

West Syndrome: Clinical Characteristics, Therapeutics, Outcomes and Prognosis

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ABSTRACT

Introduction: West syndrome (WS) is the most severe, devastating and/or catastrophic epileptic encephalopathy during the lactation period. However, until now, there are few comprehensive clinical studies in this regard in Cuba.

Objective: To identify clinical characteristics of patients with WS, the related etiology, therapeutics and prognostic factors.

Methods: An observational, descriptive and retrospective study of 39 patients with WS from the Centro Habana Teaching Pediatric Hospital, Havana, Cuba, comprising the period between January 2005 and December 2016 was carried out. Clinical data were recorded for each patient by review of clinical history. Statistical analysis was performed with use of the Statistical Package for Social Sciences.

Results: The genetic, structural/metabolic etiology was predominant. Hypoxic ischemic encephalopathy (25.6%) and neurocutaneous syndromes (17.9%) were the cause more frequent of WS. The combined treatment of adrenocorticotrophic hormone (ACTH) and vigabatrin (VGB) was used in 25 patients (64.1%). In 18 of them (72%) there was control of infantile spasms or reduction $\geq 50\%$, while in 14 patients (56%) the hypsarrhythmia disappeared in the first 6 months ($p < 0.05$). All patients that used ACTH had transient hypertension as an adverse effect of this drug. 71.8% of the patients had moderate to severe delay in psychomotor development, 35.9% were diagnosed with Lennox-Gastaut syndrome and 43.6% with other epilepsies. There was an unfavorable evolution in 74.3% of the patients. The most significant prognostic factors for unfavorable evolution were male gender, symptomatic etiology, psychomotor delay and/or abnormality in the neurological examination, epileptic seizures, previous paroxysmal electroencephalogram, poor response to the treatment, persistence of hypsarrhythmia, and combination of more than three factors in 68.9% of the patients with unfavorable evolution ($p < 0.05$).

Conclusions: Our findings showed that the combined treatment with ACTH and VGB may decrease the time to disappearance of infantile spasms and hypsarrhythmia in patients with WS. Moreover, the unfavorable evolution of these patients is related with the etiology and combination of prognostic factors.

Keywords: syndrome, spasms, infantile, epileptic encephalopathy, etiology, prognosis

INTRODUCTION

West syndrome (WS) is the most severe, devastating and/or catastrophic epileptic encephalopathy during the lactation period. WS was first described by Dr. William James West in 1841 in his 4-month-old son. He reported the first evidence on infantile spasms (IS) associated with such syndrome (1-5). According to the 2010 International League Against Epilepsy (ILAE) classification (6), WS comprises a triad of epileptic spasms (ES), with hypsarrhythmia detected by electroencephalogram (EEG), and delay or regression in psychomotor development (PD), but this last characteristic is not essential for its definition.

WS, moreover, corresponds to an age-dependent epilepsy. The age of onset of this syndrome varies from 4 to 10 months,

with a higher occurrence between 5 to 7 months, which can be extended until 2 years (3,7,8). An incidence of 1 case of WS per 4,000 children has been estimated in the literature (3,4,9,10). Such disease represents around 2 to 10% of the epilepsies in childhood and it is the most frequent encephalopathy which occurs before the first year of life (with the exception of the Ohtahara syndrome). A higher prevalence of WS has been observed in males (3,7,8).

In accordance with the ILAE classification in force until 1989 (10), ES were named as infantile spasms, due to their broad association and exclusivity to WS, and occurrence in early childhood and lactation period. More recently, the ILAE classification 2010 (6) named these alterations as ES, because their relationship with other epileptic syndromes with occurrence outside of the mentioned period. Despite of this,

the term IS (3) continues to be used when referring to spasms that occur before 2 years of age and related to the WS.

Several authors have demonstrated the existence of patients with ES without hypsarrhythmia in the interictal EEG (11,12). This has been interpreted as a variant of the WS and not another type of epileptic syndrome. Consequently, in this context it is relevant to perform critical EEG to focus the differential diagnosis with other epilepsies (that occurs in similar periods) and paroxysmal non-epileptic events (11).

IS usually occur in clusters (spasms with different intensity, frequency and/or duration). They correspond, in turn, to axial contractions in flexion, extension or mixed extension–flexion, lasting from 2 to 3 seconds, which are most commonly observed during the transition from slow sleep to REM sleep. IS are subtle as the deviation of the eyes upwards, slight movements of head or elevation of the shoulders, and autonomic signs. Furthermore, they are generally symmetrical, but can also be asymmetric or focal, alternating, and associated with focal seizures. In this last case, together with a possible focal lesion or agenesis of the corpus callosum (3-5, 9,11,14-16).

Etiologically, according to the previous ILAE classification (3,10) in relation to aggressions or prenatal, perinatal and postnatal antecedents, IS are classified as symptomatic, cryptogenic or probably symptomatic, (being these the most frequent) and idiopathic cases (rare).

The new ILAE classification (6,10,14) proposes the use of the term genetic, structural/metabolic and unknown cause. Approximately 64% of patients with WS have known etiology (13). Currently, with the advent of neuroimaging studies with great specificity and sensitivity, such as nuclear magnetic resonance (NMR) and single positron emission tomography, and the increase in the number (around 80%) of studies of metabolic screening and molecular genetic techniques, it has been possible to diagnose a greater number of patients with related structural/metabolic and genetic alterations (16-18). In view of this, the findings in anamnesis and the neurological and/or general physical examination (PE) abnormalities can be associated with the etiological diagnosis and the results of the complementary examinations. In this respect, the knowledge about the etiology is of great importance, since this may lead to the optimal treatment, with positive implications on the evolution and prognosis (7,16-18).

