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Research Article

West Syndrome: Clinical Characteristics, Therapeutic, Evolution and Prognostic Factors

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Abstract

Introduction: West syndrome (SW) is the most severe, devastating and/or catastrophic epileptic encephalopathy of breastfeeding.

Objective: To identify clinical features of West syndrome, etiology, therapeutics and prognostic factors.

Methods: An observational study was performed based on review of clinical files. Inclusion criteria were defined. We included 39 patients admitted from January 2010 to December 2016. Statistical analysis was applied.

Results: The genetic, structural/metabolic etiology was predominant. Hypoxic-ischemic encephalopathy (25.6%) and neurocutaneous syndromes (17.9%) were more frequent. In 25 (64.1%) the combined treatment of adrenocorticotropic hormone (ACTH) and Vigabatrin was used, in 18 (72%) control of the IE or reduction was achieved ≥ 50% and in 14 (56%) hypsarrhythmia disappeared in the first 6 months ($p < 0.05$). 100% had transient hypertension as an adverse effect to ACTH. 71.8% developed moderate to severe psychomotor retardation, 35.9% to Lennox-Gastaut syndrome and 43.6% to other epilepsies. There was an unfavorable evolution in 74.3%. The most significant prognostic factors for unfavorable evolution were male gender, symptomatic etiology, psychomotor retardation and/or abnormality on neurological examination, epileptic seizures and previous pathologic electroencephalogram, poor response to treatment and persistence of hypsarrhythmia and Combination of factors by more than 65% ($p < 0.05$).

Conclusions: Combined use of Vigabatrin and ACTH may reduce the length of spasms and the EEG Hypsarrhythmic pattern. Poor outcomes are related to a combination of prognostic factors.

Keywords: *Infantile Spasms; Hypsarrhythmia; Etiology and Prognostic Factors*

Introduction

West syndrome (SW) is the most severe, devastating and/or catastrophic epileptic encephalopathy of breastfeeding [1]. It was first described by Dr. William James West in 1841 in his 4-month-old son, who recounted in a letter sent to the Lancet magazine the first semiology of Infantile Spasms (EI) [2-5]. Recognized and updated in the 2010 ILAE Classification proposal [6], which defines it as a triad of epileptic spasms (EE), electroencephalogram (EEG) Hypsarrhythmia, and retardation or regression in psychomotor development (DPM) last not essential for its definition.

It is an age dependent epilepsy, the age of onset varies from 4 to 10 months with maximum peak of appearance between 5 to 7 months and can extend until 2 years [3,7,8]. It is estimated an incidence of 1 per 4,000 children [1,3,4,9], there are no studies in this regard in our country. It has a frequency between 2 to 10% of the total epilepsies in childhood, it is the most frequent encephalopathy of appearance before the first year, excluding the neonatal Otahara syndrome, with which there is a close relationship of continuity. There is a slight predominance in males of 1.5 to 1.3 [7,8].

The EE in the classification of the ILAE in force until 1989 [3,10,11], were named Infantile Spasms (EI) for their close bond and SW exclusivity, presentation in early childhood and lactation. In the new classification, ILAE 2010 [6], they were recognized as EE due to their relationship with other epileptic syndromes outside of this period, although the term of EI [3] continues to be used when referring to those that occur before 2 years of age and nexus with the SW Fejerman N [11], Caraballo RH and collaborators [11], Navas-Sánchez and collaborators [12] in recent investigations and series of published cases observed patients who had EE without Hypsarrhythmia in the interictal EEG, interpreting it as a variant of SW and not a different epileptic syndrome, that it is relevant to perform critical EEGs to focus the differential diagnosis with other epilepsies of this stage and paroxysmal non-epileptic events [10].

The IE usually occur in salvas or cluster (spasm groups of different intensity, frequency and/or duration), are axial contractions that last from 2 to 3 seconds, can be in flexion, extension or mixed, more on waking or in the transition from slow sleep to REM. As subtle as the deviation of the eyes upwards, slight movements of pitch or elevation of the shoulders and autonomic signs. They are usually symmetrical, but may be asymmetric or focal, alternating and associated with focal seizures; evidencing in this case the possibility of focal lesion or agenesis of the corpus callosum [1,3-5,10,13-15].

Etiologically, they are classified as symptomatic, cryptogenic or probably symptomatic, as the most frequent and rare idiopathic cases according to the previous classification of the ILAE [3,9]; in relation to aggressions or prenatal, perinatal and postnatal antecedents. In the new classification, ILAE [6,9,13] intends to use the term: genetic, structural/metabolic and unknown cause. A few decades ago, patients with symptomatic SW were around 50% to 60% of the known etiology, currently with the advent of neuroimaging studies of great specificity and sensitivity, such as nuclear magnetic resonance (NMR) and single positron emission tomography. PECT studies of metabolic screening and molecular genetic techniques has increased up to 80%; which allows identifying a greater number of patients with structural/metabolic and genetic alterations responsible [15-17]. The correlation of the interrogation or anamnesis and the abnormality of the general and/or neurological physical examination (EF) inevitably allow an approach to the etiological diagnosis and the rationality of the complementary examinations; being the knowledge of the etiology of importance, by conditioning the optimal treatment and its response, with implication in the evolution and prognosis [7,15-17].

Most of the cases have an unfavorable evolution, related to different prognostic factors that alone or combined influence the severity [3-5,7,15]. There is evidence of different effective drugs in their management and it continues to be controversial which one to use first choice. Currently, the combined treatment of Vigabatrin (VGB) plus adrenocorticotropic hormone (ACTH) is recommended, the two most effective therapies demonstrated; Other drugs such as Valproic Acid (AVP), Benzodiazepines, Vitamin B6 (VB6) and more recently Topiramate (TPM), Levetiracetam (LVT) and Zonisamide (ZSD) have shown efficacy. There are other alternatives, with more and more frequent use in reference centers in epilepsy such as the ketogenic diet, intravenous gammaglobulin and surgical treatment in refractory cases and specific situations [4,5,7,8,13,15,18-30].

