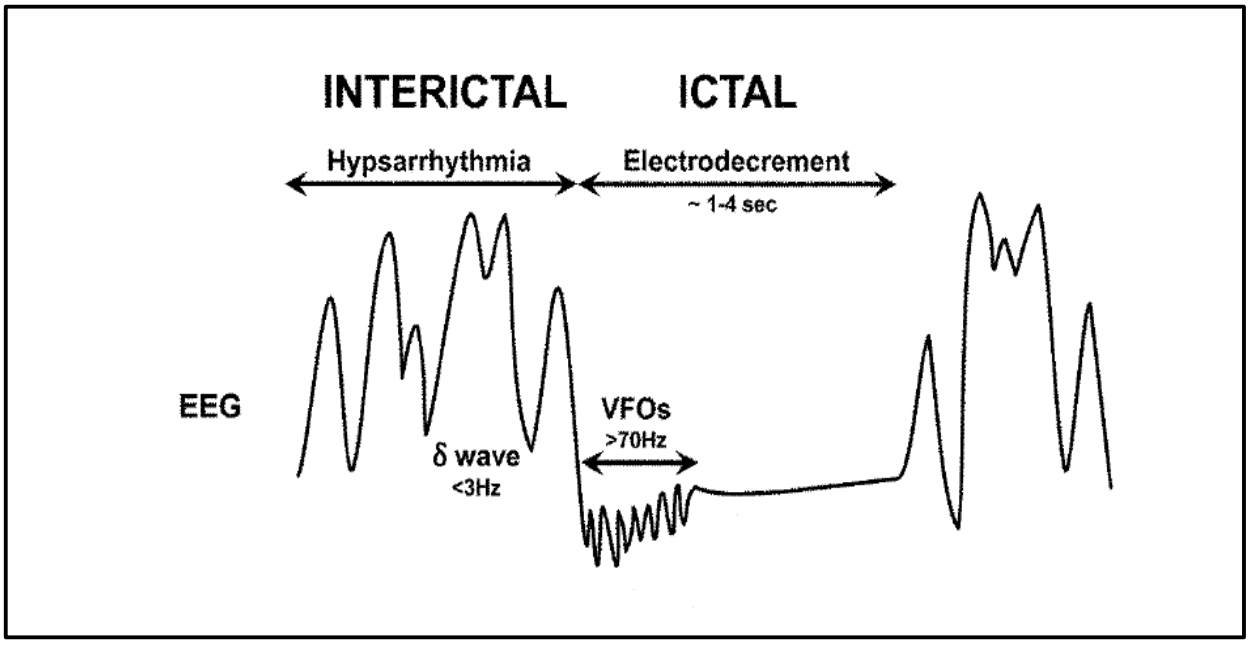

FIGURE 2. Scheme of EEG findings in Infantile Spasms.
Hypsarrhythmia consists of a chaotic, high-voltage, irregular slow waves (delta range <3 Hz) with superimposed sharp waves and spikes. The ictal phase shows an electrodecrement (attenuation of voltage during the clinical spasm). Once the spasm ends, the electrodecrement ceases and hypsarrhythmia resumes. According to Remi Janicot et al., 2020.[17]
Abbreviations: VFO, very fast oscillations.

TERMINOLOGY

In 2017, the International League against Epilepsy (ILAE) updated the classification of epilepsies, looking for a classification that would allow the association of causes, dysfunctions or comorbidities associated with the diagnosis and evolution of various epileptic phenotypes. [1] Thus, epileptic seizures were divided into three groups: focal onset, generalized onset and unknown onset seizure.

The creation of a separated group of epileptic syndromes, where several syndromes were included due to common electroclinical characteristics, was fundamental. These syndromes were grouped by its typical age of onset, common clinical semiology and specific EEG patterns, which enable diagnosis, provide indications about possible etiologies and about the drug therapy recommended by evidence.[18]

In addition, it was proposed to replace the term Infantile Spasms by Epileptic Spasms, since the spasms are not specific to infancy, and may appear whether during the neonatal period or after infancy. Traditionally and historically, IS were classified into three groups: 1) Symptomatic, when there was developmental delay prior to the onset of spasms or there was

a previous neurological pathology, i.e. an associated underlying morbid condition, corresponding to 75% of cases 2) Cryptogenic, when the child had normal neurodevelopment prior to the onset of spasms and the cause or etiology was not identifiable; and 3) Idiopathic, when the cause could not be identified and it had a benign prognosis.[11]

Although this classification is still widely used, it has shown clear weaknesses. A better prognosis has been associated to the idiopathic spasms group and worst outcomes have been assigned to those who showed an underlying and observable cause. Nowadays, it is known that most IS cases classified as cryptogenic/idiopathic are, in fact, symptomatic, since the etiologic assessment requires appropriate and careful genetic, metabolic and imaging investigation, not always available, mainly in countries with fewer resources. On the other hand, a more systematic classification including etiological subgroups will gather detail hence improving the existing knowledge; furthermore, the development of animal models mimicking each particular etiology will provide the opportunity to implement more targeted therapies. Gathering data from studies on IS etiology, ILAE, in 2013, recommended a new classification of epilepsies, including the particular group of Epileptic/Infantile Spasms emphasizing the different underlying etiologies: 1) genetics; 2) structural/metabolic; 3) unknown cause. Even so, this classification was updated, as many structural and metabolic defects almost always have a genetic basis.[11] Since 2017, the Epilepsies are classified by seizure type and by etiology and Epileptic Syndromes by age of onset and by etiology namely 1) Structural, 2) Genetic, 3) Metabolic; 4) Infectious, 5) Immune and 6) Unknown. [19]

PATHOPHYSIOLOGY

Since 1841, multiple studies and research have allowed greater knowledge on this pathology. However, there is still a long way to go before its pathophysiological mechanisms are fully understood. This difficulty relates to the multiple etiologies that underlie IS, displaying disturbing factors in an early period of brain development. The prenatal, neonatal and infancy are critical stages, since these are periods of organogenesis, growth and neurological maturation. Any genetic, structural or metabolic deviation from the neurobiological program may represent a risk. The causes of IS are very heterogeneous, with more than 200 etiologies correlated.[10] Thus, it was considered that these etiologies resulting in the same epileptic phenotype, would most likely converge in a common final mechanism, by which this specific clinical semiology would be produced.[2] IS corresponds to the prototype of epileptic encephalopathies where epileptic and cognitive prognosis is unfavorable. The refractoriness to therapy with conventional antiepileptics, the limited options for effective therapy and known side effects, the recognition of the heavy burden that it has

on patients, caregivers and the health system has engaged efforts among the scientific community. Numerous clinical studies have contributed to what is known about IS. Even so, the elucidation of its pathophysiological mechanisms has proved to be an arduous task and is still far from the end.

The WS and IS have certain peculiarities that limit the achievement of large-scale clinical studies. Firstly, their low incidence and prevalence and the wide geographic data dispersion makes systematic collection difficult; secondly, the fact that they have multiple etiologies and present themselves in the context of innumerable underlying pathologies, associated with changes in a large number of distinct genes, obliges to account for a too extensive spectrum of variables that are difficult to group and categorize.[17] On the other hand, IS are considered to result from a disorganization of the neuronal network or as a systemic epilepsy to which an encephalopathy is associated.[14] What are the mechanisms of pathogenesis? Many hypotheses have been put forward: a) Brainstem pathology with changes in interneuronal neurotransmission; b) changes in subcortical-cortical interaction with consequent occurrence of electrical anomalies at the cortical level, either with focal characteristics or diffuse distribution; c) dysfunctional activity of the hypothalamus-pituitary-adrenal hormonal axis; d) genetic defects; e) inflammation.[14][17][10] The hypothesis that IS could have been originated in the brainstem instead of a cortical origin was suggested, when it was found that a child with hydranencephaly had spasms clinically identical to those recorded in children with a complete Central Nervous System (CNS). It was suggested that the spasms could originate in the brainstem. Also, it was found that newborns with documented subcortical and mesencephalic lesions due to hypoxic-ischemic encephalopathy developed infantile spasms. The second hypothesis arose with the verification that the spasms could be triggered through an interaction between the cortex and the subcortical structures. By activating the subcortex, brainstem or both, spasms could be generated.[14] The theory of dysfunctional activity of the adrenal hypothalamic-pituitary hormonal axis or Stress Theory of IS was based on the observation that ACTH therapy and high doses of glucocorticoids were effective in suppressing seizures in many IS patients. It has been proposed that several stress factors, engendered by different etiologies, during the early stage of brain development, lead to the release of Corticotropin releasing hormone (CRH), a peptide with documented convulsive activity, with a consequent increase in neuronal excitability. Data obtained from clinical studies, showing that children with IS had decreased levels of ACTH in the cerebrospinal fluid (CSF) and, in addition, the demonstration of the effectiveness of ACTH and glucocorticoids in many of the IS cases, supported the hypothesis.

