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A Retrospective Cohort Study of Combined Therapy in West Syndrome associated with Trisomy 21

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Abstract

Background: West syndrome (WS) is a frequent epileptic encephalopathy associated with Down syndrome (DS). This study evaluated an outpatient protocol for WS in patients with DS who received vigabatrin (VGB) or VGB plus adrenocorticotrophic hormone. **Methods:** We analyzed infants treated in two neuropediatric centers from 2001–2021. We reviewed perinatal and familial history of epilepsy, spasm onset, treatment lag, electroencephalogram, neuroimaging, progression to epilepsy, and other neurological conditions. The outcomes were electroclinical resolution (ECR), relapses, and epilepsy progression. **Results:** Nineteen infants were included; 57.8% were male. The average spasm onset, follow-up, and treatment lag were 6.4 months, 8.15 years, and 2.33 months, respectively. Almost 74% had ECR after protocol intervention and minor epilepsy progression. Relapses occurred during combined therapy. **Conclusions:** The treatment protocol, especially combined therapy, was effective for WS in DS, impacting epilepsy progression and indicating the effectiveness of combined therapy to treat WS in patients with trisomy 21.

Keywords

Down syndrome, West syndrome, infantile spasms, adrenocorticotropic hormone, vigabatrin, trisomy 21

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Introduction

The prevalence of trisomy 21 in Brazil is estimated to be two out of 660 live births.[1] Down syndrome (DS) is the most common chromosomal disorder, with almost 26% developing epilepsy during their lives.[2] West syndrome (WS) is the most frequent epileptic syndrome in these patients and is characterized by typical spasms, hypsarrhythmia (HYP) on electroencephalography (EEG), and progressive neurological delay.[3] Lengthy time to diagnosis, treatment lag, drug refractoriness, and daily seizures may contribute to poor developmental outcomes in patients.[4,5] The primary therapies for WS are adrenocorticotrophic hormone (ACTH), prednisolone, and vigabatrin (VGB). DS has higher rates of cessation of spasms and hypsarrhythmia with these drugs.[6] Although a vast amount of literature exists confirming their effectiveness, many of these studies' methods used small sample sizes and different sequences of drug treatments.[6-10] Moreover, the benefits of pharmacotherapy do not apply to all children, mainly because ACTH is a parenteral and a high-cost drug without uniformity of the treatment regimen.[11]

Previous studies have described different WS etiologies, treatment regimens, sequence of drugs, formulations (synthetic vs natural), and rate responses.[12] Hence, it is essential to create new WS ambulatory protocols with combined therapies with attention to the accessibility of the drugs and their medium- to long-term effects. This retrospective cohort study evaluated the best treatment for WS in DS using a new treatment protocol with a standardized sequence of drugs and regimens for a specific etiology, starting with VGB and adding ACTH in cases that show lack of response. The study also analyzed epilepsy progression and developmental disorders after at least 12

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months of follow-up. We hypothesized that the protocol using VGB and VGB plus ACTH, as the first and second option or in that order, would result in electroclinical resolution (ECR) in most patients. We also hypothesized that infants after ECR would have minor progression to epilepsy and autism spectrum disorders (ASDs).

Materials and Methods

Editorial Policies and Ethical Considerations

The Ethical Committee of Research Institution of Paraná Federal University approved this study (61921316.4.3002.0096 and 61921316.4.0000.0103 CAAE) and the study respected and ensured the guidelines of the Helsinki declaration were followed. The parents' informed consent was obtained for the infants who had ambulatory appointments at the participating institutions.