Objective of the Study

The objective of this work is to identify the clinical characteristics of the SW of our patients, attending to the etiology, the semiology, the EEG, the therapeutic used and the adverse effects. Establish the prognostic factors that influenced their evolution using different variables.

Methods

Design, context and participants

An observational, descriptive and retrospective study of patients diagnosed, admitted and treated as SW at the Pediatric Teaching Hospital Centro Habana (HPCH), Havana, Cuba in the period from January 2005 to December 2016 was carried out. This study included the informed consent of parents and/or tutors and of the center's ethics-scientific committee. Their evolutionary care was completed on an outpatient basis or hospital admission according to individual needs.

All patients with IE and Hypsarrhythmia on the EEG of onset before 2 years of age, with or without alteration in the MPD, were included, diagnosed, admitted, treated and followed up in Neuropediatric consultation after 2 years. We excluded patients who left the follow-up and/or clinical history with insufficient data. Of the total of 45 patients, 39 (22 boys and 17 girls) were included and 6 patients were excluded.

Variables and interventions

The following were recorded for each patient: Age of onset of the IE, sex, semiological characteristics of the IE (frequency, type, symmetric/asymmetric) and description of the EEG, abnormalities in the neurological examination to the physical examination, psychomotor development (DPM) prior to initiation of IE and later, related Etiology, clinical evolution towards other types of epileptic seizures and/or epileptic syndromes recognized by ILAE, related comorbidities (intellectual disability and autistic spectrum disorder), therapeutic options used, response and adverse reactions, prognostic factors and unfavorable evolution.

The age of onset of the IE was subdivided at the beginning before 4 months (< 4 months), between 4 and 8 months, after 8 months (> 8 months). According to the ILAE 6 classification, the terms were used when referring to etiology, genetics, structural/metabolic and unknown cause. To all study patients in connection with significant prenatal, perinatal and postnatal antecedents, clinical manifestations and evaluation of the physical examination, biochemical studies were performed, including glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, lactic acid, lactic acid dehydrogenase and ammonia. of the results the neurometabolic study was extended to the qualitative study of amino acids in urine and quantitative in blood; serology for Cytomegalovirus and IFI Toxoplasma. A neuroimaging study was performed that included transfontanellar ultrasound, computerized axial tomography (CAT) and magnetic resonance imaging (MRI) of the skull in specific cases. That clarified the possible etiology and of not finding proven cause was called unknown [1,3-5,7,8,13,15-17].

It was defined according to the experience of different authors and publications [3-5,7,8,10,13,15,31,32]:

EEG hypsarrhythmia interictal: The presence of paroxysmal slow wave discharges, spikes and polyspikes of great amplitude of duration and variable, symmetric, asymmetric or alternating locations, with or without paroxysmal voltage attenuation, which give it a pseudoperiodic aspect. With a highly disorganized base rhythm.

Subclinical spasms: The presence of generalized slow waves of high amplitude, fast and rhythmic activity called spindle - like due to its resemblance to sleep spindles with diffuse voltage attenuation.

Prognostic factors: Male sex, the presence of significant prenatal, perinatal and/or postnatal antecedents, prior to the onset of IE: paroxysmal EEG, delay in MPD and/or neurological abnormality to PE, neonatal epileptic seizures or before the appearance of The beginning of the EI before 4 months; time lost before the start of treatment or diagnosis of more than 1 month, known etiology, no response to treatment with monotherapy (a drug) or biterapia (2 drugs), hypsarrhythmic EEG that persists after 6 months of therapy initiation and combination of more than 3 factors.

Unfavorable evolution: Persistence of spasms and Hypsarrhythmia in the EEG after 6 months of treatment, little response to bitherapy, regression of the MPD or moderate or severe DPM delay and/or abnormality in the neurological physical examination; Intellectual disability (ID) moderate or severe and/or Autism spectrum disorder (SAD), evolution to Lennox-Gastaut syndrome (SLG) or other epilepsies, death.

Adverse reaction to medication: Irritability, weight gain, immunosuppression or added infections, transient arterial hypertension (HT), hydroelectrolytic disorders and hyperammonemia.

All patients underwent EEG with sleep deprivation, before and after the start of treatment (15 days, 1 month, every 3 months during the 1st year) when evaluating their response and according to clinical evolution. It was observed if the Hypsarrhythmia disappeared before 2 months (< 2 months), between 3 to 5 months or persisted after 6 months (> 6 months). According to the clinical characteristics, they were evaluated by the ophthalmology, genetics and child psychiatry service.

Scheme of treatment used according to etiology [18-30,32-34]

If known etiology or symptomatic/structural, except neurometabolic disease attending to the absence of symptoms and/or acute infectious signs, dermatological conditions, hypertension, liver or kidney damage. The combined treatment of synthetic adrenocorticotropic hormone (ACTH) plus Vigabatrin (VGB). ACTH at a dose of 0.0125 mg/kg/day intramuscular with presentation of 1 mg/1 ml ampules, at intervals of alternate days the first and second week, according to the response 2 times the third week and once a week without exceeding 6 weeks; most frequent dose used 2 tenths. VGB at doses of 50 to 200 mg/kg/day every 12 hours, with an initial dose of 25 mg/kg/day increasing every 3 days; maximum dose 3000 mg (6 tablets), if a good response is observed between 4 to 6 weeks, the treatment was continued for 4 to 9 months, then it was replaced taking into account clinical characteristics and EEG for Valproate sodium (AVP) at a dose of 20 to 60 mg/kg/day in 2 or 3 sub-doses, increasing at a rate of 5 mg/kg/day every 5 days. If contraindication to use ACTH started only with VGB.

If there was no response to GBV in the first 4 to 6 weeks: no disappearance of IE and Hypsarrhythmia persisted on the EEG or no IE was reduced by more than 50% of the initial number. It is added or replaced with consent of parents and/or guardians by AVP, if not answer topiramate (TPM) at doses of 3 to 25 mg/kg/day in 2 sub-doses, increasing at a rate of 0.5 to 1 mg/kg/day every 10 days and maximum dose of 400 mg and Levetiracetam (LTV) at doses 30 to 60 mg/kg/day in 2 sub-doses, increasing at a rate of 10 mg/kg/day every 7 days, maximum 3000 mg. If not responding as a third line clobazam (CLB) at doses of 0.1 to 1 mg/kg/day in 2 to 3 sub-doses or clonazepam (CLN) at a dose of 0.025 mg to 0.2 mg/kg/day in 2 or 3 sub-doses.