Most of the cases of WS have an unfavorable evolution, related to different prognostic factors that alone or combined influence the severity of this syndrome (3-5,7,16). There are evidences about the efficacy of several drugs for the treatment of WS. However, the selection of the first choice drug is still a controversial subject. Currently, the use of vigabatrin (VGB) in combination with adrenocorticotrophic hormone (ACTH) has been recommended as the most effective therapy for these patients. Other drugs, such as prednisolone (1), valproic acid (VA), benzodiazepines, vitamin B6 (VB6), topiramate (TPM), levetiracetam (LVT), and zonisamide have also shown efficacy. In addition, the ketogenic diet, intravenous gammaglobulin therapy and, surgical treatment in refractory cases and specific situations are also useful options for the treatment of such disorder, which have been used increasingly in specialized centers for epilepsy (4,5,7,8,14,16,19-31).

Up till now, there are few comprehensive clinical studies about this subject matter from Cuba. Thus, the present research intends to identify the clinical characteristics of

patients with WS, the aspects inherent to the related etiology, semiology, EEG results, the used medications and their adverse reactions, as well as to determine the prognostic factors that can influence the evolution of these patients.

METHODS

Design, Context and Participants

An observational, descriptive and retrospective study of patients with WS from the Centro Habana Teaching Pediatric Hospital, Havana, Cuba, comprising the period between January 2005 and December 2016 was carried out. Informed consent of parents and/or persons responsible, and approbation of the ethics committee of the institution were obtained. Patients were treated on an outpatient basis or by hospital admission according to their individual needs.

All patients with IS and hypsarrhythmia on EEG beginning before two years of age, with or without alteration in PD, diagnosed with WS, admitted, treated and followed up in Neuropediatric consultation by more than two years were included in this study. We excluded patients who left the follow-up and /or had clinical history with insufficient data. Of the total of 45 patients, 39 (22 boys and 17 girls) were included. The other six were excluded.

Variables and Interventions

The following data were recorded for each patient: age of onset of IS, sex, semiological characteristics of IS (frequency, type, symmetric/asymmetric), description of EEG alterations, abnormalities in the neurological examination during PE, PD prior to initiation of IS or a posteriori, 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 (ASD)), the used therapeutic options, response to the treatment and adverse reactions, prognostic factors and unfavorable evolution.

The age of onset of IS was subdivided into three categories, i.e., before 4 months (< 4 months), between 4 and 8 months, and after 8 months (> 8 months). According to the ILAE (6) classification, this subdivision should be used when referring to genetic and structural/metabolic etiology, and unknown cause. In this study, all patients with relevant prenatal, perinatal and postnatal antecedents, presence of clinical manifestations and data on evaluation of PE were subjected to biochemical studies, which included glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, lactic acid, lactic acid dehydrogenase and ammonia. In addition, the neurometabolic study was extended to the qualitative study of amino acids in urine and quantitative in blood, including serology for Cytomegalovirus and indirect immunofluorescence for detection of *Toxoplasma gondii*. A neuroimaging study was performed in specific cases with use of transfontanellar ultrasound, computerized axial tomography and magnetic resonance imaging of the skull. When a cause was not determined, it came to be called unknown (3-5,7-9,14,16-18).

The definition of related concepts was based on the previous experience of different authors (3-5,7,8,11,14,16,32, 33):

- EEG hypsarrhythmic interictal: characterized by the presence of paroxysmal slow wave discharges, spikes and polyspikes with a great amplitude of duration and variable location (symmetrical, asymmetric or alternating locations), with or without paroxysmal voltage attenuation, which give it a pseudoperiodic aspect. There is also a highly disorganized base rhythm.
- Subclinical spasms: comprise the occurrence 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 gender, presence of relevant prenatal, perinatal and/or postnatal antecedents prior to initiation of IS including paroxysmal EEG, delayed PD and/or abnormality in the neurological PE, neonatal epileptic seizures or before onset of IS, and onset of IS before 4 months; time lost prior to treatment initiation or diagnosis greater than 1 month, known etiology, no response to treatment with monotherapy (one drug) or bitherapy (2 drugs), hypsarrhythmic EEG persisting after 6 months of initiation of therapy and combination of more than three prognostic factors.
- Unfavorable evolution: persistence of spasms and hypsarrhythmia on EEG after 6 months of treatment, little response to bitherapy, regression of PD or, moderate or severe PD delay and/or abnormality in the neurological PE, moderate or severe intellectual disability (ID) and/or ASD, evolution to Lennox-Gastaut syndrome (LGS) or other epilepsies and death.
- Adverse reaction to medication: irritability, weight gain, immunosuppression or added infections, transient arterial hypertension (TAH), 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). The aim of this step was to evaluate the response of the patients to the treatment according to their clinical evolution. It was observed if the hypsarrhythmia disappeared before 2 months (< 2 months), between 3 and 5 months or persisted after 6 months (> 6 months). According to the clinical characteristics, they were evaluated by the ophthalmology, genetics and child psychiatry services.