However, in the last 15 years, there have been substantial advances in animal models. Animal experiments seek to elucidate the pathophysiological mechanisms involved,

according to the different etiologies involved. Simultaneously, they are crucial instruments on the discovery of new mechanism-directed therapeutic, enabling evaluation. As a matter of fact, although the final common mechanism of all etiologies may be common, these mechanisms may eventually present different peculiarities depending on the underlying etiology. About 30% of IS cases do not respond to ACTH or vigabatrin, so animal models are a resource to be explored. On account of the differences and specificities of the two species (humans and rodents) in terms of brain development, it is important to define age equivalences. Seventh postnatal day (PN7) in the rat corresponds to the period of brain development, PN10 corresponds to the human brain already developed and PN14-21 corresponds to the period in which the spams begin in humans. Each model investigates every hypothetical pathophysiological mechanism involved, seeking to reproduce the pathology, testing possible drugs and collecting results. Several models were created to mimic genetic etiologies, acquired etiologies and structural etiologies.(Table I)

In animal models, it was used two types of animals: mice of normal genetic substrate and mice with specific genetic alterations predisposing to IS. Models using genetically normal mice are those such as N-methyl-D-aspartate (NDMA) model and tetrodotoxin (TTX) model and models using genetically modified mice are those of ARX model, TSCN 65, APC, and TSC. The TTX model is the only model that is a chronic model. The multiple hit model enables to test acquired lesions yet not always exhibiting their age-specificity of IS.[20]

GENETIC MODELS

1. ARX mutations: hypothesis of decreased GABAergic neuronal inhibition as a pathophysiological mechanism of IS

ARX (aristaless-related homeobox gene) mutations have a perfect established association with a large group of neurological diseases that associate mental retardation and epilepsy (such as X-linked lissencephaly) with genital ambiguity, X-linked non-syndromic intellectual disability and X-linked infantile spasms.

The ARX homeodomain genes are involved in a critical stage of brain development, playing a crucial role in the controlling process. The ARX homeodomain gene is a transcription factor that acts primarily on the migration of GABAergic interneurons from the ganglionic eminences of the ventral forebrain to the telencephalon and on the initial recruitment of cholinergic neurons. It is involved in the transcription of more than 80 subsequent genes in an essential pathway for normal brain development. This way, ARX mutations may produce changes in the neurodevelopment and may underlie some forms of epilepsy such as IS, as

they yield disruptions of GABAergic inhibition systems, with increased hyperexcitability of neural networks. These are called interneuropathies.

1.1. Deletion or knockout ARX model

The complete knockout or full ARX deletion in mice models displays severe migratory changes showing almost invariably perinatal death. The conditional ARX "knockout" model is an alternative deletion model in which is only produced ARX deletion of GABA cortical interneurons. As a result, epileptic spasms can be seen with documented electrodecrement on EEG, both in female and male adult mice. This model provides information and clarifies ongoing mechanisms in the IS pathogenesis, despite age inconsistency (as it only occurs in adulthood) and the impossibility of testing drugs. Furthermore, it highlights the association between interneuropathies and the failure in GABAergic inhibition mechanisms, with the consequent occurrence of different types of epilepsy, including IS.[17]

1.2. Expansion ARX Model

As a matter of fact, the vast majority of ARX mutations in the human species are expansions, not deletions. These expansions involve the first polyalanine segment of the gene. Just like in humans, rats with ARX expansion (ARX (GCG) 10 + 7) have epileptic spasms in infancy and other types of seizures in adulthood. Histological studies of these rats show selective reduction of peptides such as calbindin, neuropeptide Y and cholinergic interneurons, while other populations of interneurons that expressed parvalbumin or calretinin show no alterations. In addition, the administration of 17 beta-estradiol, between PN3 and PN10, caused the GABAergic function to be restored, leading to neonatal spasms resolution. In the expansion ARX model, the initial polyalanine segment has a greater number of codons, going from the usual 16 codons up to 23, since this is the most frequent mutation found in the human species. This rat presents the infantile spasms phenotype between PN 7-20, matching the infancy period. Later, other seizure types occur. Cognitive changes and social interaction have been documented, suggesting similarity with an autism phenotype.[10]

2. The Ts65Dn Model: Theory of Excess GABA-B Receptors, mediated by potassium

The incidence of epilepsy in Down Syndrome is about 8%. Out of these 8%, approximately a third have epileptic spasms during infancy.[21] The Down Syndrome mouse model allows to clarify the pathogenesis of IS, in the context of this Trisomy. With the use of GABA-B receptor agonists such as baclofen or gamma-butyrolactone, it would be expected to reproduce seizures or spasms in rats. Surprisingly, with the use of GABA agonists, absences were produced in the control group (normal rats), while cluster spasms, accompanied by hypsarrhythmic recording, were found in the group of mice TS65DN model. Drugs such as ACTH, valproic acid, ethosuximide and vigabatrin were tested effective in controlling these

spasms. This means that spasms, in Trisomy 21, can respond to conventional epileptic medication. The neuron culture of the Ts65Dn mice showed changes in the potassium channels of these receptors, GIRK-2 (G-protein-regulated inward-rectifier potassium channel 2) mutations that promote potassium efflux and increase calcium influx, thus promoting excitability. This model shows the importance of GABA-B receptor and the regulatory role of the associated potassium channel in the IS pathogenesis, also allowing for the testing of new therapeutic procedures.[21]

3. Increased synaptic excitation model – The conditional deletion APC model

The APC gene (adenomatous polyposis coli gene) regulates the amount of beta-catenin. An excess of beta-catenin causes abnormal dendritic branching with an increase in the number of excitatory synapses.

APC forms a protein that binds to mRNA, decreasing beta-catenin and at the same time interacts with 5 different genes: FOXG1 (Forkhead Box G1), LIS1(Lissencephaly gene), , STBX1 (Syntaxin-binding protein 1 gene), DCX (Doublecortin gene) and NR2F1 (nuclear receptor subfamily 2, group F, member 1, gene). These are also involved in the genesis of IS. It means that changes in the APC gene will produce increased neuronal excitability. The model of APC deletion of neurons CamKIIα8 (glutamatergic neurons of excitation), as it leads to the production of IS in flexion and extension, in mice, during the neonatal period, seems to stress the role of glutamatergic mechanisms on brain development, synaptic plasticity and learning.[17]

4. Mammalian target of rapamycin (mTOR)

The mTOR pathway is a central pathway receiving converging signals from a big number of sources, including energy and metabolism related processes, inflammatory signaling pathways, growth factors, hormones, neurotransmitters. It also is engaged in neuronal differentiation and function. It appears, therefore, as a likely candidate target for many of etiologies of IS, whether pre and perinatal acquired etiologies (i.e. hypoxia-ischemia, inflammation) whether genetic etiologies such as TSC and cortical dysplasia.[20]

In fact, TSC is a genetic disease linked to mutations in either hamartin (TSC1) or tuberin (TSC2). About 10-40% of TSC patients develop IS, [11] whereas 20–25% of patients with IS have TSC. [22] Mutations of TSC1 or TSC2 genes enable the activation of the mTOR complex TORC1. As a result of disinhibited TORC1 activity, key functions in the cellular biology are dysregulated, contributing to the formation of malformed and giant or balloon cells characteristic of tubers. Rapamycin, an mTOR inhibitor may act in TSC animal models or in those presenting cortical dysplasia, improving survival and developmental outcome. However, none of the animal models TSC or PTEN (Phosphatase and tensin homolog

gene) knockouts expresses IS, raising the question if mTOR inhibition is really beneficial for IS.

Similarly, some acquired pathologic conditions associated with seizures, including IS may produce changes in mTOR pathway, such as hypoxia, stress, endocrine/metabolic disorders and inflammation. In preliminary studies, rapamycin has been shown to have beneficial effects in the multiple-hit model of IS. However, more testing is necessary as it must to be administered during a sensitive infantile period.[22]

5. Prenatal Stress/NDMA model (glutamate receptor activation)

The intraperitoneal injection of the N-methyl-D-aspartate (NMDA), a glutamatergic receptor agonist, in rats, induces hyperactivity, torsion of the tail and emprosthotonic seizures (tonic flexions), associated with electrodecrement and chaotic interictal waves. These events occur during infancy and are related to the administered dose. Low doses of NDMA trigger emprosthotonic seizures in mice, while high doses trigger other types of motor seizures.