If unknown etiology/probably symptomatic or Down syndrome or suspected metabolic error, treatment with VB6 was started at a dose of 300 mg per day in 3 sub-doses. Response was evaluated in the first 4 days, if there was no variation of the EI or was increased, the same scheme of known or symptomatic/structural cause was used. If I suspect or confirm congenital error of the metabolism, treatment with GBV was started, according to the answer other drugs were used except PVA (metabolic disease of urea cycle disorder, mitochondrial disease or hyperglycinemia without ketosis).

We did not use other corticosteroids or other therapeutic options, the drugs were used according to the pharmaceutical availability and treatment was adapted according to evolution to other epileptic syndromes. Patients treated with ACTH, its use was under medical supervision and hospital admission. The response to treatment was evaluated: disappearance of the IE and Hypsarrhythmia, free of IE and maintains the Hypsarrhythmia, reduction of more than 50% of the IE and persistence of the Hypsarrhythmia; if they were not reduced by 50% and Hypsarrhythmia persists as a non-response.

Statistical processing

The data was collected in a Microsoft® EXCEL 2010 database, tables and graphs were made, expressed in absolute frequency and some quantitative variables as percentages. Chi^2 test was used for columns and rows, $p < 0.05$ was considered significant. A Confidence Interval (CI) of 95% was used. For the statistical analysis, the SPSS 16.0 program for Windows® was used.

Results

Of the 39 patients studied, there was a distribution by sex (22 male and 17 female), with a male predominance of 56.4%. According to the age of onset, there was a higher frequency of onset of IE between 4 and 8 months with 23 (58.9%) and less than 4 months with 12 (30.7%) without statistical significance (Figure 1).

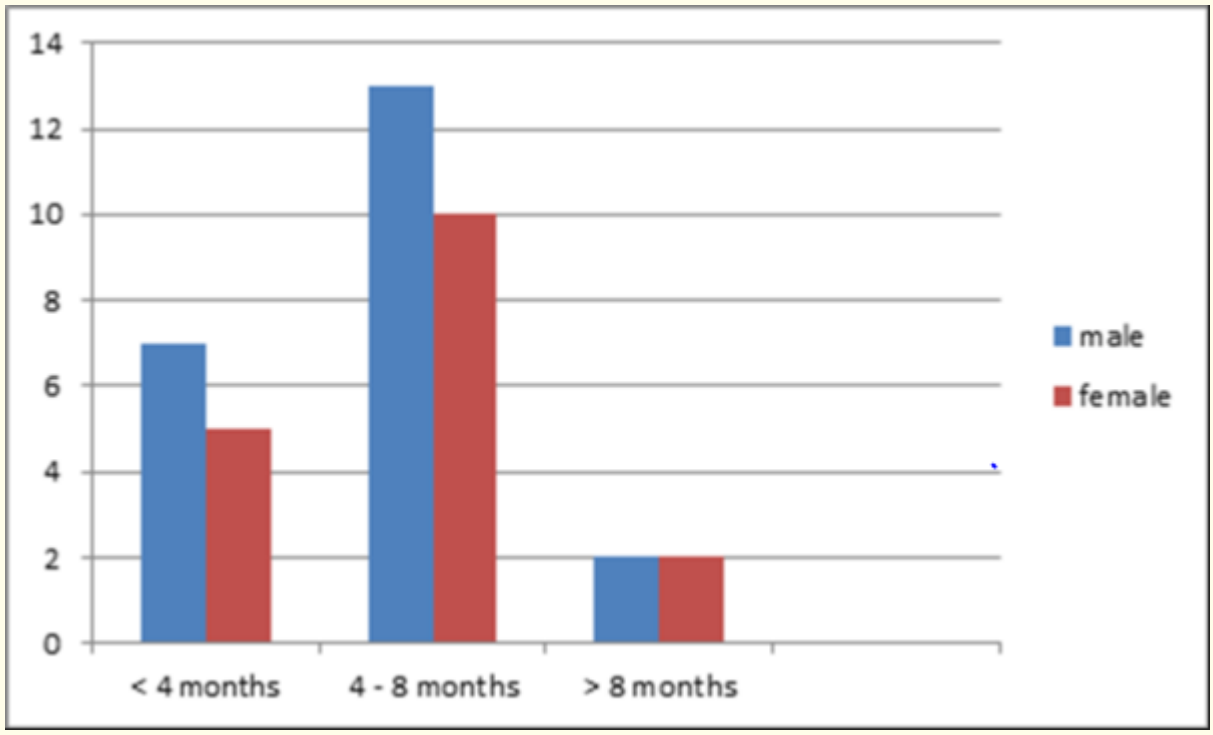

Figure 1: *Distribution of patients according to age of onset of IE and sex. Pediatric Hospital Teaching Center Havana. 2005- 2016.*

EI (Infantile Spasms) Chi2 = 0.09 p = 0.95.

Source: Clinical history.

There was a predominance of the structural/metabolic etiology with 30 (76.9%), of them had: Hyperammonemia (1) as a metabolic cause, Kernictero (2 ABO conflict) and sequelae lesions in white matter and basal ganglia, Post infectious (1 to Meningoencephalitis bacterial one month of life with hydrocephalus and 1 congenital Cytomegalovirus), neurocutaneous syndrome (4 tuberous sclerosis, 1 pigmentitis, 1 Sturge-Weber syndrome, 1 Proteus syndrome and Hemimegalencephaly), neuronal migration disorder (2 polymicrogyria), Hydrocephalus (2), Agenesis of the corpus callosum (2), ischemic cerebrovascular disease (CVD) of prenatal (2) and perinatal origin (1),

intraventricular hemorrhage (2 pre-terms between 30 to 32 weeks) and hypoxic ischemic encephalopathy (HIE) with periventricular leukomalacia as sequela (10) in one combined with intraventricular hemorrhage. The genetic cause (2) for INV 21 (P112-q21) 13 pst 5tk and Down syndrome or trisomy 21, no known cause was defined in 7. Of the total in 32 (82%) it was related to specific/known cause and the most frequent were the HIE (25.6%) and the neurocutaneous syndromes (17.9%) of structural etiology, the unknown represented 18% (Figure 2).