Scheme of treatment used according to etiology (19-31,33-36):

- ACTH in combination with VGB was used in cases of known or symptomatic/structural etiology, except to neurometabolic disease with absence of symptoms and/or acute infectious signs, dermatological conditions, TAH, liver or kidney damage. ACTH was given intramuscularly at a dose of 0.0125mg/kg/day intramuscular (with presentation of 1mg/1ml ampules), at intervals of alternate days in the first and second week. According to the response its use was of two times during the third week and once in the other weeks without exceeding six weeks (the most frequent dose used was 2 tenths). VGB was used 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 was observed between 4 and 6 weeks, the treatment was continued for 4 to 9 months. In this case, VGB was replaced (taking into

account clinical characteristics and EEG) for Valproate sodium (VS) 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 there was any contraindication to the use of ACTH, the treatment was started only with use of VGB.

- If there was no response to VGB in the first 4 to 6 weeks (no disappearance of IS and persistence of hypsarrhythmia on EEG, or IS were not reduced in more than 50% of the initial number), we used additionally VS, or VGB was replaced by VS with consent of parents and/or guardians. In case of no response, TPM was used 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 with a maximum dose of 400 mg. In addition, LVT was also used at doses 30 to 60 mg/kg/day in 2 sub-doses, increasing at a rate of 10 mg/kg/day every 7 days with a maximum dose of 3000 mg. In case of no response, 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 were used.
- In case of unknown etiology/probably symptomatic, Down syndrome or suspect of metabolic error, treatment with VGB was instituted at a dose of 300 mg per day in 3 sub-doses. The response to medications was evaluated during the first 4 days. If there was no alteration in IS or their increase, the same therapeutic scheme of known or symptomatic/structural cause was used. In case of suspect or confirmation of inborn error of metabolism, the treatment with VGB was used. Depending of the achieved response, other drugs were used with exception of VS, which can be associated with complications, such as 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 in accordance with the pharmaceutical availability and the treatment was adapted according to evolution to other epileptic syndromes. The use of ACTH was performed under medical supervision and hospital admission. The response to the treatment was evaluated based on the following parameters: disappearance of IS and hypsarrhythmia, free of IS but with hypsarrhythmia, reduction of more than 50% of IS and persistence of hypsarrhythmia, reduction of IS less than 50% and persistent hypsarrhythmia (without response to the treatment).

Statistical Processing

Data were collected and, tables and graphs were made in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA). Variables were expressed in absolute frequency. Some quantitative variables were also expressed in percentages. Chi2 test was used for statistical analysis. P <0.05 was considered significant and confidence intervals at 95 % were calculated. The statistical analysis was performed with use of the Statistical Package for Social Sciences (SPSS), version 16.0 program for Windows®.

RESULTS

Among the 39 studied patients, a higher number of males (56.4%, 22 males and 17 females) was observed. Regarding the age of onset of IS, a higher frequency was observed in the age range between 4 and 8 months (n=23, 58.9%), while before 4

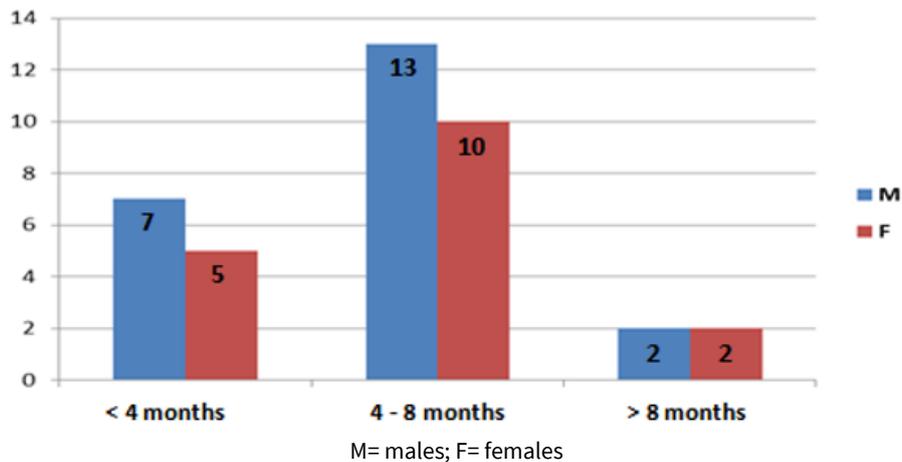
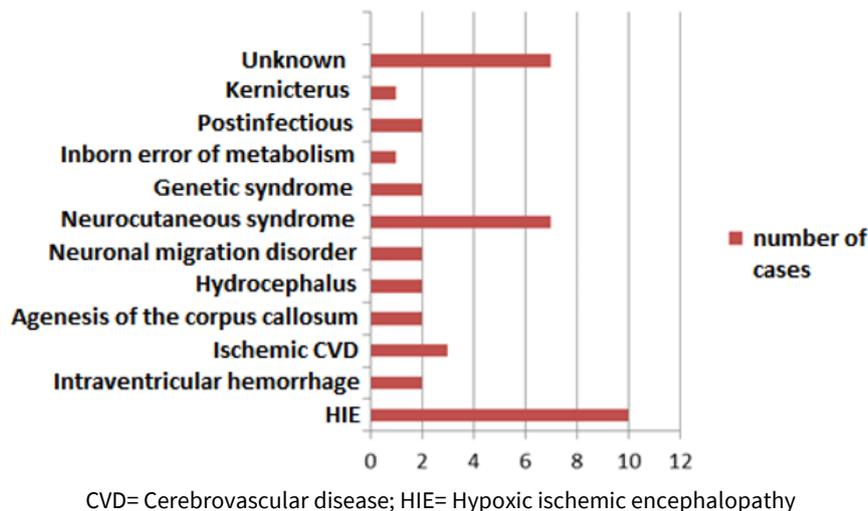


Figure 1. Distribution of patients according to age of onset of IS and sex. *Hospital Pediátrico Docente Centro Habana* (Centro Habana Teaching Pediatric Hospital) from 2005 to 2016

Source: Clinical history



Two patients had (bacterial meningoencephalitis + hydrocephalus), (HIE+ intraventricular haemorrhage)

Figure 2. Etiologies related to West syndrome

Source: Clinical history

months of age we had 12 cases (30.7%) registered. There was no statistical association between these variables (**Figure 1**).