Uptake studies of 2-deoxyglucose showed increased uptake in limbic areas, hypothalamus and brainstem structures, during the seizure period. Learning and coordination deficits and stereotypies have been reported, at older ages. Some drugs have been tested. The drugs were administered before the onset of seizures, the opposite of what usually happens in a clinical setting. It was found that the previous administration of ACTH and vigabatrin prevents the induction of NDMA spasms. Pyridoxine reduced NDMA spasms frequency, but induced later epileptiform activity. Valproate showed a modest effect. Clonazepam had no effect in minimizing seizures. Paradoxically, hydrocortisone increased the induced NDMA spasms. This was one of the major limitations of the model. Additionally, there was no evidence that the administration of NDMA was able to produce chronical seizures as seen in IS.

However, there were adaptations to NMDA models. The forced immobilization and/or swimming in cold water of the gestating female rats introduced prenatal stress factors in the experiments. This allowed the cubs to be sensitized to the subsequent induction of spasms by the administration of NDMA, probably because prenatal stress causes a negative regulation of the GABAergic systems, with decreased expression of the potassium chloride cotransporter (KCC2). This cotransporter is responsible for establishing a chloride gradient, with a decrease in the intracellular Cl^-. The lower expression of the co-transporter produces less intracellular hyperpolarization, facilitating hyperexcitability. Calpain, a calcium-activated protease increases dephosphorization and cleavage of KCC2, thus, contributing to hyperexcitability. A calpain inhibitor was tested and there was a reduction in the induced NDMA spasms, in the models which had been subjected to previous sensitization by prenatal stress, thus introducing a new potential treatment approach.

There was another adaptation to this model by administering the gestating female rats corticosteroids *in uterus, such* as betamethasone. It was found a significant decrease in the transcription of genes related to the GABAergic and glutamatergic synaptic transmission, in the hypothalamus, showing a different pattern according to gender. This would, probably, justify the greater incidence of IS, in males. The effectiveness of beta-estradiol was tested, but, quite the reverse of what happens in the ARX model, the spasms showed no reduction. There was response to ACTH and vigabatrin, suggesting that steroid hormones and GABAergic inhibition could play a critical role in the IS genesis. Pretreatment with ganoloxone, a synthetic neurosteroid hormone and GABA-A enhancer, delayed and decreased the number of spasms. Similarly, the prolonged treatment with beta-hydroxybutyrate (ketone body) showed a reduction in the spams' frequency, an increase in the latency time and a clear improvement in the models' memory function.[17][26]

6. Tetrodoxin model: sodium channel blocker

The tetrodotoxin model was first created to examine the role of neuronal activity in postnatal development of the hippocampus, not to develop a model of childhood epilepsy.[21] The tetrodotoxin model (TXT model) tests the hypothesis that IS result from a temporal desynchronization of two or more brain development processes. Tetrodotoxin is a sodium channel blocker, which inhibits normal neuronal activity as it prevents the influx responsible for depolarization, consequently making it impossible to conduct signals. This desynchronization can be the result of several disturbing factors, namely, brain trauma, hypoxia, mutation in genes associated with development. In an attempt to reproduce the situation, tetrodotoxin is injected into the hippocampus or neocortex of the mice, creating blocking zones without neuronal activity, while other zones are in function. It was hypothesized that the existence of a chronic suppression of neuronal activity in certain areas, during the period of brain development, could lead to excitability or seizures (neuronal desynchronization theory). In fact, after injecting tetrodotoxin in PN10-12 rats, it was observed, after a latency period of 10 days, the appearance of seizures consistent with spasms, which remained, even after the injection pump was removed. This model allowed to document both the ictal and the interictal electrical patterns, on EEG, reproducing almost perfectly what occurs in the child. In addition, the model confirmed the positive response to ACTH and vigabatrin. High-dose ACTH administration (32 U/Kg/day) eliminated spasms in 66% of the mice and alleviated the interictal hypsarrhythmia. Vigabatrin, often used in TSC cases, also reduced the occurrence of spasms and hypsarrhythmic activity. One of the limitations of the TXT model consisted in showing an absence of temporal correspondence between the critical phenomena, that occur in the model, and in the child. Other drugs were also tested: carisbamate, galanin (Nax 5055), belcanasan, the GABA-B receptor inhibitor

(CGP35348) and beta-estradiol. Carisbamate, a drug that acts on Na^+ channels independent targets, exerted positive results suppressing electroclinical spasms.[17][26]

7. Multiple aggression model (multiple-hit rat model)

The "multiple-hit rat model" model for infantile spasms has also been used as an investigational model for symptomatic infantile spasms originated either by acquired causes or by genetic causes. In this model, seizures only occur in the animal in the period corresponding to adolescence, but the model is able to show that both genetic and environmental factors can disturb the process of brain development. The model uses three highly toxic compounds: doxorubicin (DOX), lipopolysaccharide (LPS) and p-chlorophenylalanine (PCPA) administered sequentially, which produce cortical and subcortical damage, with serotonin depletion. It is based on the loss of GABAergic interneuronal transmission. The IS development seems to require the interruption of the cortical and subcortical neuronal networks as a mandatory condition, with a decrease in serotonin in the CSF. The evolution of IS for other types of seizures, cognitive deficits and behaviors with no social interaction consistent with autism after PN9 is also documented. In this model, ACTH and vigabatrin were tested.

Vigabatrin suppresses spasms, despite the high mortality rate observed. Thus, the vigabatrin analog CPP-115 was tested, which has a greater affinity for GABA aminotransferase and less retinal toxicity. Low doses of CPP-115 have been found to reduce spasms without increasing mortality. However, the use of higher concentrations has a similar toxicity to vigabatrin. The effectiveness of vigabatrin and its analogs can be explained by the selective reduction of cortical parvalbumin interneurons observed in histological studies of this model.

However, one of these models, using heterozygous rats for STXBP1 (Sintax Binding Protein1, MUNC18-1) when subjected to high frequency stimulation, paradoxally showed an increased glutamatergic activity, instead of showing the loss of the expected GABAergic effect. Even so, the production of epileptic seizures was not achieved. In the model, DOX and LPS interrupt cortical and subcortical neuronal networks, while PCPA reduces the amount of serotonin in the CNS.[17]

8. Inflammation Theory

Inflammation is another factor involved in IS etiopathogenesis. A study[23] (Iacobas et al, 2018) investigated alterations in the transcriptome found in rats with changes in neurotransmission at the arcuate nucleus of the hypothalamus. These changes showed an association with the IS occurrence. One of the main goals was to determine how these spasms were corrected by anti-inflammatory treatment and if there were differences between genders. IS were induced by intraperitoneal administration of NMDA, followed by anti-

inflammatory treatment – ACTH and PMX53 (complement factor C5a antagonist). Also, there was a control group of rats previously exposed to betamethasone which were administered normal saline solution. It was found that, with the use of ACTH and PMX53, there was a genomic recovery of all types of injured synaptic transmission. PMX53 showed even greater efficiency than ACTH, something that was not expected. Inhibition of the complement factor 5a receptor (C5ar1) during status epilepticus reduced tumor necrosis factor alpha (TNF-α). Both TNF-α and IL-1β (interleukin1beta) initiated the immune response in the CNS, causing neuronal damage and hyper excitability. It was found marked difference by sex in the alteration of the transcriptome in IS having shown predominance of alterations in males. Likewise, there was a greater efficiency of treatment with PMX53 in males. This study suggested that anti-inflammatory treatment could be a promising IS therapy and a not negligible approach to ASD as it shares high comorbidity with IS.[23] It was not possible to reproduce the mechanism consistently, experimentally.[24][25]

Therefore, there is much to be investigated before a true pathophysiological model can be established. The ideal pathophysiological model will have to mimic the disease, with its typical early onset, during the early stage of brain development, with the characteristic appearance of spasms in relation to the sleep-wake cycle, the presence of characteristic hypsarrhythmia, the lack of response to conventional antiepileptics and a satisfactory response to drugs that have demonstrated efficacy in therapy. [2][24][25][21] Thus, it is important to highlight the importance of animal models as an available tool for the study of either common or singular pathophysiological mechanisms involved in the genesis of IS and in the testing of new therapies.[17]