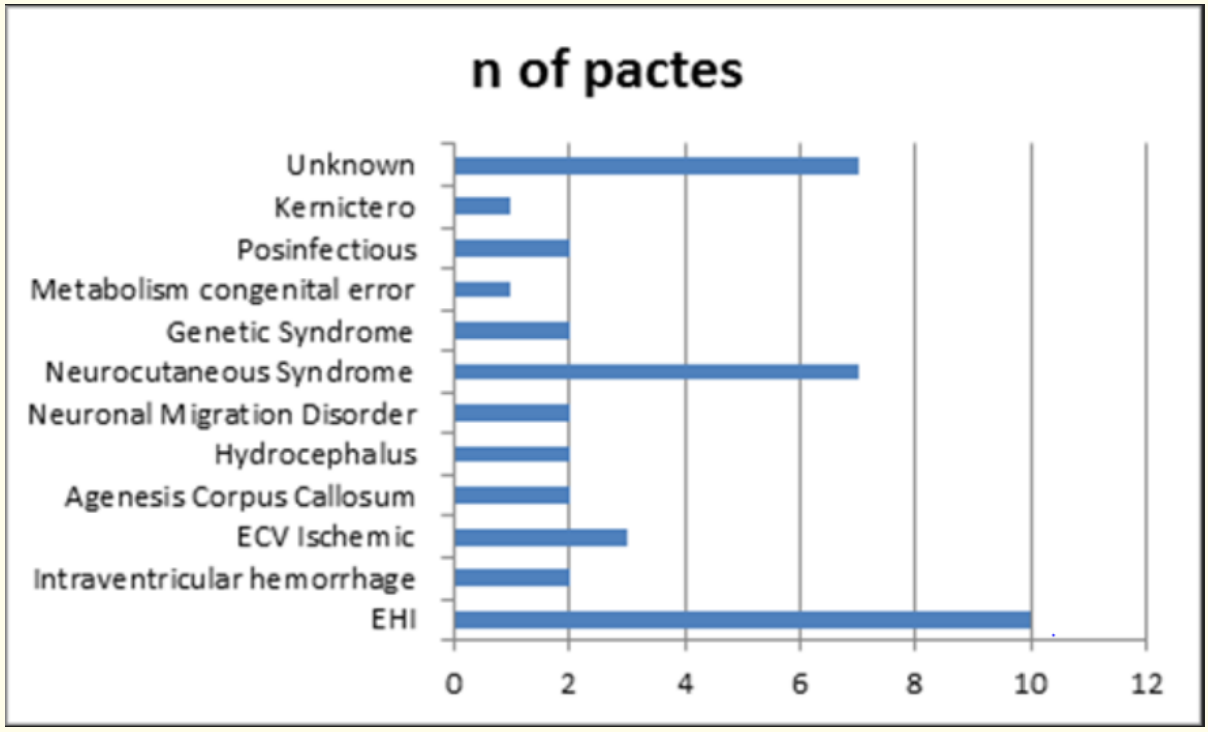

Figure 2: *Etiologies related to West Syndrome.*
CVD: Cardiovascular Disease; EHI: Ischemic Hypoxic Encephalopathy.
2 patients combined (Bactrian meningoencephalitis + hydrocephalus), (EHI + intraventricular hemorrhage).
Source: Clinical History.

According to the clinical characteristics and EEG (Table 1). According to the semiology the IS in flexion (51.2%) and mixed (35.8%) are the most frequent being 92.3% symmetrical, of the 3 asymmetric, 2 had Agenesis of the corpus callosum and 1 a porencephalic cyst secondary to ischemic CVD, although they also had symmetric EI. In 4 (10.2%), IE was associated in particular with discogenic motor focal crises (upward gaze deviation, palpebral colonies and disconnection). In the EEG, symmetric characteristics of Hypsarrhythmia were described in 92.3% according to the semiology and in 3 was recorded the subclinical (spindle - like).

T (39)	N (%)
# by EI	(15-350)
Fashion	106
Semiology of EI	
Flexion	20 (51.2)
Extension	5 (12.8)
Mixed	14 (35.8)
Associated with focal crisis	4(10.2)
Symmetrical	36 (92.3)
Asymmetric	3 (7.7)
EEG	
Symmetrical	36 (92.3)
Asymmetric	3 (7,7)

Table 1: *Clinical characteristics and Electroencephalogram.*

EEG: Electroencephalogram; EI: Infantile Spasms.

Source: Clinical History.

The clinical evolution of the children studied (Table 2) shows that 30 (76.9%) had abnormality to neurological EF from the beginning of IE accompanied by moderate or severe PDD delay in 25 (71.8%) and 4 (10.2%) had a regression of the DPM, of them 5 developed an APR and when arriving at the school age they had moderate DI (14)/severe (9) and mild (3) when evaluated in conjunction with the psychiatry and psychology service of the center, 2 patients have average normal intelligence (CI), DPM and normal EF. 53.8% did not have good control of the EI and 35.9% evolved to the SLG and other Epilepsies (43.6%), of them 10 with focal characteristics on the EEG and 7 with multifocal spikes. The deceased patient had a Proteus Syndrome and the cause of death unrelated to SW (Bronchopneumonia and respiratory failure).

Total (39)	N (%)
Moderate or Severe DPM Delay	25 (71.8)
DPM Regression	4 (10.2)
Síndrome Lennox-Gastaut[a]	14 (35.9)
Other Epilepsies*	17 (43.6)
Without control EI	21 (53.8)
Positive neurological physical examination	30 (76.9)
Mild intellectual disability	3 (7.6)
Death	1 (2.6)

Table 2: *Clinical evolution of the patients studied.*

DPM: Psychomotor Development; EI: Infantile Spasms.