There was a predominance of structural/metabolic etiology. This etiology was observed in registered cases (30.7%). A genetic cause due to the INV 21 (P11 2-q21) 13 pst 5tk and Down syndrome or trisomy 21 were verified in two patients, and no known cause was defined to seven. Among all patients with WS in the study, 32 (82%) had a specific/known cause. The most frequent related causes were hypoxic ischemic encephalopathy (HIE) (25.6%) and neurocutaneous syndrome (17.9%) with structural etiology (**Figure 2**).

According to the semiology of IS (**Table 1**), IS in flexion (51.2%) and mixed (35.8%) were the most frequent findings. IS were asymmetric in only three patients, being that two of them had agenesis of the corpus callosum and one porencefalic cyst secondary to ischemic CVD (cerebrovascular disease), although they also had symmetric IS. In four patients (10.2%), IS were associated in particular with discognitive motor focal crises (upward gaze deviation, palpebral ptosis and disconnection). The symmetric characteristics of

Table 1. Clinical characteristics and findings in the electroencephalogram

Total (39)	
Range of IS	(15-350)
Mode	106
Semiology of IS	
Flexion	20 (51.2)
Extension	5 (12.8)
Mixed	14 (35.8)
Associated with focal seizures	4(10.2)
Symmetric	36 (92.3)
Asymmetric	3 (7.7)
EEG	
Symmetric	36 (92.3)
Asymmetric	3 (7.7)

EEG= Electroencephalogram; IS= Infantile spasms

Source: Clinical history

hyparrhythmia on EEG were verified in 92.3% of the cases. Subclinical IS (spindle - like) were observed in three patients.

Table 2 shows data on the clinical evolution of the studied children. Thirty of them (76.9%) had abnormality in

Table 2. Clinical evolution of the studied patients

Total (39)	N (%)
Moderate or severe delayed PD	25 (71.8)
PD regression	4 (10.2)
Lennox-Gastaut syndrome ^a	14 (35.9)
Other epilepsies*	17 (43.6)
Uncontrolled IS	21 (53.8)
Positive neurological examination	30 (76.9)
Mild intellectual disability	3 (7.6)
Death	1 (2.6)

PD = Psychomotor development; IS= Infantile spasms a-5 with Autistic Spectrum Disorder; *-10 with focal and seven with multifocal

Source: Clinical history

neurological PE from the beginning of IS. Four children (10.2%) had a regression of the PD, being that five developed ASD. At the school age, nine patients presented severe ID, 14 moderate ID and three mild ID. In accordance with the evaluation of the psychiatry and psychology services of our Center, two patients presented average normal intelligence, normal PD and PE. Ten of these patients had focal characteristics and seven had multifocal spikes (based on results of EEG). The deceased patient had Proteus syndrome and the cause of death was unrelated to WS (bronchopneumonia and respiratory failure).

When observing the relationship between the different therapeutic options and EEG (**Figure 3**), it was verified the use of ACTH combined with VGB (as a first choice therapy) in 25 patients (64.1%), and of VGB alone or combined with other drugs in 14 (35.9%). The patients who used VGB alone or combined with other drugs were those who had inborn error of metabolism (n=1) or other contraindications to the use of ACTH (including acute respiratory or diarrheal infections and infested skin lesions), as well as the children of cases that the parents did not give consent for the use of ACTH (n=3).

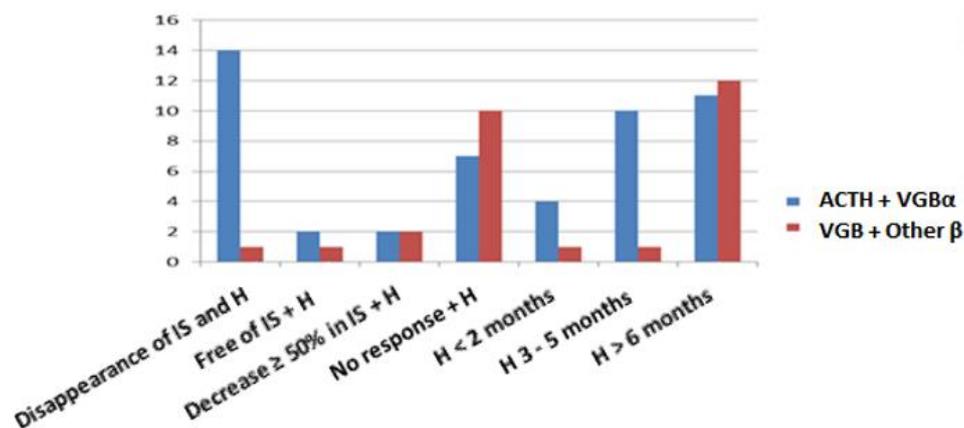
Among all patients that used ACTH and VGB as a combined therapy, a control or decrease $\geq 50\%$ of IS was verified in 18 of them (72%) and, disappearance of IS and hypsarrhythmia in 14 (56%). In four of these patients (28.5%) only VGB was used (without the need for combination with other drugs), and in seven cases regardless of the use of combined treatment (due to the persistence of hypsarrhythmia and absence of total control of IS) were used other drugs in combination. Out of a