This retrospective cohort study examined outpatient treatments for WS in DS. We accessed medical registries from November 2001 to 2021 from two neuropediatric ambulatories, including a Tertiary Hospital of Paraná Federal University group. The researchers obtained any missing data through telephone interviews with parents. The participants were selected by convenience, considering WS is a rare encephalopathy. DS was selected because it is a prevalent genetic disorder associated with WS with similar clinical findings and responses to treatment. Despite the diverse classifications of WS in DS, the proposal by the West Delphi group and the symptomatic WS form were selected in this study.[4] The inclusion criteria were age ≤10 years, trisomy 21 confirmed by genetic testing, adherence to WS protocol treatment in the two neuropediatric ambulatories, and at least one year of available follow-up data. The exclusion criteria were hypoxic-ischemic or vascular injuries. The variables analyzed were sex, age, onset spasms, clinical spasms observed by parents or medical providers, gestational and neonatal problems, lag to start treatment, neuroimaging, and electroencephalogram (EEG). During follow-up, the data analyzed were spasms, seizure relapses, and conventional antiseizure drug (CASD) responses. The last evaluation reviewed the progression to epilepsy, antiseizure drugs (ASDs), and whether the participants performed activities expected for their age group.

The two neuropediatric centers were chosen as they were guided by the same epileptologist and applied the protocol. Infants treated at other institutions with differing prescribed drug regimens had their treatment changed to the protocol**.** The WS **treatment started with VGB at 50 mg/kg, increasing 50 mg/kg every week to a maximum of 200 mg/kg or until** a clinical response was achieved**. The treatment should be discontinued after 6 months of therapy.** A combined treatment of VGB plus ACTH after a lack of response to therapeutic doses of VGB was the recommended protocol for patients with persistent spasms or HYP on EEG. ACTH is the drug of choice for WS; however, the Brazilian Health System does not dispense it to children. After obtaining parental consent, children were given the same dose of VGB as before (80 to 200 mg/kg) and started on synthetic ACTH at 0.5 mg/kg once daily for 7 days, for a maximum of 3 weeks. After 7 days of therapy, the participants with ECR continued with the same dosage for 14 days. Children with clinical spasms or HYP on EEG completed 21 days of treatment with 1 mg/kg of ACTH and an additional two weeks of oral prednisone starting at 1 mg/kg and decreasing in tapering doses until withdrawal. The ECR after three months of treatment with the protocol was the primary study outcome. This protocol was chosen based on better long-term ECR and fewer relapses than lower doses.[13] WS was defined as a history of epileptic spasms associated with HYP on EEG and developmental delay.[4,14] Epileptic spasms were defined as flexor fits occurring in clusters reported by parents and trained medical providers. To investigate HYP, EEG was combined with a sleep–arousal–wake register for at least 30 min or by video EEG in particular cases, all approved by a neurophysiologist. The study applied Gib's (1965) pattern to define HYP and included the modified HYP in the same group.[4] The children proceeded with the EEG to define the ECR on the seventh and ninetieth days and evaluate spasms or suspected relapse during the follow-up. The treatment lag was defined as the interval between the onset of clinical spasms and the first treatment of WS. The study evaluated neurodevelopment by physical exam during the appointments and was omitted based on retrospectively collected data.

After three months, we considered ECR as the absence of HYP on EEG and clinical spasms. Infants with persistent clinical spasms (CS) or HYP on EEG were delineated as the group with a negative electroclinical response (NECR). EEG resolution was defined as non-HYP patterns on EEG, including diffuse slow spikes and waves, diffuse or multifocal epileptic discharges, focal epileptic discharges, and no epileptic discharges.[4]

We considered relapses such as the new CS and HYP on EGG in patients with ECR after completing the ACTH therapy or one month after the maximum dose of VGB. All CS and HIP on EEG, which developed during the period of the treatment with ACTH and until 30 days of the maximum dose of VGB, were considered part of the treatment response. Other epileptic seizures were classified as progression to epilepsy. Controlled seizures were indicated by the cessation of seizures for a year; uncontrolled seizures were classified into two types: frequent or sporadic. Clinical examination ranked the landmarks as expected or delayed. We reviewed the progression to epilepsy and developmental disorders during the follow-up and classified them as age-dependent or age-independent activities. For diagnosis of autism spectrum disorder, the pediatric neurologist utilized the DSM-5 criteria and the three symptom domains: impaired social interaction, impaired communication, and stereotyped and/or repetitive behavior according to the International Classification of Diseases-Tenth Revision (ICD-10 2019).[14] Among 107 patients with WS treated in the two neuropediatric ambulatories, 23 had DS and 19 participated in the research. The study excluded four patients: two who did not complete follow-up, one who was premature and had hypoxic-ischemic encephalopathy, and one with incomplete medical records.

