

Does Early Recognition of Treatment Failure and Changing Anti-Epilepsy Medication Regimen Improve Short-Term Seizure Remission Rates In Childhood Absence Epilepsy?

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Abstract

Purpose: To study the role of early serial EEGs in improving seizure freedom rates after initiation of ethosuximide or valproic acid for childhood absence epilepsy.

Methods: Retrospective data analysis study of AED naive patients with childhood absence epilepsy undergoing treatment at the community-based epilepsy clinic. Due to small sample size Fisher's exact test was used to determine two-tailed p value at < 0.05 statistical significance..

Results: At 2-month study period 71.4% patients in the ethosuximide and 87.5% in the valproic acid group achieved seizure freedom, with EEG normalization in 21.4% and 50% respectively. At 6-month study period, in patients continuing ethosuximide, seizure freedom and EEG normalization rates were 89.5% and 52.6% respectively; while in patients continuing valproic acid, results were 100% and 78.6% respectively. Both at 2-month and 6-month study periods, a trend towards higher seizure freedom was noted in patients with typical versus non-typical epileptiform discharges at baseline with the valproic acid group showing a superior response.

Conclusion: Although no statistically significant difference in response rates was noted, 1) a shift towards higher seizure freedom with valproic acid; 2) improved response after switching to valproic acid at 2 months, if warranted; and 3) superior response rate in patients with typical EEG epileptiform discharges at baseline were observed. A larger study is needed to define the role of early serial EEGs to delineate higher drug failure probability; and to determine the importance of non-typical EEG characteristics at baseline in relation to the choice of AED and long-term outcome.

Keywords: childhood absence epilepsy, ethosuximide, valproic acid, non-typical epileptiform discharges

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INTRODUCTION

Childhood absence epilepsy (CAE) is the most

common pediatric epilepsy syndrome⁽¹⁻³⁾ with onset in early to middle childhood and is characterized by brief staring spells which may be associated with eyelid

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myoclonia and/or perioral automatisms⁽⁴⁻⁸⁾. The typical pattern of EEG is bilateral, symmetrical and synchronous discharges of regular 3-4 Hz spike and slow wave (s/w) complexes with normal background activity^(7,9). Often misperceived as a benign epilepsy, CAE is associated with variable remission rates and affected children may have attention deficit, cognitive disability and long-term psychosocial difficulties⁽¹⁰⁻¹³⁾. Frequent seizures and epileptiform discharges which are associated with CAE may be contributing factors to these comorbidities.

CAE Cochrane review-2017 (originally published in 2003, and updated in 2005)⁽¹⁴⁾ identified no placebo controlled trials; 8 small trials which could not be used in meta-analysis due to differing methodologies used; and only 1 large randomized, parallel double-blind controlled trial comparing ethosuximide (ESM), lamotrigine (LTG) and valproic acid (VPA) in the initial treatment of CAE^(1,13) meeting International League Against Epilepsy (ILAE) Class I evidence criteria. This study established similar efficacy of ESM and VPA in the short term (16-20 weeks)⁽¹⁾ and medium term (12 months)⁽¹³⁾ management of CAE, while LTG was found to be not as efficacious as previously reported.

In community-based practice it is not uncommon to detect absence seizure after hyperventilation activation procedure or on EEG even though caregivers have not reported any clinical seizures. Therefore, at our center early serial EEGs are performed to help guide the treatment. Also, in clinical settings, treatment outcome may be different as initiation and maintenance of AED regimen, even though guided by clinical trials, is controlled not by a fixed study protocol but by a flexible treatment regimen decided by patients. Because of prolonged titration period required for its initiation to minimize serious side effects, as a routine LTG is used not as an initial monotherapy but as an add on therapy at our center.

We are reporting seizure freedom and EEG normalization rates in AED naive patients with CAE treated with ESM and VPA at 2-month and 6-month study periods.

METHODS

This was a Kaiser Permanente IRB approved

retrospective data analysis study of AED naive patients with CAE undergoing treatment at the community-based epilepsy clinic between 2008 and 2016. The epilepsy syndrome was classified according to the diagnostic criteria defined by the ILAE-1989 proposal for the revised classification of epilepsies and epileptic syndromes⁽⁹⁾. Children with history of any other type of nonfebrile seizures or any clinically significant psychiatric or behavioral conditions were not included in the study.

A total of 57 consecutive CAE patient charts were identified. An absence seizure was defined as a staring spell associated with generalized s/w or poly s/w activity at a frequency of 3-4 Hz lasting for > 3 seconds. Video EEG (vEEG) studies were of 5-hour sleep-deprived patients and were recorded for 1 hour which included periods of sleep, hyperventilation and intermittent photic stimulation. Seizure diary, and results of hyperventilation activation procedure and vEEG studies which were performed at the baseline, and at 2-month and 6-month study period after the baseline, were reviewed. The patients were treated with ESM or VPA depending on parents' choice after discussing the AED side effect profile with them. ESM was started as initial therapy in 28 (64%) and VPA in 16 (36%) patients. Starting dose of ESM was 15 mg/kg/day and for VPA was 20 mg/kg/day which was incrementally increased per clinical response (either seizure freedom attained or side effects limiting the dose given). The maximum permissible dose for ESM was 50 mg/kg/day (upper limit of 2000 mg per day) while maintaining therapeutic trough plasma levels between 50 and 100 µg/ml, and for VPA was 60 mg/kg/day (upper limit of 3000 mg per day) with therapeutic trough plasma levels between 50 and 150 µg/ml.