[a]: 5 Autistic Spectrum Disorder. Fo 10 focal, 7 multifocal.

Source: Clinical History.

When observing the relationship between the different therapeutic options and EEG (Figure 3) it is shown that the combination of ACTH and VGB was used as a first option in 25 (64.1%) and GBV alone or combined with other drugs in 14 (35.9%), the patients who used this combination were those who had congenital error of metabolism (1) or other contraindications (acute respiratory or diarrheal infections and infested skin lesions) and in 3 that the parents did not give consent for the use of ACTH.

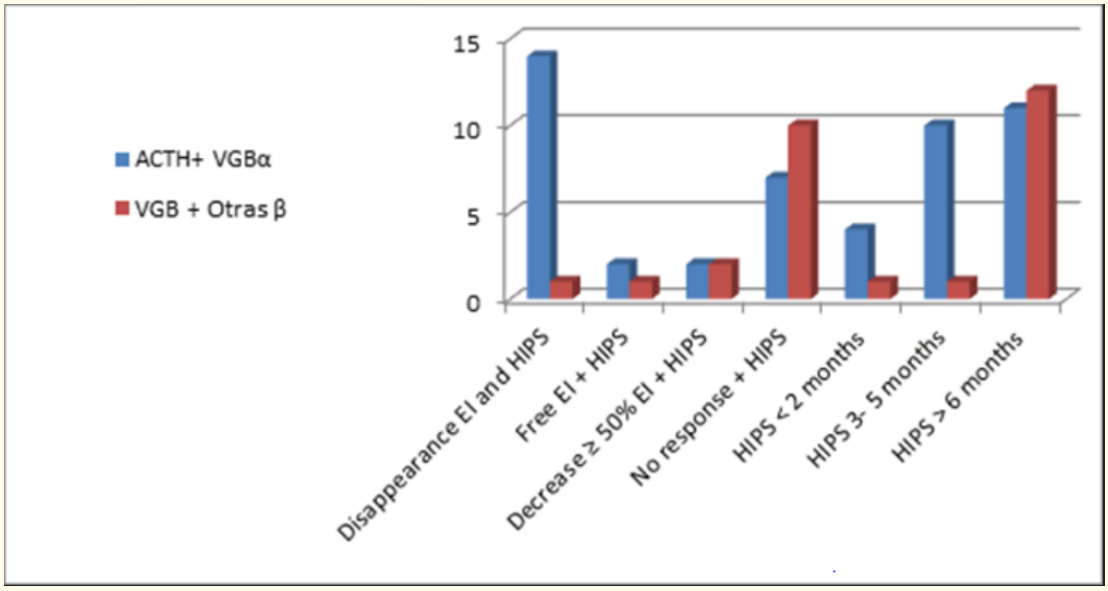

Figure 3: *Relationship between the response to different therapeutic options and Electroencephalogram. ACTH: Adrenocorticotropic Hormone; VGB: Vigabatrin; HIPS: Hypsarrhythmia. Response-therapeutic options: chi² = 9.92, p = 0.019; EEG: chi² = 6.63, p = 0.034. Source: Clinical history.*

Of the total that was used ACTH and VGB as combined therapy there was a control of the EI or decrease ≥ 50% in 18 (72%) and a disappearance of the EI and Hypsarrhythmia in 14 (56%) without need of other drugs vs 4 (28.5%) when using only GBV, in 7 patients regardless of the combined treatment or not due to the persistence of Hypsarrhythmia and not total control of the IE, other drugs were associated. Of the total of 17 (43.5%) of them, 7 (with ACTH and VGB) vs 10 (with VGB and others) had no response, poor control EI and persisted Hypsarrhythmia despite the association of other drugs (polytherapy) with significance statistics of $p < 0.05$. When evaluating only the therapeutic response and the EEG, it was noted that of the 25 patients who were treated from the beginning with combined treatment of ACTH and GBV in 14 (56%) there was disappearance of the Hypsarrhythmia in the first 6 months vs 2 (14.2%) of the 14 with GBV and other drugs, of them 5 in the first 2 months (4 with ACTH and VGB) with statistical significance of $p < 0.05$ between both groups.

A better response was observed when using combined ACTH and GBV (14), in patients with known or symptomatic etiology: 5 with neurocutaneous syndromes (except 2 with tuberous sclerosis), 2 with genetic syndromes, 2 with CVD of prenatal origin, 2 with EHI and 3 of unknown etiology. The 2 who had the same response with initial GBV treatment in monotherapy were 1 with hyperammonemia and 1 EHI.

Of the patients with initial treatment of ACTH and combined GBV, in 11 due to a low response to GBV or relapse, this AVP was associated and in 4 benzodiazepines (2 CLB and 2 CLN) were added, in 3 the MPR; Of these, 7 despite polytherapy, they did not respond well

and Hypsarrhythmia persisted and evolution to SLG with association in 3 of LTG. The most frequent adverse reaction was the use of ACTH, transient hypertension in the 25 patients used; less frequent 2 with immunosuppression and infection added and 2 with irritability. Of those 14 who only remained with GBV monotherapy after completing 6 to 9 months of treatment, after clinical evaluation and EEG, AVP was replaced and adapted according to the evolution to electro-clinical syndrome, except for the 2 with tuberous sclerosis that remained. In the ophthalmological evaluation there was no evidence of visual damage due to the use of GBV.

Of the 14 with initial treatment of GBV and others, in 12 due to a low response to GBV, it was associated with AVP and other drugs (3 TPM, 3 LVT and 2 CLB) and the electro-clinical evolution to SLG in 3 (LTG). In the 7 patients of unknown etiology who started VB6 treatment, in the absence of the expected response, combined therapy and 3 VGB were used in 4 and others, VB6 in 1 with Down syndrome was also used. VGB was eliminated after 6 to 9 months of treatment according to clinical evolution and EEG. Adverse reaction to GBV was observed in 2 patients with weight gain and 2 with irritability, not significant to withdraw the medication. In the ophthalmological evaluation there was no evidence of visual damage due to the use of GBV. Of all the patients who used AVP, only 1 had an adverse reaction to hyperammonemia and it was a cause of suspension.