R software 4.1.2 and GraphPad Prism 9.3.0 were used for statistical analysis. The results are expressed as mean, median, standard deviation, interquartile range, and percentage. The

data were analyzed using the χ^2 and Fisher's exact test for categorical variables. The correlation between quantitative and categorical variables was examined using a non-parametric test (Spearman correlation test).

Results

The main characteristics of the cohort with rare epileptic encephalopathy and DS are presented in Table 1.

Altogether, 19 patients were included in the study, and 11 were male (55%). All patients developed neurological regression based on the WS diagnoses. Six patients had started WS treatment at other institutions, mostly with valproate (VALP). In our tertiary hospital, the drug choices were VGB and ACTH. Three infants had registries of different types of seizures. The spasms started between 3 and 13 months (first quartile, 4; median, 4; mean, 6; third quartile, 8).

The computed tomography (CT) scan or magnetic resonance imaging (MRI) revealed no abnormalities in six patients (CT and four MRI), while seven had abnormalities (one had an arteriovenous malformation of the cerebral peduncle without clinical manifestation, and six had atrophy), and six had minimal changes typical of DS. Of the 19 patients, seven had a familial history of epilepsy in their first-to-second-degree relatives, and eight had perinatal problems. The treatment lag ranged between 7 and 330 days (first quartile, 10; median, 30; mean, 72; third quartile, 75) and to VGB as the first drug, between 7 and 330 days (first quartile 10; median, 30; mean, 74, 85; third quartile, 60). Nine of the 19 infants had undergone medical follow-ups at the same neuropediatric center since birth.

The protocol started with VGB, used as the first, second, and third therapies in 13 (68%), four (21%), and two (10%) of the 19 infants, respectively. ACTH therapy was added for 11 infants who did not respond to VGB. Fourteen (73.6%) of the 19 infants presented with initial ECR after the treatment protocol. Seven followed VGB plus hormonal therapies, and six refused and followed treatment with CASDs. After one year, 12 of the 19 (68.4%) patients did not have spasms. The VGB had resolved the spasms and HYP in 42.1% of the treated patients, as the first drug in 5/13 (38.4%) and as second and third drug in 3/6 (50.0%) patients, at a dose of 80 to 100 mg/kg (mean 96.5 mg/kg). VGB plus ACTH was effective in 6 of 7 infants (85%); in one of the patients, the epileptic disorders and HYP resolved on the seventh day, and others after the fourteenth day. In the six other children who presented with HYP on EEG, their therapy was extended until 21 days. The combined treatment of VGB (>100 mg/kg) and synthetic ACTH (ACTH 30 at 40 UI/day, mean 38.5 UI/day) demonstrated ECR in 85.7% of the treated patients.

Relapses occurred in 3/7 infants in the ACTH group. One patient in the combined therapy group manifested dyskinesia and basal ganglia impregnation at a dose of 150 mg/kg/day of VGB. The dyskinesia resolved after ACTH therapy was completed, and neuroimaging was performed after VGB withdrawal until 6 months.

Another child developed hypotonia and irritability without neuroimage abnormalities, which resolved after the VGB reduction from 180 to 100 mg/kg/day. Most patients treated with the two drugs had side effects attributed to ACTH. Two had hypertension, three had choreiform movements, and one patient had pneumonia. The drug reactions disappeared after

Table 1. Characteristics of the Sample.