TABLE 1. Summary of Selected Pre-Clinical Models of Infantile Spasms

Model	Induction Method	Pathophysiology	Clinical Relevance	Limitations
Genetic Models				
ARX delection (knockout)	Mouse: Delection of ARX, from cortical GABAergic interneurons	↓ GABAergic interneurons	Relevant to human ARX mutation, males more afected	Spasms only in adult mice Cognitive change not known No treatment testing
ARX expansion (knockin)	Mouse: Expansion of poly-alanine tract in ARX gene, causing interneuronopathy	↓ GABAergic interneurons	Mimics known human ARX mutation; spontaneous spasms and other seizures later; Evolution of seizure type; EEG abnormalities	No hypsarrythmia
Ts65Dn mice	Mouse: GABA-B receptor agonist (intraperitoneal)	Overexpression of GIRK2	Mimics Down Syndrome	No chronic spontaneous seizures. Requires exogenous agent (GABA-B receptor agonist) to elicit spasms
APC knockout	Mouse: Delection of APC	↑ beta-catenin → ↑ layer 5 glutamatergic synapses	Involves multiple relevant IS-susceptible genes	EEG changes not similar to human; drug effects not yet reported
Acquired/Provoked Models				
CHR/stress	Rat: i.p. or i.c.v. injection of CRH	Variety of "stressors" → ↑ release of CRH → ↑ neuronal hyperexcitability	CRH is an endogenous convulsant in developing brain	Limbic seizures, not spontaneous; no response with ACTH
Chronic Neonatal Stress	Limiting nest material	NMDA receptor overactivation	Spontaneous spasm; Appropriate age; Cognitive deficit	Preliminary results (abstract only); Effects of ACTH not tested
NMDA or betamethasone/NMDA	Administration of NMDA i.p. or bethamexasone i.p. on G15, followed by NMDA on P15		Model of cryptogenic IS with flexion spasms; Allows drug testing; Cognitive changes	No spontaneous, chronic seizures; Treatment (ACTH, VGB) prior to spasms
TTX	Rat: intracerebral injection of TTX by osmotic mini-pump, for 28 days, beggining on P10	↓ cerebral activity	EEG changes consistant with human pattern; Chronical block of neuronal activity → ↑ hyperexcitability and seizures Video-EEG: hypsarrithmia and electrodecremental seizures Spasms in clusters, during slow wave sleep	Spasms occur late in maturation; Uknown why TTX induced reduction of neuronal activity leads to spasms; Treatment response unknown; Cognitive changes unknown
Multiple hit model	Rat: DOX, LPS on P3; PCPA on P5	Severe cortical and subcortical structural brain damage	Mimics human symptomatic IS	ACTH has no effect; toxin vs seizure effects

Abreviations: ACTH, adrenocorticotropic hormone; ARX, Aristaless-related homeobox; CRH, corticotropin releasing hormone; G, gestational day; icv, intracerebroventricular; ip, intraperitoneal; IS, infantile spasms; NMDA, N-metyl-D-aspartate; P, postnatal day; TTX, tetradoxine;↑, increase; ↓, decrease; →, leads to.

Adapted from Remi Janicot et al, 2020 and from Stafstrom et al, 2011[17][26]

ETIOLOGY

The determination of the etiology is an important step in the diagnosis of IS, since permits to assess the prognosis, has implications for genetic counseling and allows decisions when instituting therapy.[27] The causes and pathologies underlying infantile spasms are multiple and varied. Traditionally, both in clinical studies and in clinical practice, IS have been classified as symptomatic and cryptogenic/idiopathic. This classification was based on clinical semiology, investigations carried out by means of complementary diagnosis and the presence or absence of developmental delay prior to the onset of epileptic spasms. Although it has already been replaced and updated by ILAE, as there is consensus regarding its evident limitations, this classification continues to be frequently used in many different scientific publications, probably because it easily allows to refer to both different groups of patients: those in which it is possible identify an underlying pathology and those in which no underlying pathology has been identified. In fact, consensus on classification is and will always be difficult, since the preference for certain classification criteria over others is justified by the specificity of the scientific area of ongoing research or by the classification applicability in clinical practice. Thus, in our presentation of Infantile Spasms etiology, we will not fail to mention less universal forms of classification, since many of them respond to the need for systematic organization of knowledge by criteria, contributing to a better etiology understanding.

Recently, the ILAE classification scheme proposed a new scheme for the classification of epilepsies, according to the etiology: 1) genetic, 2) structural, 3) metabolic, 4) immune, 5) infectious and 6) unknown etiology.[19] For IS, the most frequently remarkable etiology is genetic, structural, metabolic and unknown. It was considered that there is some overlap between these etiological groups, since the structural, the metabolic etiologies and the unknown etiology may also have a genetic basis. In fact, another proposed scheme for genetic etiologies was to subdivide them into three groups: 1) genetic causes of developmental epilepsies, 2) genetic causes associated with specific brain malformations and 3) genetic causes associated with innate errors of metabolism.

Developmental epilepsies include mutations in genes involved in the embryonic development processes of the CNS, some of which are involved in the IS phenotype. The genes involved include ARX, CKDL5, FOXG1, GRIN1, GRIN2A, MAGI2, MEF2C, SCL25A22, STPAN1 and STXBP1.[14][28] In 2011, a study by the Department of Neurology at the University of

Washington proposed a genetic and biological classification of IS based on the evidence that: 1) children with IS had disorders in the genetic signaling pathways of brain development and that although not all of these patients had the phenotype, this would be justified by incomplete penetrance or expression variability; 2) there is a biological link between autism and infantile spasms, especially in patients with tuberous sclerosis and Down syndrome; 3) some children with IS presented dyskinesia, with a predominance of involuntary movements, with mutations in the ARX gene and MEF2C, genes involved in the development of the ventral forebrain, when the migration of the GABAergic interneurons occurs, which may present CDKL5 deletions or STXBP1 mutations. [29] This classification identified groups of patients according to the presence or absence of predisposing genotypes for Infantile Spasms. [31] Patients with alterations in these genes may develop IS. These gene mutations and other candidate genes known as CNV (copy number variations) point out anomalies in the process of differentiation of the ventral prosencephalon and in the functional development as a pathophysiological mechanism involved in the IS genesis.[5]

In a majority of cases (60 to 90%), a known etiology for IS is identified: genetic, structural or metabolic. The causes of IS can be prenatal, perinatal or postnatal.[30]

Prenatal causes are about 50% of symptomatic cases of IS and include CNS malformations (focal cortical dysplasia, lissencephaly, holoprosencephaly, hemimegaloencephaly, Aicardi syndrome, neurocutaneous syndromes such as TSC, neurofibromatosis type 1, pigmentary incontinence), chromosomal abnormalities (Down syndrome, Miller Dieker syndrome), monogenic anomalies, congenital CNS infections. About 75 to 80% of patients with TSC will develop epilepsy/IS and can also develop ASD.[2]

Perinatal causes include hypoxic-ischemic encephalopathy, one of the most frequent causes of IS and hypoglycemia.[2]

Postnatal causes include trauma, hypoxic-ischemic attacks, SNC infection and tumors.[2][31]

The UKISS Study (United Kingdom Infantile Spasms study) proposed a distribution of the etiologies of Infantile Spasms, by a greater number of groups, in order to obtain more detail. Considering the ILAE classification of etiologies in the three recommended groups (genetic, structural / metabolic and unknown) consistent, but feeling the need for greater specificity and a greater number of etiological categories, there was a study based on a sample of 207 children with IS. This study identified that in 61 % (n = 127) of the cases there was a defined etiology, in 33% (n = 68) there was no proven etiology and in 6% the etiology was merely not investigated. In 63 participants, the etiology was referred to prenatal causes; in 38 cases, the etiology referred to perinatal causes; in 8 cases, the etiology was postnatal; 18 cases had other causes. The most common etiologies found were hypoxic-ischemic (HIE), n = 21

(10%), chromosomal, n = 16 (8%), stroke malformations, n = 16 (8%), (TSC), n = 15 (7%), periventricular leukomalacia or hemorrhage (PVL/PVH) ,n = 11 (5%). There were more than 32 unusual etiologies. So, it is recommended that future studies report on etiology, using the ICD 10 pediatric classification, and that the results are also grouped into 1) no identified etiology, 2) proven etiology, and 3) not fully investigated (when an important piece of information is missing). They also recommend the subgroupings of HIE, TSC, chromosomal disorder, PVL/PVH, malformations and stroke.[29]

