University Hospitals

Clinical response to vigabatrin in relation to time and dose: parental perception, EEG confirmation

Introduction

West Syndrome (WS) is an infantile epileptic encephalopathy, which typically occurs within the first 2 years of life, with an incidence of 2 to 5 per 10,000 live births. A triad of epileptic spasms (ES), developmental plateau or regression, and hypsarrhythmia on EEG characterize WS. Standard FDA approved therapies for ES are intramuscular adrenocorticotropic hormone (ACTH), oral corticosteroids (OCS), and vigabatrin (VGB). One small study of 20 children with ES, not due to TSC, reported a response rate of 35%[1] on VGB as initial therapy. Other literature comparing ACTH, OCS, and VGB show on-going discussion regarding best initial therapy, preferred dose, and adjunctive therapies. For example, a large multi-center prospective study enrolled 230 participants and compared the three above standard therapies. Their conclusion showed that ACTH was superior and more effective than VGB (55% vs 36%) for children with ES, regardless of etiology or development [2]. Other studies of mixed cohort of children with Tuberous Sclerosis Complex (TSC) and other etiologies, utilizing VGB as first-line therapy, reported various response rates such as 26%[3], 30%[4], 36%[2], 42%[5], and 56%[6].
Treatment response reported by the latter studies reflected mixed cohorts (that included TSC patients) who received either ACTH, VGB, or steroid as first line therapy for ES. Therefore, patient selection bias may have been a factor in the reported response rate. Although treatment response, clinical and electrographic, after initiation of a therapy is validated with video EEG, there are no data regarding when to obtain the first VEEG after initiation of therapy. In addition, there are no data regarding reliability of parental report regarding resolution of ES.

Objective

The aim of this study was to answer two questions: 1. What is the efficacy of VGB, when used exclusively as initial treatment for ES, regardless of etiology other than for tuberous sclerosis complex (TSC)? 2. Can a parental report of ES resolution be used as a guide when to obtain the first VEEG after initiation of treatment for ES?

Methods

We performed a single-center, retrospective analysis of all newly diagnosed cases of ES between January 2014 and October 2021 (n=39) at RBCH. VGB dose of 100 mg/kg/day to 200 mg/kg/day was used as first-line therapy for all patients admitted to the Epilepsy Monitoring Unit. Diagnosis was based on VEEG after obtaining detailed history and physical examination. Patients with genetic diagnosis of TSC were excluded. Duration of follow-up was up to 1 year from treatment initiation. All patients were followed *at scheduled times* with VEEG: At the 2nd and 4th week, 3-, 6-, and 12- month. Various clinical variables were collected, such as gender (21 male, 18 female), age at onset of diagnosis (range 2 - 36 months; median age 8.8 months), gestational age (range 24 - 41 weeks; median 36 weeks), ethnicity, presence of seizures prior to ES, current and past use of anti-seizure meds (ASMs), developmental assessment (normal or abnormal based on neurologist's assessment), etiology of ES (acquired structural, metabolic,

genetic, cryptogenic), length of VGB treatment (range 3 - 60 months; median 16.7 months), duration and dose of VGB when parents reported resolution of ES, time of resolution of ES and/or hypsarrhythmia by VEEG. Note: one patient grouped under “acquired structural” had calcification as the only abnormality.

Resolution of ES, with or without hypsarrhythmia, was defined as sustained absence for 3 months after treatment initiation and VEEG confirmation of resolution. Children were considered early (clinical and EEG confirmation of spasm-freedom at 2 weeks of scheduled VEEG) or late responders (clinical and EEG confirmation of spasm-freedom after 2 weeks), or non-responders. This study was approved by the UH Rainbow Babies and Children’s Internal Review Board.

Table 1: Clinical Variables

Variable	Entire Cohort (N=39)	VGB Responders (N=19, 49%)	VGB Non-Responders (N=20 51%)
Sex, N (%)			
Female	18 (46%)	9 (47%)	7 (35%)
Male	21 (54%)	10 (53%)	13 (65%)
Ethnicity, N (%)			
Black	10 (26%)	6 (32%)	4 (20%)
White	21 (54%)	10 (53%)	11 (55%)
Asian	2 (5%)	1 (5%)	1 (5%)
Hispanic	6 (15%)	2 (10%)	4 (20%)
Gestational age (wks) median (range)	36 (24-41)	37 (24-41)	37.5 (32-40)
Age at diagnosis (mos), median (range)	8.8 (2-36)	8.1 (5-36)	9.9 (2-36)
Etiology, N (%) Structural			
Genetic	18 (47%)	7 (37%)	11 (55%)
Metabolic	11 (28%)	4 (21%)	7 (35%)
Cryptogenic	2 (5%)	1 (5%)	1 (5%)
	8 (20%)	7 (37%)	1 (5%)
Development at diagnosis, N (%)			
Abnormal	33 (85%)	14 (74%)	19 (95%)
Normal	6 (15%)	5 (26%)	1 (5%)
Development after Diagnosis, N (%)			
Abnormal		15 (80%)	20 (100%)
Normal		4 (20%)	0
Development after Diagnosis, N (%)			
Abnormal		15 (80%)	20 (100%)
Normal		4 (20%)	0
Seizures before ES, N (%)			
Yes			
No	22 (56%)	8 (42%)	14 (70%)
	17(44%)	11 (58%)	6 (30%)
Presence of AEDs before ES, N (%)			
Yes	22 (56%)	8 (42%)	14 (70%)
No	17 (44%)	11 (58%)	6 (30%)