total of 17 patients (43.5%), seven (with use of ACTH and VGB) and 10 (with use of VGB and other drugs) had no response to the treatment, poor control of IS and persistent hypsarrhythmia despite the association of other drugs (polytherapy). When evaluating only the therapeutic response and EEG, it was noted that of the 25 patients who were treated from the beginning with combined treatment of ACTH and VGB, in 14 (56%) there was disappearance of the hypsarrhythmia in the first 6 months. In two (14.2 %) of these 14 patients was also used VGB in combination with other drugs. In five patients the disappearance of the hypsarrhythmia was verified in the first 2 months (in four of them was used ACTH in combination with VGB). Statistical significance was observed between the groups ($p < 0.05$) regarding the used drugs and disappearance of hypsarrhythmia.

A better response was observed with the use of ACTH in combination with VGB in patients with known or symptomatic etiology (n=14): five of them with neurocutaneous syndromes (except two with TSC (tuberous sclerosis complex)), two with genetic syndromes, two with CVD of prenatal origin, two with HIE and three with unknown etiology. The two patients who had the same response to the initial treatment with VGB alone presented hyperammonemia (n=1) and HIE (n=1).

Among all patients with initial combined treatment of ACTH and VGB, in 11 was also administered VA due to a low response to VGB or relapse. Moreover, benzodiazepines were used in four patients (n=2 to CLB, n=2 to CLN) and TPM in three. Although polytherapy was used, seven of these patients did not respond well. Hypsarrhythmia persistence and evolution to LGS occurred. In this case, lamotrigine (LTG) was used in three patients. The most frequent adverse reaction due to the use of ACTH was transient hypertension (n=25), while the less frequent were immunosuppression and infection (n=2), and irritability (n=2). In addition, in 14 patients after completing 6 to 9 months of treatment with VGB monotherapy, this drug was replaced by VA (after clinical evaluation and EEG) and the treatment was adapted according to the evolution to electro-clinical syndrome, except for the two patients with TSC. In the ophthalmological assessment there was no evidence of visual damage due to the use of VGB.

Of the 14 patients submitted to the initial treatment with VGB and others drugs, in 12 was also administered VA and other



ACTH= Adrenocorticotrophic Hormone; VGB= Vigabatrin; H=Hypsarrhythmia; IS= Infantile spasms

Response - therapeutic options: χ^2 test = 9.92, $p = 0.019$; EEG: χ^2 test = 6.63, $p = 0.034$

Figure 3. Relationship between the response to different therapeutic options and electroencephalogram

Source: Clinical history

Table 3. Relationship between prognostic factors and clinical evolution

Total (39)	Unfavorable evolution	Favorable evolution	95% CI
Male	19 (65.5%)	3(30%)	0.86(0.67 - 1.09)
Pre-natal antecedents	14(48.3%)	4(40%)	0.94(0.70 - 1.97)
Perinatal antecedents	15(38.5%)	3(30%)	0.89(0.68 - 1.18)
Postnatal antecedents	3(7.6%)	0	0.74(0.62 - 0.89)
Previous delay of the PD and/or abnormality in the neurological PE	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)
Onset of IS < 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 \geq 1 month	8(27.5%)	1(10%)	0.84(0.62 - 1.12)
No response to monotherapy or combined therapy	19(65.5%)	2(20%)	0.82(0.65 - 1.04)
hypsarrhythmic EEG > 6 months	19(65.5%)	1(10%)	0.78(0.63 - 0.97)
More than three factors	20(68.9%)	1(10%)	0.78 (0.63 - 1.97)

CI = Confidence intervals; PD= Psychomotor development; PE= Physical examination; EEG= Electroencephalogram; IS= Infantile spasms; * - nine with neonatal crises

More than three factors: chi2 test = 3.97, p = 0.043

Source: Clinical history

drugs (n=3 to TPM, n=3 to LVT and n=2 to CLB) due to a low response to VGB, with electro-clinical evolution to LGS observed in three patients that used LTG. Of the seven patients with unknown etiology who started the treatment with VB6 (in the absence of expected response), in four of them was used combined therapy, in three VGB and other drugs, and VB6 was also used in one patient with Down syndrome. VGB was stopped after 6 to 9 months of treatment according to clinical evolution and the EEG results. Adverse reactions to VGB were observed in two patients with weight gain and two with irritability, without need to withdraw the medication. In the ophthalmological assessment no visual damage due to the use of VGB was also verified for these patients. Of all the patients who used VA, only 1 had an adverse reaction to hyperammonemia, which was a reason for stopping the medication.

When describing the relationship between prognostic factors and clinical evolution (**Table 3**), we observed an unfavorable evolution in 29 patients (74.4%), while 10 (25.6%) had a favorable evolution. The most frequent risk factors in patients with unfavorable evolution were the symptomatic or known etiology, and delay of the PD and/or abnormality in the neurological PE (n=26, 89.6%). Among the patients with favorable evolution, the prognostic factors were present in less than 40% of the cases, with the exception of the known etiology (n=6, 60%).