The National Consortium of Infantile Spasms, in the northern United States, prospectively evaluated 251 cases of infantile spasms who had no known ab-onset cause, and came to the conclusion that, in 55% of cases, it was possible to reach the diagnosis only by clinical evaluation and brain MRI.[32] Compared to the UKISS results, prenatal causes were more frequent, accounting for 57.8% of known etiologies compared to 49.6% in the UK study. Of the prenatal causes, genetic etiologies were identified in approximately two thirds of the cases, with or without brain malformations, which highlights the importance of genetics in this group of children. Parallel to the UKISS cohort, perinatal etiologies were present in a quarter of cases. The most common etiologies were HIE and brain injury due to prematurity. This highlights the importance of ideal prenatal and perinatal care in epilepsy prevention. Postnatal causes accounted for 18% of known causes compared with only 6.3% in the UKISS cohort. In this study, clinical history allowed the identification of the etiology without the need for further investigation; in 45 cases out of 203 cases, clinical examination (including fundoscopy in 2 cases) made it possible to identify the etiology in seven cases. Brain MRI allowed the diagnosis of 55 cases, chromosomal analysis allowed to explain five cases and confirmed Down's Syndrome in 11 cases. Other investigations explained the etiology in three cases (through muscle biopsy and therapeutic test with pyridoxine). In this study, urinalysis did not allow clarification of inconclusive diagnoses.[32]

The metabolic etiology of West Syndrome is rarer, but it is equally important, as it can respond to a therapeutic approach. A study included the analysis of patients with changes in the metabolism of aminoacids, glucose, fatty acid oxidation, pyridoxine deficiency, mitochondrial or lysosomal diseases allowing to emphasize the importance of early recognition of these etiologies, as it enables a timely therapeutic intervention from an early age, minimizing the prognostic impact that this disease involves. In this study, the greatest evidence found for the association of metabolic diseases with IS refers to: phenylketonuria (PKU), non-ketotic hyperglycinemia (NKH), Menkes disease, pyridoxine-dependent epilepsy, methylmalonic aciduria and mitochondrial diseases.[25]

DIAGNOSIS

Usually, parents are the first to notice the onset of spasms, taking the child to the general physician. These episodes are often confused with colic or gastroesophageal reflux. The existence of videos recording the episodes noted by parents or caregivers is useful, since these episodes are more frequent when waking up and during the first phases of sleep and may not be witnessed in due time by the physician during the medical appointment. If suspicious episodes occur, a pediatrician or neuropediatrician should be referred quickly.[16] The importance of early diagnosis, the importance of detecting the etiology and the institution of adequate therapeutic control were demonstrated to improve the prognosis. The determination of the etiology is an important step in the diagnosis of IS, since it allows for the assessment of the prognosis, has implications for genetic counseling and allows decisions when instituting therapy. [27] One approach to the diagnosis of infantile spasms is outlined in Figure 3.

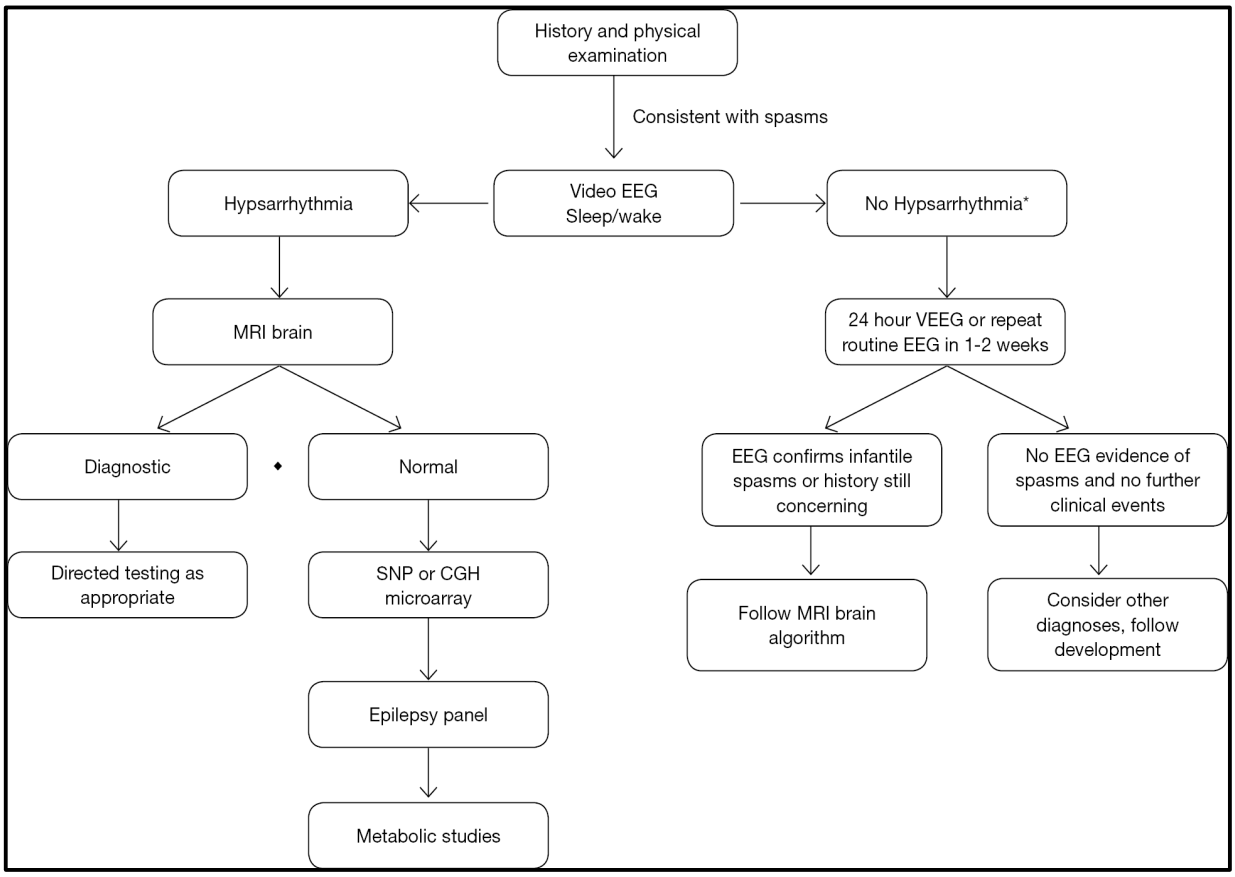

FIGURE 3. Diagnosis approach on infantile spasms, according to Nelson et al., 2015.

Footnote: Epilepsy panel can be performed first to SNP or CGH microarray.

Abbreviations: CGH, comparative genomic hybridization; EEG, electroencephalogram; MRI, magnetic resonance imaging; SNP, single nucleotide polymorphism; VEEG, video-electroencephalogram.

Clinical history

Thus, it is suggested to proceed with the clinical history, including the prenatal, perinatal and family history.[33] It is possible to determine the etiology of about 70% of children with IS, without the need for metabolic evaluation, following a systematic protocol in clinical practice: clinical history with careful collection of prenatal and perinatal antecedents, physical examination and neurological, EEG and MRI analysis.[11] By collecting pre and perinatal history, it is possible to identify etiologies such as HIE, trauma, herpetic encephalitis, meningitis, heart defects, neonatal hypoglycemia, pregnancy toxicity, transplacental infections.

Physical and neurological examination

Physical and neurological examination can detect or highly suspect tuberosis sclerosis, neurofibromatosis, nevus sebaceous syndrome, pigmented incontinence, nevus epidermal syndrome, macrocephaly, Miller-Dieker syndrome, Trisomy 21, Menkes syndrome.[11]

The physical examination must include somatometry with evaluation of the cranial perimeter, allowing the diagnosis of a macro or microcephaly; search for signals with careful skin inspection (diagnosis of tuberous sclerosis, Sturge-Weber syndrome, neurofibromatosis, Menkes syndrome), inspection of the face, eyes, neck and other dysmorphisms (Aicardi syndrome, Trisomy 21, William syndrome and Leigh's syndrome), research for alopecia (biotinidase deficiency).