Patients	Sex	Spasms O (Mo)	Seizure before WS	H of Epilepsy	First drug to WS	ECR drug	Lag to treat	Epilepsy late	ASD
1	M	3	No	No	VALP	VGB	120	No	Yes
2	M	11	No	No	Pred	VGB	90	Yes	Yes
3	F	7	No	Yes	VGB	VGB	45	No	Yes
4	F	6	No	Yes	VGB	No	11	LGS	No
5	M	8	No	No	VGB	No	8	LGS	Yes
6	F	5	No	No	VGB	VGB	45	No	No
7	M	4	No	No	VGB	ACTH	60	No	No
8	M	9	No	Yes	VGB	ACTH	30	No	No
9	M	4	Focal	No	VGB	ACTH	60	Yes	No
10	M	3	Focal	Yes	VGB	No	7	Yes	No
11	F	10	No	No	VGB	VGB	10	No	No
12	F	8	No	Yes	Nitraz	VGB	30	No	Yes
13	F	7	No	Yes	Nitraz[a]	No	7	Yes	No
14	M	4	No	No	VGB	VGB	30	No	Yes
15	F	6	Focal	No	VGB	VGB	7	No	No
16	M	4	No	No	VGB	ACTH	330	Yes	No
17	M	5	Myoclon	No	VGB	ACTH	330	Yes	No
18	M	13	No	Yes	VALP	ACTH	120	No	No
19	F	5	No	Yes	PHE[a]	No	30	Yes	No

Abbreviations: Mo, months; F, female; M, male; O, onset; H, history; WS, West syndrome; ECR+, electroclinical resolution; Nitraz, nitrazepam; VGB, vigabatrin; PHE, phenobarbital; VALP, sodium valproate; Pred, prednisone; LG, Lennox Gastaut syndrome.

[a]Failure after vigabatrin therapy.

the completion of ACTH treatment. None of the patients needed to stay in the hospital or suspend the medication before the proposed duration. At the final follow-up, three of the 19 children had ECR with another drug outside the protocol (one after ACTH relapse and two in the NECR group).

After a follow-up of 1 to 18 years (average 8.15 years), 11 of 19 (57.8%) patients progressed to epilepsy and six to ASD (31.5%). No patients developed ASD after the VGB plus ACTH therapy ($P = .05$). Two had concomitant ASD and epilepsy. ECR patients had a significantly lower probability of developing epilepsy ($P = .04$) than NECR patients (42.8% vs 100%). In the NECR group, all patients developed epilepsy, and two progressed to Lennox–Gastaut syndrome. Furthermore, two children did not respond to the drug protocol, but had a late electroclinical remission with CASD, and other patients were treated with high doses of VGB.

In the last follow-up, 31.5% of patients were diagnosed with ASD, 5/14 (35.7%) were in the ECR group, and 1/5 (20%) were in the NECR group ($P = .99$). Eight of 11 infants with epilepsy exhibited seizures; six were classified as frequent, and two were sporadic seizures. The last seizure control did not correlate with initial ECR ($P = .34$). All patients presented with intellectual disabilities. Half of the patients were dependent on age activities; 8 of 14 (57.1%) had ECR, and 80% had NECR ($P = .60$). Table 2 describes the sample's characteristics and correlation with clinical and drug response, epilepsy progression, and seizure control. Relapses were significantly associated with frequent seizures in the last evaluation ($P = .05$), and they were correlated with long treatment lag ($r = 0.46$ and $P = .04$).

Discussion

In this study, the treatment protocol showed beneficial responses in 73.6% of the infants and had higher efficacy in the VGB plus ACTH treated group. Minor epilepsy progression was observed after ECR for ASD in the combination therapy.

Our study reported similar proportions of sexes as a previous study, although WS was more prevalent in male infants.[15] In general, the age of spasm onset is 4 to 7 months in patients with WS, although, in the DS population, spasms occur 2 months later.[9] Theoretically, the inherent structural abnormalities in the frontal lobe are involved in this delay.[16] We kept one child with brain malformation in the sample, considering that the lesion was not related to abnormalities on the physical exam. Moreover, patients have multiple comorbidities and developmental problems commonly associated with WS symptoms.[17] In our data, the onset of spasms occurred after 6.4 months on average, similar to 7 months in other recent reports.[6,10,18] The treatment lag ranged from 7 to 330 days (30 of median), which is very different from that reported by Tapp et al[19] and Beatty et al[6] at 5 to 90 days and 4 to 41 days, respectively. This delay depends on parents' attention to their child's medical condition.[7] Moreover, other variables, such as access to the health system and socioeconomic conditions, can influence this factor. In our study, nine patients with DS had multidisciplinary appointments since birth and were diagnosed with WS at 7 to 30 days of life. Of the 19 patients, 6 started therapy in primary care based on provider preference. This may explain the broad range of the treatment time (7–330 days).