DISCUSSION

IS are a classic component of the WS epileptic seizures. They usually are related to a devastating and unfavorable prognosis, which brings great uncertainties on the patient evolution to both the physicians and family members. Therefore, WS corresponds to the most serious and catastrophic epileptic encephalopathy after the neonatal period and in the first 2 years of life, because of the high probability of its evolution to intractable and drug-resistant epilepsy forms, with significant cognitive deficiencies, motor disabilities and severe neurodevelopmental impairment (16,20,37,38).

It is also worth mentioning that IS are specific disorders associated with the age, which occur as a result of the neuronal

excitability and cerebral immaturity due to various etiologies (genetic, metabolic, teratogenic, prenatal infectious and, perinatal and postnatal causes). A remarkable and variable number of individual predisposing factors are related to IS. In addition, regardless the moment of the beginning of the underlying insult (pre-, peri- and/or postnatal), IS begin at a different stage of development and/or as a "final common route" to all the described etiologies (typically between 3 and 7 months of life on average), with occurrence in a critical period of the common brain maturation (21). It is for this reason that any theory concerning this must respond to the different unknowns still existing:

How can a single disorder have different etiologies? Why do IS arise or occur only in childhood and independently of their causes? Why do their consequences have such an impact in all levels of neurodevelopment?

Little is known about the IS pathophysiology. Although the causes related to IS and their etiologies are usually variable, a common mechanism has been proposed concerning this subject. Current IS animal models focus on a specific cause of IS, such as the loss of interneurons and/or, inflammatory or immune responses (according to the findings in the ARX and TTX mouse models), stress and action of the corticotropin-releasing hormone (CRH). IS cause an increase in oxidative stress and promote release of CRH in the limbic, hypothalamic, amygdala and brainstem regions of rats with IS. Other animal models suggest the occurrence of a common mechanism for the loss of inhibition related to γ -aminobutyric acid (19-22). This explains the origin of IS, which occur due to a developmental abnormality or can be related to cortical or subcortical desynchronization (focal or diffuse), leading to an abnormal functional interaction with the brainstem (23).

Both the usual age of onset of IS and their slight predominance in males are data confirmed from different sources (3,4,7,14,16). In our study we observed onset of IS between 4 and 8 months of age in the majority of the cases, with a slight predominance in males. Regarding the semiology of IS and EEG, there is a consensus that the symmetric axial contraction of muscles occurs in flexor muscles in about 40% of cases, or as a mixed contraction in 50% (with symmetric hypsarrhythmic EEG) (3,4,14,15). In our patients the flexor IS was predominant in comparison to the mixed IS. Although we also observed focal seizures associated to a smaller number of

cases (4), such finding has also been evidenced by other researchers (4,5,11).

With the advent of new neuroimaging technologies and, metabolic and genetic studies based on a correct PE and adequate clinical history, it has been possible to achieve the clarification of the etiology related to WS in most cases (3,16). In connection with this, it has been demonstrated the occurrence of symptomatic or known origin in about 80% of patients affected with IS. According to the new classification proposed by ILAE (5,6), this is due to the genetic and structural/metabolic causes.

In our research, a similar percentage was observed. The etiology was classified as known in 82% of the cases and as unknown in 18% (despite the limitations existing in the health system of Cuba). The prenatal and perinatal causes were the most commonly related to the described etiology, including HIE (with its structural sequels), neurocutaneous syndromes, especially TSC, metabolic and genetic errors, and CVD of pre and perinatal origin. This has also been reported in several studies (3-5,9,14,16,17,20).

In this sense, a greater importance should be attributed to NMR, which allows to define and visualize sequential structural alterations in HIE (such as periventricular leukomalacia and multicystic encephalomalacia) and CVD (such as porencephalic cysts), as well as lesions described in different neurocutaneous syndromes, including TSC and Sturge-Weber Syndrome, such as was previously reported by Arce-Portillo et al (7) and Galicchio et al (17). It is noteworthy that, despite we have had only a 0.35 tesla NMR system, in this study we were able to identify other alterations like neuronal migration disorders (5.1%) and agenesis of the corpus callosum (5.1%). Therefore, at present, it would be relevant the use of a 1.5 tesla NMR system or higher to the elucidation of the number (percentage) of alterations that still remains unknown and, from that, to reveal new findings, as for example the occurrence of cortical dysplasias and neuronal migration disorders (18).

Another important point is that the overall prognosis of WS is conditioned by the etiology and epileptic activity, which is why the affected children require psycho-pedagogical support and rehabilitation during their development (16,20,37,38). More than 70% of patients with WS present previous abnormalities in neurological PE and PD delay, others have regression in PD (posteriorly), and those with a previous PD abnormality after the onset of IS lose the skills they had acquired untimely (16,20), with ID of up to 90% and comorbidity with ASD (4,7,15,16,20). In our findings the rate of patients that had a similar behavior was 67%, with five patients with ASD.

Furthermore, 55 to 60% of patients with this syndrome have frequent relapses, poor control of IS and subsequently develop other types of epilepsies, such as LGS and focal epilepsies with focal dyscognitive seizures or, motor, consciousness alterations (or others), with multifocal spikes on EEG (7,15,16,31-33). In our study, 53.8% of the patients did not have a good control of IS and, 79% evolved to other epileptic syndromes (35.9% to LGS and 43.6% to other epilepsies) together with a higher proportion of symptomatic or known etiologies. In the patients with detected multifocal spikes, the focal dyscognitive seizures (motor or non-motor) were predominant, with evolution sometimes to bilateral seizures without evidence of generalized seizures during sleep and/or their predominance, since these children did not present

typical clinical features of LGS (they were in a possible transition state, or not even that), with good response to VA and benzodiazepines.