Length of VGB treatment (mos), median (range)	16.7 (3-60)	17.9 (1-60)	14.9 (2-48)
VF complications, N (%) **Prior CVI** **No prior CVI** **VF loss**	 23 (59%) 16 (41%) --	 9 (47%) 10 (53%) --	 14 (74%) 5 (26%) -- *one pt has not seen Ophthalmology as of yet
Hypsarrhythmia on video EEG at diagnosis, N (%) **Abbreviations:** **VGB: vigabatrin** **ES: epileptic spasms** **AEDs: anti-epileptic drugs** **VF: visual field)**		11 (55%)	10 (52%)

Table 2: Time and Dosing of Parental Report of ES Cessation

Dose at which parents report ES resolution	Time when ES resolution reported	EEG confirmation (Y/N)	Relapse (Y/N/NA)	Length of tx duration (months)	Transitioned to ACTH/Oral Pred
150	2 weeks	Y	N	6	N
100	2 weeks	Y	N	(81) taking	N
165	2 weeks	N	NA	24	Y
105	2 weeks	Y	N	10	N
150	2 weeks	Y	N	12	N
150	2 weeks	N	NA	12	Y
140	2 weeks	Y	Y	24	Y
150	2 weeks	Y	N	16	N
160	2 weeks	Y	N	15	N
160	2 weeks	Y	N	12	N
150	2 weeks	Y	N	11	N
100	2 weeks	Y	N	35 (taking)	N
150	2 weeks	Y	N	21	N
160	2 weeks	Y	N	1	N
150	2 weeks	Y	N	15	N
150	2 weeks	Y	Y	12	Y
140	2 weeks	Y	N	6	N
160	2 weeks	N	NA	19 (taking)	Y
160	2 weeks	N	NA	19 (taking)	N
165	2 weeks	Y	N	88 (taking)	N
200	2 weeks	Y	N	13 (taking)	N
100	4 weeks	Y	N	67 (taking)	N
170	3 months	Y	N	25(taking)	N

Results

Thirty-nine patients were treated with VGB as first line medication between January 2014 to October 2021. None of the patients were excluded due to incomplete data. No serious adverse

reactions led to discontinuation or reduction of drug doses. Etiology of ES was classified as acquired structural, metabolic, genetic, or cryptogenic (**Figure 1**). Monitoring of vision, including assessment of visual acuity and visual field (VF), was done based on the VGB REMS recommendation. This included initial assessment within 4 weeks of treatment initiation and every 3-4 months while on therapy, with electroretinogram (ERG) performed at least once during duration of treatment. No infant experienced VF deficits related to VGB usage. Twenty-two (56%) parents (each parent representing one patient) *reported* complete or partial resolution of ES: 20 @ 2wks*, 1 @ 4wks**, 1 @ 3 months***.The EEGs confirmed that 19/22 (86%) parents were correct with their report of ES resolution. The remaining 3 (14%) parents, who reported complete resolution of ES, were incorrect (**Figure 2**). Also, all parents (17) who did not report resolution of ES (partial or complete) were confirmed to be correct. Of note, not all of the patients had an EEG finding of hypsarrhythmia at the time of diagnosis, while all had abnormal EEG. Nineteen of the 39 infants (49%) with ES were either early responders (13) or late responders (4), while 2 were early responders who relapsed. The 20 of the 39 patients, who did not respond to VGB, transitioned to ACTH (11), OCS (2), ketogenic diet (2), surgery (1), or none of these treatments due to parent refusal (4). Seven (of 11) patients from the ACTH group and all patients from the OCS, Ketogenic diet, and surgery groups had resolution of ES. One patient's ES resolved after evacuation of subdural hygroma[8]. Thus, 12 of the 20[#] patients' ES resolved (**Figure 3**).