Patients with DS account for 17% of those with WS and may be a homogenous group considering their drug response.[5,8,20] The adrenocorticotrophic hormone is the drug choice to treat WS in trisomy 21 children, and VGB is the second choice with less efficacy.[6] Our protocol for WS with two regimens effectively resolved the spasms and HYP in most patients (73.6%), corroborating a good treatment response.[21] Those patients who did not respond after the seventh day of therapy completed 21 days of treatment with more than two weeks of prednisolone tapering. Although the evidence is insufficient regarding use of oral corticosteroids in WS, it may have influenced our results.[14] However, some protocols described the efficacy as approximately 50%, reflecting the different sequences of drugs offered to patients, ACTH regimens, and VEEG to define the treatment response.[9,22] Comparing WS treatment in DS is difficult because research reporting the efficacy of VGB and VGB associated with synthetic ACTH is scarce. Most studies on DS describe results from isolated drugs and exclude potential

Table 2. Main Clinical Characteristics, Drug Response, ASD Correlation with Progression to Epilepsy, Dependence on age Activities, and Seizure Control in the Last Follow-up.

Progression to	Epilepsy	Relapses	ASD	Dependency in age activities	Seizure control
Response to:					
VGB, ACTH, NR	$P^{**} = .07^{*}$		$P^{**} = .05$	$P^{**} = .56$	$P^{**} = .22$
Protocol; Y/N	$P = .04$		$P = .99$	$P = .60$	$P = .60$
Sex	$P = .99$		$P = .99$	$P = .37$	$P = .64$
CASD	$P = .99$		$P = .32$	$P = .33$	$P = .99$
Spasm onset	$r = -0.09$	$r = 0.49$	$r = -0.11$	$r = -0.33$	$r = 0.016$
	$P = .68$	$P = .03$	$P = .62$	$P = .6$	$P = .94$
Treatment lag	$P^{***} = .04$	$P^{***} = .9$	$P^{***} = .57$	$P^{***} = .93$	$P = .45$
	$r = 0.46$	$r = 0.02$	$r = -0.13$	$r = 0.02$	$r = -0.18$
F.H. epilepsy	$P = .99$		$P = .65$	$P = .04$	$P = .99$
Neonatal Problems	$P = .64$		$P = .99$	$P = .99$	$P = .99$

Abbreviations: ACTH, adrenocorticotrophic hormone; VGB, vigabatrin; ASD, autism spectrum disorder; CASD, conventional antiseizure drugs before to start of the study protocol; NR, no response; *P*, Fisher exact test; *P***, chi-squared; *P**** or r, Spearman correlation test***; bi-serial correlation; FH, familial history.

synergistic or antagonistic effects. We started with VGB and added synthetic ACTH for patients who did not respond to VGB. The study selected combined therapy because it represents a gap in the literature, and it seems be more effective than monotherapy.[14,23] Additionally, we created an outpatient treatment protocol using the drug choices for WS, adapting it to our country and individual responses. A recent review has reported that VGB may be as effective as ACTH in treating WS in DS.[21,24] However, their average efficacy is 55%,[20] which was observed in our patients (42.1%) at an average dose of 96 mg/kg. These differences in data are likely due to different sample sizes, dose therapy, and time taken to determine the efficacy.[7,21] Moreover, ACTH is the preferred therapy for WS in patients with DS, due to its better tolerability, with response rates of 81% to 92%.[6,22] Although ACTH may be superior to VGB,[25] some centers report worse results using low doses (28.6%), reflecting the lack of uniformity in treatment.