It should be also noted that in our study there were two patients with average intellectual quotient that had unknown etiology and a good response to the treatment, without relapse and remission of IS and hypsarrhythmia in less than 2 months. Moreover, they presented normal PD after control of IS and neurological PE without alterations. At present, these patients are without treatment with antiepileptics and with absence of evolution to other syndromes. Therefore, according to the old etiological classification we could say that these would be two idiopathic cases.

Thus, an important question arises: Are the current therapies for IS capable of promoting significant improvements in patients with WS, or they simply treat a symptom and/or clinical sign? The most effective current therapies (ACTH and/or VGB) do not suppress suddenly the occurrence of IS, but rather gradually over the course of 2 to 4 weeks (20). It has been reported an average delay of 2 days after the initiation of ACTH therapy to the suppression of IS as well as the improvement of hypsarrhythmia in the posterior EEG, proposing that transcriptional and plastic changes are important to the therapeutic effects of ACTH, with disappearance of 80 to 88% of IS in patients treated with use of this drug. On the other hand, at least 40% of patients that respond to this treatment can have relapses, which suggests that epileptogenesis has not been inhibited (21,23). The combination with VGB could prevent such relapses in patients that respond to this treatment, since there would be action of this drug by a different and inhibitory mechanism of γ -aminobutyric transferase (21-23). In this case, WS should be an example to demonstrate the electro-clinical correlation in the evaluation of the therapeutic response (7,8,14,16,31,33).

The efficacy of ACTH (not necessarily at high doses) for the rapid and complete reduction of IS has been demonstrated in prospective controlled studies (23). In rat animal model has been observed that ACTH produces glucocorticoid release and, most of its effects are attributed to the activation of glucocorticoid receptors in the central nervous system by a "common excitatory pathway", similarly to what occurs with the various etiologies of IS and the activation of the "stress system". Steroids administered as therapy or secreted by the adrenal glands after the administration of ACTH decrease the release of CRH and have direct action on melanocortin receptors, which can to reduce and/or inhibit the neuronal excitability. Moreover, in some patients the suppression of IS and hypsarrhythmia improve the neurodevelopment in the long term, while in others the neurological deficit and/or abnormality of PD persist. This happens due to the pathogenic mechanisms underlying the etiology and other independents, which are not modified by the used medication (21-24).

According to several prospectives studies (7,8,14,16,19,26,31,35) VGB should be the first-line medication for the treatment of IS, especially in patients with WS and TSC. With a dose/response effect between 100 to 200mg/kg/day, it is possible with use of VGB to achieve the suppression of IS in up to 95% of patients with TSC and in 54% of those with other etiologies (7). A rapid response (between 3 and 5 days) and control of IS between 1 to 3 weeks of treatment may also be expected (7,19,26).

On the other hand, ACTH therapy have been the first-line treatment for IS since 2005, given that was demonstrate that it

exceed the effectiveness of VGB in 2 weeks of treatment (7). In other retrospective and prospective studies (23-25,30,34) ACTH was also the first-line treatment for IS. As there is no difference in the response to the treatment using high or low doses of ACTH, it has been proposed the use of low doses to avoid adverse reactions more commonly related to the synthetic ACTH, at doses 0.0125mg/kg/day (4,7,25,28,30,31). There is still no single consensus on the duration of its use, although it is acceptable the administration during 1 to 6 weeks, and in maximum within 12 weeks (7,25,28,30,31). With use of this hormonal therapy is possible to suppress IS in 42% to 87% of cases, with an efficacy in the response to the treatment between 7 to 12 days after the beginning of the treatment (7).

There are prospective studies (but they are inconclusive), such as the International Collaborative Infantile Spasms Study (7), which propose the combined use of both drugs from the beginning of the treatment of IS, reducing thus the time of use of ACTH and possible adverse reactions, with established dose of VGB, and lower number of relapses (29,36,39-41). In the present study, we used both ACTH and VGB as drugs of choice and in combination in 64.1% of the patients. 56% of them became free of IS and the hypsarrhythmia disappeared on EEG in the first six months, which coincides with the results from other researches (36,39). In addition, TAH was observed as the more frequent adverse effect (without hemodynamic repercussion in the total of the treated patients) causing in two patients immunosuppression and respiratory infection. However, TAH was treatable and reversible in all affected patients, with absence of cardiovascular affectionation demonstrated by ultrasound, and consequently no reason to suspend the use of the drugs. The combined therapy was used at low doses and not exceeding 6 weeks, as recommended by other authors, and the observed adverse effects were similar with other previous studies (7,8,16,23,26,28,30). This therapy was more effective to the group with known/symptomatic or genetic/structural-metabolic etiology (n=5 with neurocutaneous syndrome and n=2 with TSC), in the treatment of CVD, and in 50% of the cases of unknown or probably symptomatic etiology.

Of the 35.9% patients that used VGB (alone) as initial treatment for the reasons previously cited, only two achieved disappearance of IS and hypsarrhythmia in the first six months. Therefore, in our study there was a better response with the use of the combined therapy. Of these patients, those with postinfectious etiology, HIE and unknown or probably symptomatic etiology had little response. Moreover, irritability and weight gain were observed as an adverse effect in 14% of these cases, and an adjustment of dose was done. The presence of irritability was difficult to determine if it was due to medication or WS, which corroborates the findings of Arce-Portillo et al (7). During the neuro-ophthalmological follow-up no evidence of visual alterations attributed to medication was observed.