[#]**Eight** of the 20 patients who continued to have ES were classified as: 1 with a partial response to ACTH, 1 with no response to ACTH, 2 who initially responded to ACTH, then relapsed, and 4 who did not transition to ACTH/OCS/KD due to parental refusal.
***Two** of twenty parents reported partial resolution at 2 weeks; VGB dose was further increased, however, were lost to follow, thus VEEG confirmation of complete resolution occurred at 3 months. One of these two patients was found to have ES resolution at 200 mg/kg/day. Cannot exclude the possibility that the patient may have had resolution at 150 mg/kg/day.
****Parent** reported partial response at 2wks but was only on 50mg/kg, thus instead of repeat VEEG at that time, the VGB dose was increased to 100mg/kg, 1 week later, mom reported resolution, but was lost to f/u until 4 wks post VGB initiation. VEEG completely normalized.
*****Parent** reported partial response to treatment at 2wks, (confirmed by EEG), thus dose increased from 150mg/kg to 170mg/kg. Mom reported complete resolution of ES shortly after dose increase. Because of COVID and unit closure, did not complete f/u VEEG until at 3 months post VGB initiation. VEEG confirmed complete resolution.

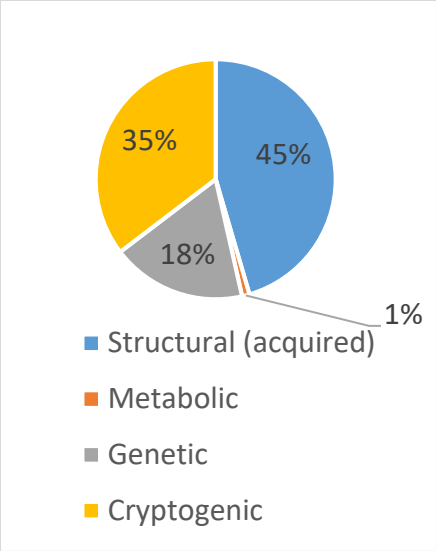


Figure 1: Etiology for Responders

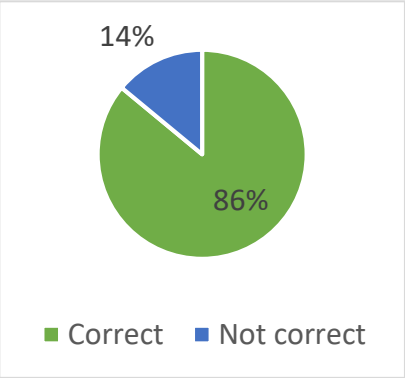
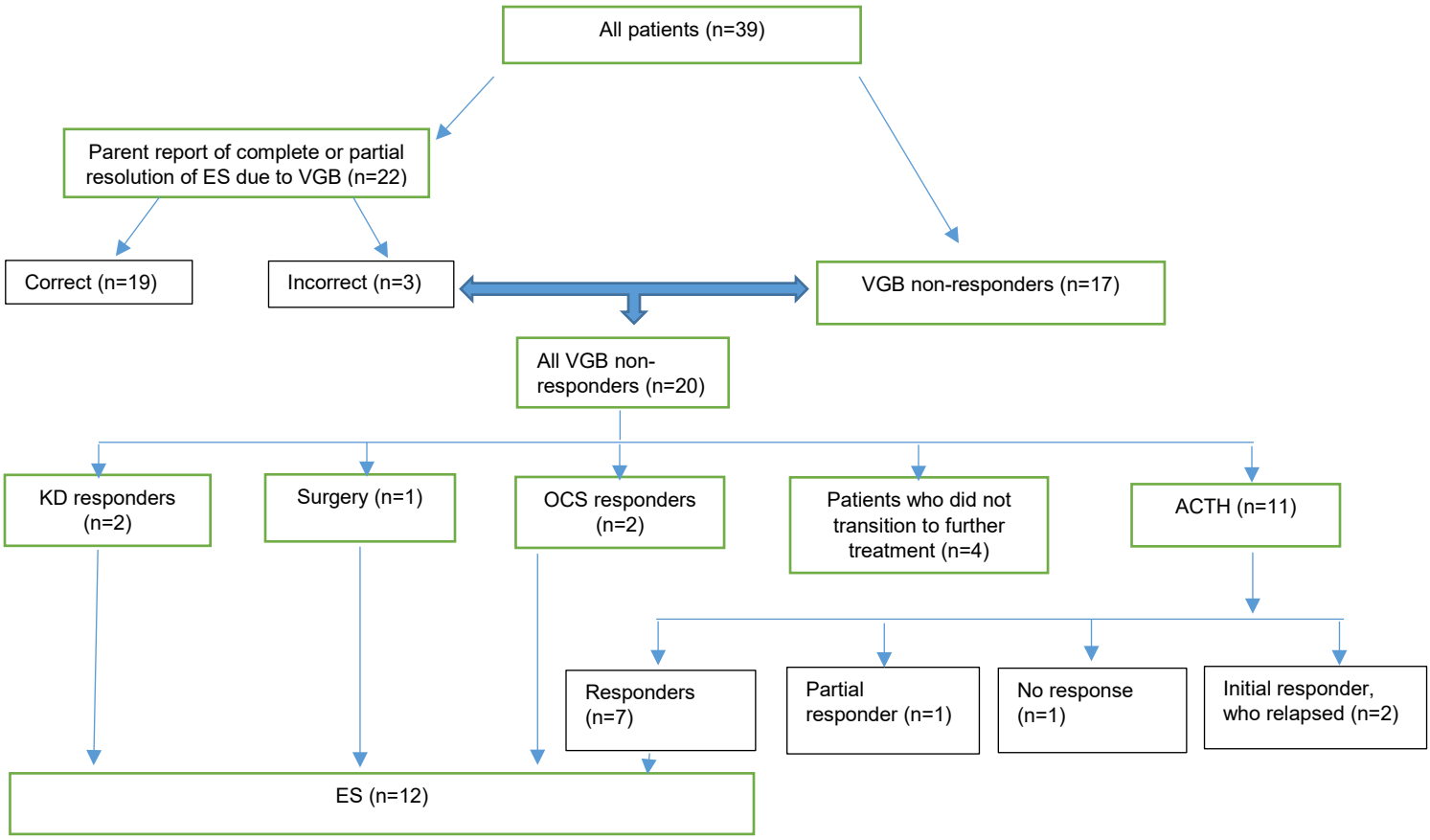