When describing the relationship between prognostic factors and clinical evolution (Table 3), it was observed that of the total 29 (74.4%) had an unfavorable clinical evolution and 10 (25.6%) favorable. Being the most frequent risk factors in patients with unfavorable evolution: the symptomatic or known etiology and the delay of the MPD and/or abnormality to the neurological EF in 26 (89.6%), the epileptic seizures and paroxysmal EE in 21 (72.4%) prior to the onset of IE, the male sex in 20 (68.9%), the persistence of the hypsarrhythmic EEG after 6 months and the non-response with mono or biterapia with 19 (65.5%); Particularly when the IE started before 4 months the 15 (51.7%) its evolution was unfavorable and in 20 (68.9%) when I combine more than 3 factors, with a significant confidence interval of 95% and more than 3 factors ($p < 0.05$) significant. Of those that evolved favorably, these factors were below 40% except the known etiology with 6 (60%).

Total (39)	Unfavorable evolution	Favorable evolution	IC 95%
Male	19 (65.5%)	3 (30%)	0.86 (0.67- 1.09)
Antenatal history	14 (48.3%)	4 (40%)	0.94 (0.70 - 1.97)
Perinatal history	15 (38.5%)	3 (30%)	0.89 (0.68 - 1.18)
Antenatal history	3 (7.6%)	0	0.74 (0.62 - 0.89)
Previous delay of the DPM and/or neurological abnormality to the EF	26 (89.6%)	3 (30%)	0.83 (0.66 - 1.04)
Previous epileptic seizures*	21 (72.4%)	4 (40%)	0.89 (0.69 - 1.14)
Previous paroxysmal EEG	21 (72.4%)	4 (40%)	0.89 (0.69 - 1.14)
Start of the EE < 4 months	15 (51.7%)	0	0.74 (0.62 - 0.89)
Symptomatic or known etiology	26 (89.6%)	6 (60%)	0.84 (0.54 - 1.33)
Previous time lost ≥ 1mon	8 (27.5%)	1 (10%)	0.84 (0.62 - 1.12)
No response to mono or biterapia	19 (65.5%)	2 (20%)	0.82 (0.65 - 1.04)
EEG hypsarrhythmic > 6 months	19 (65.5%)	1 (10%)	0.78 (0.63 - 0.97)
More than 3 factors	20 (68.9%)	1 (10%)	0.78 (0.63 - 1.97)

Table 3: *Relationship between prognostic factors and clinical evolution.*

*DPM: Psychomotor Development; EF: Physical Examination; EEG: Electroencephalogram; EE: Epileptic Spasms; *: 9 Neonatal Crises.*

Plus 3 factors: $chi^2 = 3.97$, $p = 0.043$.

Source: Clinical History.

Discussion

IE are the classic type of SW epileptic seizures. The EI usually announce a devastating, unfavorable prognosis and raise great uncertainty in treating physicians and family members, constituting the most serious and catastrophic epileptic encephalopathy after the neonatal period and in the first 2 years. Due to the high probability of evolving into intractable and drug-resistant forms of epilepsy, with significant cognitive deficiencies, motor disabilities and severe neurodevelopment [15,19,35,36].

IE is a specific age disorder due to neuronal excitability and cerebral immaturity due to various etiologies (genetic, metabolic, teratogenic and infectious prenatal, perinatal and postnatal causes). They depend on the remarkable and variable number of predisposing factors individually and on the fact that regardless of the moment of the beginning of the underlying insult (pre, peri and/or postnatal), they begin at a different stage of development and/or "common final road" to all the etiologies described (typically between 3 to 7 months of life on average), operative in a critical period of common brain maturation for all [20]. It is for this reason that any theory in this regard must respond to the different unknowns still existing: How can a single entity have different etiologies? Why do they arise or occur only in childhood and independently of their origin? Why do their consequences have such an impact in all spheres of neurodevelopment?

Little is known about its pathophysiology, although the causes or etiologies are usually variable, a common mechanism has been proposed for all. The current animal models with IE focus on a specific cause, such as the actual loss of interneurons and/or inflammatory or immune (mouse model ARX and TTX), stress and the hypothesis of the hormone releasing corticotropin (CRH). IE causes an increase in oxidative stress and release of the neuropeptide CRH in the limbic, hypothalamic, amygdala and brainstem regions in rats with IE and other animal models that focus on a common mechanism for the loss of inhibition related to γ-aminobutyric acid (GABA) [18-21]. This explains the origin of the EI due to an abnormality in the development or cortical or subcortical desynchronization, focal or diffuse and abnormal functional interaction with the brainstem [22].

Both the age of onset of the IE and the discrete predominance of the male sex are uniform data in different publications [3,4,7,13,15]. Our series also reflects greater start between 4 and 8 months and discrete male. In relation to the semiology of the EI and EEG, there is consensus that the axial contraction of symmetric muscles, with a predominance of flexor in 40% or mixed in 50% and symmetric hypsarrhythmic EEG, is the most frequent, as described, Well Alonso AJ., *et al.* [3], Taghidiri MM., *et al.* [4], Lassonde DM., *et al.* [13] and Campistol J., *et al.* [15]; in our patients the flexor EI predominates over the mixed one. Although we also observed association in a smaller number (4) of focal seizures, this is evidenced by others [4-5,11].

With the advent of new neuroimaging technologies, metabolic and genetic studies based on a correct anamnesis and preparation of the clinical history have allowed for the clarification of the etiology and demonstrate the symptomatic or known origin in about 80% of affected patients of EI [3,15]. According to the new classification proposed by the ILAE [5,6], the genetic causes and the structural/metabolic.

Similar percentage described in our series, known (82%) and unknown (18%), despite the limitations that exist in our health system. Prenatal and perinatal causes being the most frequent, the HIE with its structural sequelae, neurocutaneous syndromes, especially ET, metabolic, genetic and CVD errors of pre and perinatal origin. This is reported by different series [1,3-5,13,15,16,19].