Our research has demonstrated 10 years of ambulatory treatment experience for WS in DS. We confirmed the efficacy of ACTH in DS.[25,26] We added ACTH to VGB at high doses, 0.5 mg/kg to 14 days, equivalent to 100 mg/m^2 or 40 UI of the natural form.[27] High doses of ACTH and combined therapies likely impacted the treatment effectiveness of WS, corroborating the findings of a recent review.[28] Our protocol was a higher dose in a short duration based on better long-term electroclinical remission and minor relapse rates compared to lower doses.[13] Our lower relapse rates may be the consequence of the study's retrospective data and broad variation (1–18 years) of follow-up and method of determining electroclinical response. Studies comparing ACTH therapies are troublesome, especially when considering dual therapy. Combined therapy studies in DS and WS show efficacy from 83% to 100%, which corroborates with our results (85%).[9,19,20] Although there is an equivalency between synthetic and natural ACTH doses in the literature, they have differences in action times, cumulative effects, possible side effects, and efficacy.[28] Our patients received VGB plus synthetic ACTH at higher doses, which increased drug reactions, such as hypertension, movement disorders, and irritability. The combined therapy seems to potentiate the VGB toxicity, manifested from hypotonia, irritability, to dyskinesias, and *vigabatrin-associated-brain abnormalities on magnetic resonance imaging* (VABAM).[29] Prospective and well-defined studies are necessary to answer these critical clinical questions.

Some patients had already been treated with CASD at other centers in our sample cohort. The delay until the start of the WS-recommended drugs can represent a treatment lag. However, earlier investigations considered that early treatment can be related to better response in genetic/symptomatic and cryptogenic forms[20,23]; these findings have not been confirmed over time.[9] The lag in treatment did not modify the initial response to VGB or combined therapy, although it was correlated with relapses.

In previous studies, the relapses varied between 0% and 53%,[6,7] with an average of 21%, corroborating our data (21%).[5,8,19,30] In our patients, relapses were more frequent with ACTH than with VGB, agreeing with a recent review,[21] and correlating with a long treatment lag ($r = 0.46$ and $P = .04$). Indeed, ACTH has higher rates of relapses, which can be explained by its initial action time compared to the later effect of vigabatrin.[9] Moreover, the definition of ECR likely increases relapse rates, as found in recent studies.[9,29] We proceeded with video EEG only in doubtful cases; regardless, it is better than EEG at detecting spasms and HYP.

Our sample excluded patients with clinical exams or neuroimages indicating hypoxic-ischemic and vascular injuries to reduce superimposed insults and consequent high probability of epilepsy.[31] Epilepsy progression was observed in 57.8%, and ASD was diagnosed in 31.5% of patients. The epilepsy rates vary, and our higher rates may have resulted from the follow-up time (average 8.15 years). ASD did not occur after combined treatment ($P = .05$).

This study reported a medium-term protocol experience as a beneficial option for treating WS in patients with DS in ambulatorial treatment. The same epileptologist guided the protocol at our two centers to reduce bias. Conducting prospective studies in WS infants with DS is problematic because it is age-dependent and rare.

The study's limitations were its retrospective design, convenient sample collection protocol, small sample, no control group, and administration of ACTH therapy subject to the parents' consent and financial conditions. Also, we did not access the neurodevelopmental outcome and comorbidities in DS children associated with WS because of the retrospective nature of the data. These methodological aspects limit the extrapolation of our results. Although the sample size was relatively small, this research proposed a new and effective protocol, with VGB and VGB plus ACTH, to treat a specific WS etiology.

Conclusions

This study showed that our treatment protocol effectively treats WS in outpatients at medium-term follow-up. Additionally, our data supported better electroclinical responses and minor progression to ASD in patients who received ACTH therapy combined with VGB. The favorable clinical response, indifferent to the choice of therapy, resulted in minor epilepsy progression. Additional research should be conducted to improve outpatient protocols using prospective data, oral corticosteroids, in order to extend their benefits to all patients with WS.

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