Regarding the total number of treated patients (with ACTH or VGB alone, or in combination), 58.9% achieved control or a reduction of IS to 50%, with disappearance of hypsarrhythmia in 41% in the first 5 months of treatment. These findings are also sustained by the results of the study of Arce-Portillo et al (7), which demonstrated efficacy of both drugs, alone or in combination.

In patients who did not respond well to the combined therapy or alone with VGB, other drugs, such as VA and TPM, or LVT and benzodiazepines were used to a lesser extent,

according to our therapeutic availability and following the recommendations of other authors (3,5,8,16,27,31). VB6 was used as initial therapy in patients with unknown etiology and in cases of Down syndrome, as advocated by Campistol et al (16) and Caraballo et al (31). A greater emphasis was directed to the cases of unknown etiology, and no favorable response was observed. This led us to suggest that error of metabolism should not be a probable etiology in most of our patients. In addition, we did not use other alternative therapies recommended for non-responders to the treatment or to those patients with drug-resistant WS (as for example the use of ketogenic diet or achievement of injury and functional surgery) (4,5,8,14,16,31), since such therapies have not been offered by our health system. It would be important the use of these alternative treatments in future researches or new health programs.

We found that although 74.4% of our patients have been treated with use of choice therapies, they had an unfavorable evolution, without much difference with the results found by Arce-Portillo et al (7). This is due in large part to the presence of factors of poor prognosis, such as patients with delay in the PD and/or abnormality of neurological PE prior to the onset of IS, epileptic seizures beginning in the neonatal period or a posteriori, previous paroxysmal EEG, and symptomatic or known etiology. A worse prognosis was observed among patients with HIE, postinfectious etiology and their structural sequels. Two of these patients presented neuronal migration disorders, one had kernicterus, three neurocutaneous syndrome (n=2 with TSC) and other three, an unknown etiology.

Another relevant aspect in this study was that when the age of onset of IS was less than 4 months and the hypsarrhythmia persisted on EEG after 6 months and/or there was a combination of more than three prognostic factors, it was observed statistical differences in IS alone or combined with other alterations, coinciding with the findings of Arce-Portillo et al (7).

Moreover, some authors noted to be relevant the time until the start of treatment when the diagnosis is made after the first month of the beginning of IS and the response to the drugs of choice is poor (7,16,31). In this sense, it should be taken into account the repercussion that these factors could have to PD, cognitive and/or behavioral spheres, as well as concerning the evolution to other epileptic syndromes later, especially LGS with onset before the age of 2 years (7,16,31,37,38). These characteristics also were observed in our patients.

By contrast, in patients with a favorable prognosis (25.6%), there was a lower presence of these prognostic factors. None of the patients had an early onset of IS and in only one of them more than one month of treatment was lost. In another the hypsarrhythmia persisted after six months on EEG and two had poor response to monotherapy or combined therapy. Moreover, a combination of more than three prognostic factors was observed in only one patient, which also corroborates the findings of Arce-Portillo et al (7).

In short, we observed (regarding our 39 cases of infants with WS followed by 11 years) the occurrence of IS with a greater frequency between 4 and 8 months of age, with predominance in males and, symmetry on EEG concerning the semiology of IS in flexion or mixed and hypsarrhythmia in most cases. The symptomatic or known (structural/metabolic and genetic) etiologies were the more prevalent. HIE and neurocutaneous syndromes were the most common etiologies

related to our cases of WS. When the therapeutic protocol existing in the hospital was used, more than half of the cases had a control of IS or their reduction greater than 50%, with disappearance of the hypsarrhythmia in the first 5 months.

It was also observed a greater response to the combined therapy of ACTH and VGB, which demonstrated efficacy of both drugs as therapy of choice. The use of ACTH also showed efficacy in the suppression/reduction of IS in an early manner and improvement or disappearance of hypsarrhythmia on EEG. Furthermore, the adverse effects of ACTH were treatable, transient and reversible, since this drug was used in low doses and for period less than 6 weeks. Other drugs, such as VA, TPM, LVT and benzodiazepines were in our context remain alternative therapies to non responders to the initial therapies, while VB6 was administered in patients with unknown etiology and suspicion of metabolic error associated with deficiency of this vitamin.

The majority of our patients had an unfavorable prognosis regardless of the etiology. There was a worse prognosis in those who had previous to the onset of the delay in the PD and/or neurological abnormality to PE, neonatal or a posteriori epileptic seizures, paroxysmal previous EEG, early onset of IS (before 4 months), persistence of hypsarrhythmia on EEG after 6 months, start of treatment after one month of onset of IS and poor therapeutic response.

This demonstrates that the repercussion of these factors of poor prognosis (alone or in combination) is determinant for an unfavorable evolution including severe forms with delayed PD, moderate or severe ID and association with ASD with evolution to other epileptic encephalopathies, such as LGS and epilepsies with multifocal spikes on EEG. Moreover, both the use of choice treatments and the control of IS do not ensure a favorable evolution, since the outcomes depend on the related etiology, epileptic activity, individual clinical characteristics and presence of factors of poor prognosis.

Finally, the conductance of multicentric studies may be needed to improve the knowledge about the variables as well as used therapies, in order to homogenize the therapeutic interventions and improve the follow-up for patients with WS.

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