Giving greater significance to MRI, which allows to define and visualize sequential structural alterations in HIE (periventricular leukomalacia and multicystic encephalomalacia) and CVD (poroencephalic cysts), as well as the lesions described in the different neurocutaneous syndromes, especially ET and Sturge-Weber Syndrome; concordant with the series of Arce-Portillo E., *et al*. [7] and Galicchio S., *et al* [16]. It is noteworthy that despite only having an NMR of 0.35 tesla, in our series we were able to identify other alterations such as neuronal migration disorders (5.1%) and agenesis of the corpus callosum (5.1%); currently emphasizing the use of MRI of 1.5 tesla or more in the elucidation of this percentage that still remains unknown and would reveal other alterations such as: cortical dysplasias and neuronal migration disorders that escape in the 0.35 [16].

The overall prognosis of SW is conditioned by the own etiology and epileptic activity itself, which is why affected children need psychopedagogical support and rehabilitation in their growth [15,19,35,36]. More than 70% of the patients have previous abnormality in the neurological physical examination (PE) and delay of the MPD, other regression in the DPM a posteriori or those with previous abnormality of the MPD, after the beginning of the EI they lose the abilities that they had acquired at untimely [15,19], with DI that can reach up to 90% and comorbidity with ASD [4,7,14,15,19], in our series 67% and 5 with ASD, had a similar behavior. 55 to 60% have frequent relapses, poor EI control and subsequently develop other types of epilepsies, such as SLG and focal epilepsies with focal crises Discognitive or altered consciousness, motor or other type and multifocal spikes on the EEG [7,14,15,30-32]. In our study, 53.8% did not have good control of IE, 79% evolved to other epileptic syndromes (35.9% to SLG and 43.6% to other epilepsies) in relation to a higher proportion of symptomatic or known etiologies. In the patients with multifocal spikes in the EEG, the focal discs were motor or not, with evolution sometimes to bilateral seizures without evidence of generalized seizures during sleep and/or predominance of these, so they do not meet the clinical characteristics to ensure an SLG and be in a possible state of transition or not with good response to AVP and benzodiazepines.

The 2 patients with normal average IHD have unknown etiology and had a good response to treatment, with no relapse and remission of IE and Hypsarrhythmia in less than 2 months with normal MPE after control of IE and normality in neurological EF, currently without treatment with antiepileptics or evolution to other syndromes; if we use the old etiological classification we could say that there would be 2 idiopathic cases.

Are the current treatments of IE the modification of the SW or simply treat a symptom and/or clinical sign? The most effective therapies currently available, ACTH and/or GBV, do not suppress the EI suddenly, but rather gradually from 2 to 4 weeks [19]. A mean delay of 2 days is reported between the initiation of ACTH therapy and the suppression of IE and the improvement of Hypsarrhythmia in the EEG a posteriori, proposing that transcriptional and plastic changes are important in its therapeutic effect with disappearance between 80 to 88% of the EI in patients treated with ACTH and on the other hand less than 40% of responders may relapse, suggesting that epileptogenesis has not been inhibited [20,22]. The association with GBV, acting by a different and inhibitory mechanism of γ-aminobutyric transferase could prevent these relapses in responders [20-22]. The SW being an example to demonstrate the electro-clinical correlation in the evaluation of the therapeutic response [7,8,13,15,30,32].

The efficacy of ACTH and not necessarily at high doses for the rapid and complete reduction of IE has been demonstrated in prospective controlled studies [22], experimentally in animal model in rats produces glucocorticoid release and most of its effects are attributed to the activation of glucocorticoid receptors in the CNS by a "common excitatory pathway" in a similar way to the diverse etiologies of the IE and the activation of the "stress system" [20-23]. Steroids administered as therapy or secreted by the adrenal gland after the administration of ACTH decrease the release of CRH and have direct action on melacortin receptors, constituting the two mechanisms of action to reduce and/or stop neuronal excitability [20-23]. Being able to suppress IE and Hypsarrhythmia in some patients, improve neurodevelopment in the long term and in others continue with neurological deficit and/or abnormality of MPD despite its control, due to the pathogenic mechanisms underlying the etiology and independent that do not were modified by medication [20-23].

From the retrospective multicentric work of Aircardi and other prospects [7,8,13,15,18,25,30] VGB is the first-line medication in the management of EI, especially in patients with SW and ET, in percentage which ranges between 26 and 64%. With dose/response between 100 to 200 mg/kg/day, which results in the suppression of IE up to 95% of patients with ET and 54% with other etiologies [7]. With such a rapid response between 3 to 5 days and control of IE between 1 to 3 weeks of treatment [7,18,25].

On the other hand, ACTH therapy constituted the first-line treatment starting in 2005, which exceeded the efficacy on GBV in 2 weeks of treatment 7 and in other retrospective and prospective studies [22-24,19,33] it was also the first line Proving that there is no difference in the response, between the use of high or low doses; proposing the use of low doses to avoid adverse reactions, more related to synthetic ACTH at doses 0.0125mg/kg/day [4,7,24,27,29,30]. There is still no single consensus on the duration of their employment, although they

agree a range between 1 to 6 weeks, maximum [7,11,24,27,29,30]. With this hormonal therapy it is possible to suppress the IE between 42% and 87% in the studies where it was used, according to the evidence level from I to III, with an efficacy in the response between 7 to 12 days of the beginning of the treatment and greater in patients with SW of unknown etiology [7].

At present there are prospective and still inconclusive studies, the International Collaborative Infantile Spasms Study [7], which propose the combined use of both therapies from the beginning, reducing the time of use of ACTH and possible adverse reactions, with established dose of GBV from the initiation of treatment and lower number of relapses [28,34,37,38]. In our series, we used both as drugs of choice and in combined therapy of ACTH plus GBV in 64.1% of our patients, of which 56% were free of IE and Hypsarrhythmia disappeared in the EEG in the first six months, coinciding with other series [34,37]. Observing as a more frequent adverse effect the transient hypertension and without hemodynamic repercussion in the total of the treated patients and in 2 (immunosuppression and respiratory infection), being the transient, treatable and reversible HT in all without reason to suspend its use, without cardiovascular affectation demonstrated by ultrasound. It was used at low doses and not exceeding 6 weeks, as recommended by other authors and also had similarity in the adverse effects found [7,8,15,22,25,27,29]. Most effectively in the group with known etiology/symptomatic or genetic/structural-metabolic (5 with neurocutaneous syndrome/2 with ET), in CVD and in 50% of the unknown or probably symptomatic.