EEG and extensive video EEG study

The routine EEG can confirm the diagnosis, showing the typical pattern of hypsarrhythmia. However, a Video-EEG study, both during sleep and during wakefulness, should be performed, since the hypsarrhythmic pattern is more frequent during stages 2 and 3 of NREM sleep, followed by the transition periods between sleep and the awakening period, being very reduced during REM sleep.[34] Twenty-four hours video-EEG recording provides best chance to detect hypsarrhytmia and recording the spasms.[35] Other diagnosis should be excluded: myoclonic epilepsy of infancy and non-epileptic etiologies such as Fejerman or Sandifer syndrome.[28]

If there were no seizures during wakefulness and sleep, it is desirable that the EEG lasts up to 30 minutes after waking up to increase the likelihood of obtaining an ictal record.[34]

Brain MRI

Brain MRI can identify tuberous sclerosis, cortical dysplasias, such as lysencephaly, pachygyria, hemimegaloencephaly, banded heterotopia, focal cortical dysplasia, HIE, tumor, stroke, Leigh's syndrome, hydranencephaly, schizencephaly, holoprosencephaly, Sturge Weber syndrome, periventricular Leukomalacia, Krabbe disease and others.[11]

In about 30% of children with West syndrome, there will be no identified cause, despite a careful history, complete physical, neurological and ophthalmological examination, EEG and brain MRI. Of these cases without an easily identifiable cause, only 50% will have a metabolic or genetic cause.

Pyridoxine-dependent seizures Exclusion

As a test diagnosis, intravenous 100mg of pyridoxine can be administered, which will allow, through electroencephalographic evaluation and in the absence of a favorable electroclinical response, to rule out pyridoxine-dependent epilepsy (PDE). As a matter of fact, empirically-based treatment with pyridoxine should be performed in all situations of early-onset epilepsy, while biochemical analyses are underway, as PDE may be underdiagnosed and is considered to respond considerably to pyridoxine. [36]

Biochemical tests/ Genetic tests /Metabolic tests

The execution of routine biochemical tests such as electrolytes, glucose, ammonia, lactate, liver function, creatine kinase; the execution of metabolic tests in serum, urine or cerebrospinal fluid (CSF), with the search for amino acids, monoamines or organic acids, the performance of specific tests to monitor certain enzymes; genetic tests for nuclear or mitochondrial defects or biopsy will allow greater accuracy in the diagnosis of possible etiologies involved.[25][33]

A study by the National Infantile Spasms Consortium evaluated the need for genetic and etiological investigations. It was concluded that, in 55% of the cases, it was possible to reach the diagnosis only by clinical evaluation and brain MRI. In patients who underwent imaging studies, brain MRI showed causal abnormalities in half of children with spasms of recent onset and was therefore considered an appropriate method as a first-line investigation required in cases without easily detected etiology. Brain MRI detected 86.2% (119/138) of the known causes at the initial presentation and 73.2% (119/161) of the causes at 3 months of follow-up.[32] If the initial MRI scan was normal and seizures persist, a brain MRI scan can be repeated at 6-month intervals to detect cortical dysplasia and after 24 to 30 months when myelination is more mature.

What is the performance of further investigations in cases of IS without obvious etiology,

after initial clinical evaluation and brain MRI?

The results obtained suggested that the genetic test, particularly with an aCGH genetic panel and an epilepsy panel, show high performance – the combination of these two tests provided a definitive diagnosis in more than 40% of children who have spasms of recent onset without obvious cause after initial clinical evaluation and magnetic resonance.[32] Other studies have emphasized the importance of careful genetic evaluation in children with epileptic encephalopathies.[5]

Metabolic studies were performed in most children without an obvious cause, but its performance was relatively low, with definitive diagnosis reached in only 4.5%. Diagnostic changes were found only in serum lactate, pyruvate, amino acids and changes in the research of organic acids from urine. It should be noted that children with findings that were suggestive of neurometabolic disorders, on initial magnetic resonance imaging, but who had not previously been diagnosed with a metabolic condition, had these metabolic diagnoses confirmed in additional tests, emphasizing the importance of targeted assessment in this subgroup.

Based on the results in the US multicenter study, it is proposed that children with recently diagnosed WS, with no obvious cause detected, after clinical history, should be submitted to magnetic resonance imaging. An aCGH test may be included, followed by genetic tests and a biochemical epilepsy genetic panel, with determination of serum lactate, serum amino acids, and a urine organic acid research. Only if the etiology is not detected, a complete exome sequencing may be requested.[32]

TREATMENT

Several studies confirm that the precociousness of both diagnosis and treatment (within one month of spasm onset) is critical in the prognosis of the pathology as it leads to improved developmental outcomes. The main treatments for WS/IS are hormonal therapy, namely ACTH or high dose steroids and the GABA aminotransferase inhibitor, vigabatrin.[10][30] Still, many other treatments have been used and there are doubts about dosing regimens and duration of therapies.

However, ACTH is the first line drug in the control of infantile spasms, in the vast majority of cases (B level of evidence).[4][35]

Study comparing high doses ACTH vs prednisone and low doses ACTH vs prednisone

The most recent comprehensive review of data on the effectiveness of ACTH was published by the American Academy of Neurology and Society for Child Neurology. Fourteen studies of ACTH therapy were evaluated. They compared the ACTH effect vs oral prednisone effect, concluding about ACTH superiority. In this review, it was concluded that the administration of high doses of ACTH (75 IU/m^2/day, bid) was more effective in the treatment of infantile spasms than oral prednisone at a dose of 2 mg/kg/day bid, for example, two weeks of treatment. It was not possible to compare the effectiveness of using low versus high doses of ACTH, due to methodological variability. The response to low doses of ACTH 20 IU/day, did not differ from prednisone 2 mg/kg/day, so there is insufficient evidence that oral corticosteroids are effective, in the treatment of IS, with a maximum response rate around 30%, which was no different from placebo.[4]

In Europe, a synthetic analogue of ACTH, tetracosactide, is used in ampoules of 1 mg/ml, for intramuscular administration (50U = 0.5mg). The recommended optimal dose is not well established. There are protocols that advise the use of high doses (about 150U, bid) for two weeks, with a progressive decrease every two weeks, until completing a treatment period that varies from 6 to 9 weeks. The lowest dose protocol establishes 20-30 U/id over a period of two to six weeks.[2]

Study comparing Vigabatrin Vs Tetracosactide

The recent UK Infantile Spasms Study compared treatment with vigabatrin versus the reduced synthetic analogue ACTH 1-24 (tetracosactide) intramuscular or prednisolone. Twenty-one patients with TSC were not included in the study. It was used a low dose of ACTH 1-24 U and a very high dose of prednisone. The primary outcome was the clinical interruption of spasms by the parents' report, without requiring the elimination of hypsarrhythmia or confirmation of the interruption of spasms by EEG. Therefore, these data cannot be directly compared to the randomized clinical trials. The data is confirmed by the nonexistence of both spasms and hypsarrhythmia, which is further confirmed by the extended video EEG. This forms the basis of the practice parameter of the American Academy of Neurology/ Child Neurology Society. Furthermore, the UK Infantile Spasms Study was not able to compare the effects of treatment with ACTH 1-24 versus prednisolone.[32]

Study comparing high doses vs low doses of tetracosactide

In Finnish studies, there was no difference in the response rate or relapse rate comparing low doses (20-40 IU/day) and high doses (120 IU/day) ACTH 1-24. Yet, better long-term cognitive outcomes have been reported with low doses.[30]

Treatment with ACTH has side effects that may include hypertension, immune suppression, infection, electrolyte imbalances, gastrointestinal disorders, ocular opacities, hypertrophic cardiomyopathy, cerebral atrophy and growth impairment. Due to these side effects, a low dose and short-term therapy is recommended. While a patient is receiving treatment, the blood pressure, serum glucose, potassium and sodium should be monitored, infection and cushingoid signs should be checked.[2]

Studies comparing vigabatrin vs ACTH

However, vigabatrin is the first-line drug in the treatment of tuberous sclerosis, showing superiority to ACTH.