Figure 2: Parental Report, EEG confirmation

Figure 3: Responders and non-responders algorithm



University Hospitals

Conclusion

The percentage of responders in this study (49%) was in line with that reported in the multicenter UK Infantile Spasms Study (UKISS). The UKISS study compared 107 infants *without TSC* (55 who received hormonal therapy and 52 who received VGB) over a *14 day* period. The infants in the hormonal arm had 73% response rate, compared to 54% VGB response rate [7].

Parental report can be utilized with a high reliability (86% correct response) as a guide when to obtain a VEEG after starting therapy. It is also important to note that in this study all parents who denied report of ES resolution were correct, confirmed by follow up VEEG. *Thus, when parents report or deny ES resolution, this information has high reliability. This may guide monitoring ES treatment* during COVID-19 pandemic or where EEG is a limited resource.

Our study showed that the lowest VGB dose at which parents first reported (and confirmed) ES resolution was 100 mg/kg/day, while the highest dose was 200 mg /kg/day. This suggests that clinicians may begin a phone follow up to check for resolution of ES at VGB dose of 100 mg/kg/day. In addition, a higher VGB dose of 200 mg/kg/day may need to be tried before switching to an alternative therapy. Finally, 31 out of the 39 patients had resolution of ES after treatment with either VGB or others therapies: ACTH, OCS, KD, or surgery.
A small sample size of our study was a limitation. However, our unique study utilizing VGB as initial treatment for all causes of ES, except for TSC, at a tertiary pediatric epilepsy center minimized treatment selection bias.

References

1. Appleton R, Peters A, Mumford J, Shaw D. Randomized, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia*. 1999; 40:1627-1633.
2. Knupp KG, Coryell J, Nickels KC, et al. Response to Treatment in a Prospective National Infantile Spasms Cohort. *Ann Neurology.* 2016; 79(3): 475-484.
3. Granström M-L, Gaily E, Liukkonen E. Treatment of infantile spasms: results of a population based study with vigabatrin as the first drug for spasms. *Epilepsia*. 1999; 40:950-977.
4. Jones K, Go C, Boyd J, et al. Vigabatrin as First-Line Treatment for Infantile Spasms Not Related to Tuberous Sclerosis Complex. *Pediatric Neurology*. 2015; 53: 141-145.
5. Wohlrab G, Bolthauser E, Schmitt B. Vigabatrin as a first-line drug in West syndrome: clinical and electroencephalographic outcome. *Neuropediatrics*. 1998; 29:133-136.
6. Camposano SE, Major P, Halpern E, Thiele EA. Vigabatrin in the treatment pf childhood epilepsy: A retrospective chart review of efficacy and safety profile. *Epilepsia*. 2008; 49(7):1186-1191.
7. Lux A, Edwards S, Hancock E, et al. United Kingdom Infantile Spasms Study (UKISS) comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomized controlled trial. *Lancet.* 2004; 364:1773-1778.
8. Rita Martins, Joana Jesus-Ribeiro, Guadalupe Fernandez-Baca Vaca, Krystal Tomei, **Jun T. Park.** "Resolution of Epileptic Spasms After Drainage of Chronic Subdural Hematoma Related to Non-accidental Traumatic Brain Injury". *Sinapse 2021 Jul;* 21(2):107-111. DOI: 10.46531/sinapse/CC/210026/2021. Journal of the Portuguese Neurological Society. ISSN: 1645-281X e ISSN: 2184-424. http://www.sinapse.pt/revista.