Of the 35.9% where VGB alone was used as the initial treatment for the aforementioned reasons, it was only in 2 patients that the IE and Hypsarrhythmia disappeared in the first six months, describing the best response in our series with the combination therapy. Of these, those with post-infectious etiology, EHI and unknown or probably symptomatic had little response, irritability and weight gain were observed as an adverse effect in 14% with readjustment of the dose without withdrawing it, irritability is difficult to determine if due to medication or is inherent in SW, coinciding with Arce-Portillo E., *et al* [7]. There is no evidence in follow-up by Neurophthalmology of visual alterations attributed to medication in all our patients.

Of the total number of patients, regardless of whether the initial therapy was used, alone or combined, ACTH and GBV show that 58.9% achieved control of the EI or reduced it to 50% and in 41% Hypsarrhythmia disappeared. The first 5 months are corroborated by the proven efficacy of both drugs alone or combined, as well as the series by Arce-Portillo E., *et al*.

In those patients who did not respond well to combination therapy or alone with GBV, other drugs such as AVP and TPM or LVT with benzodiazepines were used to a lesser extent, according to our therapeutic availability and following the recommendations of other authors [3,5,8,15,26,30]. VB6 was used as initial therapy in patients with unknown etiology and in Down Syndrome, as advocated by Campistol J., *et al*. [15] and Caraballo RH., *et al.* [30] with greater emphasis on the unknown, not observed No favorable response, which led us to rule out an error of that metabolism as a probable etiology in our series. We do not use other therapeutic alternatives recommended for non-responders or with drug-resistant SW such as the use of ketogenic diet or injury or functional surgery [4,5,8,13,15,30] because they are not developed or available in our health system and which It would be important in future research or programs.

Of the total, we found that 74.4% of our patients despite using the treatment of choice had an unfavorable evolution, without much difference with the series of Arce-Portillo E., *et al.* [7] of 66%. Dependent to a large extent on the presence of factors of poor prognosis, of which stand out: when a patient prior to the onset of IE had delayed MPD and/or abnormality of neurological EF, epileptic seizures from the neonatal period or later Previous paroxysmal EEG and symptomatic or known etiology; observing worse prognoses in those with HIE, post-infectious and its structural sequelae, 2 with neuronal migration disorders, the patient with Kernictero, 3 with neurocutaneous syndrome (2 with ET) and 3 of unknown etiology. Especially when the age of onset was less than 4 months and Hypsarrhythmia persisted on the EEG after 6 months and/or combined more than three factors, observing a statistical significance when presented alone or combined, coinciding with Arce-Portillo E., *et al* [7]. Some authors give relevance to the time lost from the start of treatment when the diagnosis is made after the first month of the beginning of the IE and the poor response to the drugs of choice [7,15,30], arguing in the repercussion that it could have these factors in the DPM, the cognitive and/or behavioral sphere and its evolution to other epileptic syndromes later,

especially to the SLG of onset before reaching 2 years [7,15,30,35,36] describing the same characteristics in our patients. In patients with favorable prognosis (25.6%), there was less presence of these prognostic factors, none of them had an early onset of IE and in only one patient more than one month of treatment was lost, in one patient Hypsarrhythmia persisted after 6 months. months in the EEG and 2 had poor response to mono or biterapia and in only one I combined more than 3 similar factors with Arce-Portillo E., *et al* [7].

Conclusion

In conclusion of our case of 11 years of 39 infants with SW, we observed a greater onset of IE between 4 and 8 months, with predominance of males, semiology of IS in flexion or mixed and Hypsarrhythmia in symmetric EEG. The symptomatic or known etiology or structural/metabolic and genetic etiology was the most frequent, being the EHI and the neurocutaneous syndromes the most present. When using the therapeutic protocol existing in the hospital more than half of the cases had a control of the IE or its reduction greater than 50% with disappearance of the Hypsarrhythmia in the first 5 months, observing a greater response with the combined therapy of ACTH with VGB demonstrating the efficacy of both drugs as therapy of choice and of ACTH in the suppression/reduction of IE in an early manner and improvement or disappearance of Hypsarrhythmia in the EEG; The adverse effects of ACTH are treatable, transient and reversible when used in low doses and less than 6 weeks. The other drugs such as AVP, TPM, LVT and benzodiazepines in our context remain alternative therapies in non-responders and VB6 in those with unknown etiology and suspicion of metabolic error associated with their deficit, as reflected in other studies.

The majority of our patients had an unfavorable prognosis regardless of the etiology. Describing worse prognosis in those who had prior to the onset of the delay in the MPD and/or neurological abnormality to the EF, epileptic seizures neonatal or a posteriori, paroxysmal previous EEG, early onset of IE before 4 months, persistence of Hypsarrhythmia on the EEG after 6 months and the start of treatment after one month of onset of IE and poor therapeutic response; constituting the same factors of poor prognosis and this is the conclusion of other reviewed works.

Demonstrating that the repercussion of these factors of poor prognosis alone or in combination is determinant for an unfavorable evolution. Inciting severe forms with delayed MPD, moderate or severe ID and association with ASD with evolution to other epileptic encephalopathies such as SLG and epilepsies with multifocal spikes on the EEG. It also shows that the use of the treatment of choice and control of IE does not ensure a favorable evolution in a group of patients, depending on these the etiology and epileptic activity itself, the individual clinical characteristics and the presence of factors of poor prognosis.

Therefore, it would be a recommendation of our work to perform multicentric studies, analyzing the same variables and therapy used that allows us to homogenize the therapeutic behavior and improve the follow-up.

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