There are several studies that compare the effectiveness of ACTH vs. vigabatrin, suggesting that the two drugs have a similar effect. However, in the 2015 ILAE Consensus, the use of ACTH and glucocorticoids was established in the case of cryptogenic infantile spasms, as a result of the best results observed in the long term, in terms of psychomotor development, when compared with vigabatrin. Vigabatrin therapy shows greater efficacy with high doses (100-150 mg/kg/day) than low doses (18-36 mg/kg/day), yet, it does not have a greater number of side effects. It is advisable to start with a dose of 50 mg/kg/day, progressively increasing to 100-150 mg/kg/day, if necessary.[35]

If there is a response to therapy, treatment should be continued for six months. If there is no response, therapy should be withdrawn quickly and as early as possible. The 2015 ILAE consensus establishes the use of vigabatrin as a first-line drug in TSC (C level of evidence).[35]

ACTH plus Vigabatrin

A 2017 study showed that the combined use of ACTH and Vigabatrin is more effective than the isolated use of ACTH. [37] The potential for loss of visual field after treatment with vigabatrin is widely reported and this side effect should be weighed against the potential benefit in children with infantile spasms. Recent data suggest that the risk of loss of visual field in babies treated with vigabatrin for infantile spasms may not be as high as in elderly individuals receiving this medication.[30]

Other anticonvulsive Therapies and Surgical Treatment

In addition, ketogenic diet (KD), valproate acid, topiramate, zonisamide and pyridoxine may add some benefits when used after hormonal therapy and vigabatrin.

The ketogenic diet (KD) has been considered an adequate treatment for IS that were refractory to AED. [4][38][35] KD is a high-fat, low-carbohydrate diet. A study in which about 100 children, treated with KD, were analyzed, reported that in 64% of the cases, there was a

spasms reduction greater than 50%, up to six months after the onset of treatment. No adverse effects on growth parameters were documented. A random study showed that the short duration of eight months showed results similar to a long duration of two years, when observed only after three-five years of follow-up. It was suggested that chronic ketosis lasting for several months might substantially modify the brain hyperexcitability.[39]

We also analyzed a Portuguese study, which considered children who had presented previous refractory epilepsy and that were subsequently treated with KD for a period of at least eighteen months. In about 43,5% of those belonging to WS group, it was found a seizure reduction equal or greater to 50%. Furthermore, about 71,4% had shown a moderate marked improvement in the level of awareness and a marked improvement in behavior. This means that the effects of KD surpass the seizure control in terms of its outcomes.[38]

Surgical treatment may play a role in selected patients with IS secondary to cortical dysplasia. In case of infantile spasms due to structural changes and refractory to medical treatments, surgical removal of the injured area may be chosen. However, in case of diffuse injury or degenerative processes, surgery is not indicated.[40]

Emerging therapeutics

The poor prognosis of IS has led to the search for new therapeutic approaches. Typical antiepileptic drugs have shown to be ineffective. Vigabatrin and ACTH were approved for the treatment of IS, showing effectiveness only in a selected group of patients. Biological data have been considered essential for the development of new therapies that target specific Key-steps of ethiopatogenical mechanisms, probably enabling disease modification.

Ganaloxone

Since ACTH efficacy has been documented, neurosteroids were proposed as potential treatment of IS, in particular ganaloxone. Ganaloxone is a synthetic neurosteroid analog that modulates GABA-A receptors. As it was already mentioned, in a NDMA model of IS pre-sensitized with betamethazone, the use of ganoloxone in the dose of 25-50 mg/kg suppressed the development of spasms. Two open trials with evidence of efficacy were reported in a study of 79 patients with refractory IS, where ganaloxone was used in progressive therapeutic escalation. About 30% of patients (aged 6 months to 15 years) showed approximately a 50% reduction in the frequency of spasms. Maintaining ganaloxone therapy for an additional two months, 10 of the 79 children showed a 25 to 50% decrease in the frequency of spasms.[41] Also, the agonist has been considered as a potential adjunct to hormonal therapy for IS. Yet, several clinical studies are still required so that its use and optimum dosage are recognized and formally established.

Flunarizine

Flunarizine is a voltage gate calcium channel blocker that has been suggested as IS potential therapy as it may have neuroprotective effects. In a randomized controlled trial (RCT), the addition of flunarizine to standard therapy has been tested but showed no protective effect on cognitive outcome in a cohort of IS as whole. Still, flunarizine showed improved cognitive outcome among children with unknown etiology.[21]

Other agents

Rapamycin is a TORC1 inhibitor. In multi-hit-rat model, a high dose pulse rapamycin (3 mg/kg at PN4, 6 mg/Kg at PN5 and PN6) suppressed spasms promptly and improved visuospatial learning at PN16-19. However, when rapamycin was given in too immature cubs, its effects were inconsistent, as it tended to worsen rather than improve learning on Barnes labyrinth. Differently, pre-treatment with low rapamycin doses was given in the prenatal NMDA model without any acute effect on NMDA spasms. Yet, this gives hope to new therapies as the mTOR pathway is implicated in the pathogenesis of TSC and other "TORopathies"- a wide spectrum of diseases involved in the dysregulation of mTOR pathway such as focal cortical dysplasia and hemimegalencephaly.[22] Furthermore, acquired pathologic conditions associated with epilepsies and IS, such as hypoxia, stress, inflammation, endocrine dysfunction and metabolic disorder can disrupt the MTOR pathway.[17][10] The phase III, prospective, multicenter, placebo-controlled study EXIST 3 (Examining Everolimus in a Study of TSC), which enrolled 366 patients, assessed the efficacy and safety of everolimus treatment on TSC epilepsy patients. Everolimus was used as an adjunctive therapy for treatment of resistant focal-onset seizures associated with TSC, in low (3–7 ng/mL) and high (9–15 ng/mL) doses. A significant reduction was found in seizure frequency on both groups, greater than 50%. There were limited adverse effects (about 15%), which included stomatitis, diarrhea, nasopharyngitis, pyrexia, and upper respiratory tract infection, although not overlapping with adverse effects from other AEDs. Thus, everolimus, a disease-modifying drug targeting the underlying molecular pathology of TSC can be a therapeutic option in refractory epilepsy in TSC patients.[43]

CPP-115 (vigabatrin analog) and carisbamate have been tested in some animal models of IS and have shown good results. Preclinical studies, using ARX-model of X-linked infantile spasms tested neonatal estradiol stimulation, with spasms prevention. Other novel therapies using insulin-like growth factor(IGF)-1 might increase synaptic development.[30]

EVOLUTION AND PROGNOSIS

The remission of spasms and the disappearance of hypsarrhythmia in patients, without therapy, seem to occur in 25% of cases, by one year of age, in 50% of patients, by two years of age and in almost all patients, by five years of life. About 50% of patients will develop another type of seizure. Frequently, those patients who had a diffuse or multifocal electroclinical dysfunctional pattern often evolve to Lennox Gastaut Syndrome.[2] In those with IS showing focal lesions, as is usual in patients with TSC, the display of focal epilepsy is more frequent. In general, the prognosis in terms of neurodevelopment in the medium to long term is poor. Some genetic mutations have specific outcomes - for instance, ARX mutations have shown great impact on autistic outcome.[14] In a cohort study of 214 patients who had been treated with ACTH therapy and were followed for 20 to 30 years or until the date of death, only 24% had a normal or borderline cognitive profile. About 50% had motor impairment.

It is recognized that the underlying pathology of patients with IS/WS has a marked influence on prognosis. Only the group of those with a history of IS in which the etiology is unknown presents a good percentage of cases with normal cognitive evolution, corresponding to about 50 to 80%. Those who had presented IS and included the category of genetic, structural or metabolic etiologies, belonging to the traditional symptomatic group, had a normal cognitive profile in only 5 to 20% of cases. A greater compromise of neurodevelopment is expected for those who present ab-onset of IS with a structural or genetic syndrome or delayed psychomotor development.[2][10][20][24][25] This means that if there is a gene mutation underlying a structural lesion probably it will be also responsible for the epileptic phenotype and the cognitive delay.

A retrospective study, conducted in Turkey, followed a cohort of 104 patients diagnosed with IS, followed up on an outpatient basis at the Pediatric Neurology Clinic at the University of Cukurova. The results were as follows: patients who had an early onset of spasms showed moderate and severe mental retardation, while patients who had normal intelligence or mild mental retardation (MR) started epileptic spasms later. About 29 patients (85%) who had a known etiology had had neonatal seizures, previous to spasm, with a poor cognitive prognosis. Parental consanguinity showed a greater association with reserved epileptic prognosis than with worse cognitive prognosis. The study showed that the presence of etiology, the age of onset of spasms and the fact that they started treatment in one center and not in another were the variables that most influenced the prognosis, both epileptic and

cognitive. Interestingly, the circumstance of starting treatment at a given center and not at another influencing the prognosis was not attributed to the time that elapsed before the start of treatment, since no significant temporal differences were found. The researchers related this result to differences in the administered therapy.[44]

In fact, the UKISS study published in 2011 showed that, regardless of the age at onset of the spasms, the etiology and type of treatment, the waiting time for treatment (the period between the onset of the spasms and the start of treatment) was significantly associated to a decrease in the development score at 4 years of age. There was no threshold value of waiting time below which the development was not affected, which could be used by the doctor as a reference for a critical limit for initiating therapy. What happened was a steady decline in the values of the development scores as that time increased. This study also showed and confirmed that the earlier the onset of spasms, the worst results in terms of neurodevelopment, regardless of the effect of the waiting time for treatment. This suggests that the adverse effects of epileptic encephalopathy are more severe in those with more immature brains. It could be suggested that those patients with the greatest neurological lesion had an earlier onset of spasms, but no significant difference was found in relation to the onset of spasms between the symptomatic groups and those of unknown etiology. In addition, the study confirmed the superiority of hormonal therapy in the group of children with IS of unknown etiology in terms of neurodevelopment. [45]

RELATIONSHIP WITH AUTISM

Written documents, throughout the monitoring of James Edwin West's illness, account for peculiarities of behavior with growth, namely "unexplained laughs", "repetitive nodding movements", "notorious fixation for specific interests, such as music and cheerful colors" and also "a great tendency towards automatisms and rhythmic actions".[13] Such reports raised the hypothesis that children with IS presented a greater risk of developing ASD.[5][46] About 30% of patients with ASD have associated epilepsy and there is evidence that there is an association between epileptic encephalopathies and autism.[47] In fact, in the general population, the prevalence of ASD (1%) is lower than that found in the population with IS (from 9 to 15%). Investigations in Genetics field have suggested that there will be a cerebral synaptic dysfunction common to infantile spasms and ASD.[46] In addition, patients with ASD present alterations in the genes involved in brain development processes, with cortical interneuronal dysfunction and associated epilepsy. This is the case of TSC, one of the etiologies of IS that presents an increased risk of ASD.[47] In fact, TSC is an important cause of ASD: a clinical syndrome defined by impaired social interaction and communication, restricted interests and repetitive behaviors.[48]

In TSC, ASD has a prevalence of 26% - 61%, with an average value of 32%.[49] The diagnosis of autism did not show to be determined by a previous history of infantile spasms, even if this variable was adjusted for the group of children with symptomatic IS. What was found is that there was an association between ASD and IS if they were symptomatic. This means that it is probably the presence of a metabolic, genetic or structural etiology that predicts the likelihood of developing ASD and not so much the presence of infantile spasms.[10][50]

In another retrospective cohort study of patients with TSC, which has demonstrated an association with a high prevalence of ASD (36%) and also closely related to IS, it was shown that not all patients with IS developed ASD and not all patients with ASD had previously had IS. “This suggests that spasms were a marker of the liability for autism spectrum disorders rather than a risk factor.” It was documented that “the association between autism spectrum disorders and a history of spasms was no longer evident when age to seizure onset and evidence for a temporal lobe epileptiform focus were included in an exact logistic regression model”.[51] This clearly suggests that in TSC, ASD does not straightforwardly depend on IS. Hence, ASD and IS may be two separate end-results of a common CNS defect.[50]

In addition, a multicenter prospective Canadian study published in 2015 confirmed the relationship between infantile spasms and the development of ASD, but not in all patients. In this study, only patients with IS classified as symptomatic presented this type of disorder. Other characteristics, such as presenting chronic electrical activity in the frontotemporal region, subsequent to the disappearance of hypsarrhythmia, showed concomitance with the development of ASD in patients, who had had a history of symptomatic IS.[46]

DISCUSSION

Infantile spasms appear as a clinical entity that is expressed in a very high number of underlying pathologies, which seem to be very distinct and relatively rare. This means that innumerable morbidities, during its natural history, can present an age dependent Infantile Spasms state, which is itself an increased morbidity factor, with a high risk of neurocognitive deterioration. Thus, it is crucial to identify the underlying etiologies that, in the course of their evolution, are associated with this presentation.

Yet, we think that the classification is also not negligible. The ILAE classification recommends a wide range classification in three groups: genetic, structural/metabolic and unknown. Clearly, this proposed classification recognizes the enormous importance of etiology in IS prognosis and approaching therapies. The predecessor classification used only

3 groups (symptomatic, cryptogenic and/or idiopathic) and showed clear scarcities.

We believe that adding detail to classification, incorporating ICD10 as it was emphasized in some studies that we analyzed[29] will enable further explanatory studies while simultaneously clinical decision making could be empowered. It is important to identify if the etiology is prenatal, neonatal or post-natal, whether genetic or acquired, since outcomes can be anticipated. At the very least, this enables genetic counseling and allows further clarification on parents' fears regarding having another child.

It is the group with proven etiology or with known etiology that has the worst cognitive and epileptic prognosis. Many of the etiologies are easily recognizable on objective examination and easily confirmed by EEG or neuroimaging. Special care must be taken in those cases of metabolic etiology. These cases may require other approaches which are particularly directed to the etiology, making the administration of the currently recommended drugs unnecessary, useless or even iatrogenic.

Obviously, factors related to the methodology used in the diagnostic approach of this clinical entity influence the prognosis. In fact, IS/WS are epileptic encephalopathies that appear, as we have seen, in an early period of brain development and have a very reserved prognosis in terms of neurodevelopment, with high emotional and social costs. It is known that the early control of spasms, with a reduction in the period of exposure of neural networks to aggressions, is fundamental in terms of psychomotor development. Shortening the duration of the encephalopathic epileptic condition is essential to minimize the cognitive consequences.

Parents and caregivers who are in charge of children with basic pathology that increases the risk of presenting IS should have access to information that allows them to be attentive. Primary care physicians should also be trained to be able to refer to specialized care: Neuropediatrics.

A rapid diagnosis, a systematic protocol that allows the rapid detection of the etiology and the rapid implementation of an effective and targeted therapy contributes unequivocally to minimize its encephalopathic effect. Video recording, EEG, neuroimaging, epilepsy panel, metabolic and autoimmune panel should be sequentially performed, if there are persisting doubts on the etiology.

Only then will it be possible to minimize the time between the onset of infantile spasms, the diagnosis of the clinical entity, the determination of the etiology and the implementation of a specific and recommended therapy, capable of allowing the control of this encephalopathy. As a matter of fact, the clear definition of an etiology for SW is of great relevance as it guides treatment. A good example is cortical dysplasia with the possibility of surgical approach.

Another example is the finding that patients with SW and TSC benefit from vigabatrin to control spasms.

Concerning treatment, adrenocorticotropic hormone is preferred for short-term control of IS (B level of evidence). Oral steroids can probably be effective in short-term control of spasms (C level of evidence) and a shorter lag-time for treatment after IS onset and diagnosis may improve long-term neurodevelopmental outcomes (C level of evidence). The Ketogenic diet can be used as add-on treatment on refractory IS and, additionally, constitutes the treatment of choice for epilepsy related with glucose transporter I (GLUT1) deficiency syndrome and pyruvate dehydrogenase deficiency (expert opinion, level U of evidence). Vigabatrin is the treatment of choice of IS, TSC related (C level of evidence). Surgery can be considered in potential candidates.[35]

Regarding pathophysiology, we put the emphasis on experimentation on animal models. This is still an unknown theme, which demands further investigation. So far, many IS animal models were not able to exactly replicate what happens with the child. In many of them, the spasms and the hypsarrhythmia did not appear in the expected timeframe and it was not possible to perform pharmacological tests or the pharmacological test results were not the same as what was anticipated. Either way, there is a necessity to continue experimenting with animal models, besides working on clinical trials, since that is the only way that it will be possible to evolve from the actual state of the art to a new state that involves a more accurate management, knowledge and better control of this encephalopathy's prognosis.

CONCLUSION

In conclusion, the etiology is the major predictor of the prognosis of IS/WS. Definitely, the treatment of IS has remained unchanged over the last several years. About a third of IS cases do not respond to the conventional recommended drugs ACTH and vigabatrin.

This highlights the need for further investigation both on clinical trials and on animal models. Mimicking infantile spasms would certainly provide a better understanding of pathophysiology and new therapies could be explored.

We believe that there are a number of issues that can contribute to improving the prognostic impact of this epileptic encephalopathy: the identification of the underlying etiologies of infantile spasms, the elucidation of the pathophysiological mechanisms involved, an accurate therapeutic management of recommended therapies and, more importantly, research on new drugs and therapies, either targeting each etiology/group of etiologies, or targeting a common mechanism.

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