A total of 44 patients completed the 3 serial vEEGs within the specified time interval; at baseline, and at 2-month and 6-month (+ 1 week) study period. We collected and analyzed data on age, sex, birth history, family history, age at the onset of seizure, semiology of seizures, EEG characteristics, and response to AED regimen. EEG epileptiform discharges lasting > 3 seconds were considered electrographic seizures. Figure 1 & Figure 2 are examples of typical and non-typical epileptiform discharges respectively. Seizure freedom (both, clinical and electrographic) and persistence of any EEG epileptiform discharges were assessed at the 2 study periods. Failure to achieve seizure freedom, or side

Table 1. Patient demographic data and seizure characteristics

Sex	Male 16 patients Female 28 patients
Age at diagnosis	7.5 ± 2.4 years
Age at onset	6.8 ± 1.8 years
Seizure characteristics	
Stare	44 patients
Perioral automatism	32 patients
Eyelid myoclonia	24 patients
Patients with 3 characteristics	23 patients
Patients with 2 characteristics	10 patients
Stare with automatism	9 patients
Stare with eyelid myoclonia	1 patient
Patients with 1 characteristic (Stare)	11 patients

Table 2. Characteristics of EEG at baseline and treatment response at 2-month study period and at 6-month (unchanged AEDs) study period in ethosuximide and valproic acid groups

	Ethosuximide	Valproic acid
EEG characteristics at baseline		
S/W *	28	16
S/W* at rest, HV** and PS***	5	2
S/W* at rest and HV**	22	1
S/W* at rest or HV**	1	2
S/W* Single	14	10
S/W* Poly	14	6
Seizure freedom at 2-month study period	11(78.6%)	10(100%)
Single S/W	9(64.3%)	4(66.7%)
Poly S/W		
Combined AED single vs poly s/w $p=0.15$, not significant		
Seizure freedom at 6-month study period who continued AED unchanged		
Single S/W	10(90.9%)	10(100%)
Poly S/W	7(87.5%)	4(100%)
Combined AED single vs poly s/w $p=1$, not significant		
S/W* - spike and wave; HV** - hyperventilation; PS*** - photic stimulation		

or non-typical EEG discharges at 3-4 Hz in association with clinical absence seizures.

Patient study flow chart describes changes in EEG characteristics and AEDs used for all 44 patients during the study period.

Table 2 depicts the characteristics of EEG at baseline, and response to treatment at 2-month study period and at 6-month study period (for those who continued AED regimen unchanged at 2-month study period) between ESM group and VPA group, and Table 3 shows the rates of seizure control and EEG normalization for the same ESM and VPA groups.

At 2-month study period a total of 34 (77.3%) achieved seizure freedom. In the ESM group, no seizures were noted in 20 (71.4%) but EEG normalization was seen in only 6 (21.4%); while in the VPA group the corresponding numbers were 14 (87.5%) and 8 (50%) respectively. No statistically significant difference in seizure response rate was found between the two groups ($p=0.28$). In the subgroup of patients with typical EEG discharges at baseline, seizure freedom was reported in 21/24 (87.5%) at 2-month period, while in the subgroup with non-typical EEG discharges it was 13/20 (65.0%) which was not statistically significant ($p=0.15$). When

Table 3. Seizure control and EEG normalization rates for ethosuximide or valproic acid monotherapy at 2-month study period and in those who continued AED regimen unchanged at 6-month study period

EEG characteristics	2-month study period	6-month study period
Ethosuximide Group	28 patients	19 patients
S/W*	22 (78.6%)	9 (47.4%)
S/W with clinical seizure	8 (28.6%)	2 (10.5%)
S/W without clinical seizure	14 (50.0%)	7 (36.9%)
No S/W and no seizure	6 (21.4%)	10 (52.6%)
Valproic acid Group	16 patients	14 patients
S/W*	8 (50.0%)	3 (21.4%)
S/W with clinical seizure	2 (12.5%)	0 (0%)
S/W without clinical seizure	6 (37.5%)	3 (21.4%)
No S/W and no seizure	8 (50.0%)	11 (78.6%)
Ethosuximide vs Valproic acid group	$p=0.28$, not significant	$p=0.50$, not significant
S/W*- spike and wave		

Table 4. Seizure control and EEG normalization rates at 6-month study period after modification of ethosuximide and valproic acid treatments at 2-month study period

EEG characteristics	VPA switch*	ESM + VPA**	VPA + ESM***
	8 patients	1 patient	2 patients
S/W	2 (25.0%)	0	2 (100%)
S/W with clinical seizure	2 (25.0%)	0	2 (100%)
S/W with no clinical seizure	0	0	0
No S/W and no seizure	6 (75.0%)	1 (100%)	0
Modified AED ESM vs VPA group	$p=0.11$, not significant		

ESM = Ethosuximide; VPA = Valproic acid; * Ethosuximide failure, switched to valproic acid; ** Ethosuximide failure, added valproic acid; *** Valproic acid failure, added ethosuximide

analyzed by AED given, in the ESM group 11/14 (78.6%) with typical EEG discharges, and 9/14 (64.3%) with non-typical EEG discharges at baseline reported seizure freedom at 2 months, with same being 10/10 (100%) and 4/6 (66.0%) respectively in the VPA group.

After reviewing 2-month EEG results and AED tolerability with the parents, 19 patients in the ESM group and 14 patients in the VPA group continued their original AED regimen. At 6-month study period, out of 19 patients who continued ESM, 17 (89.5%) patients had no seizures with normalization of EEG noted in 10 (52.6%); while all 14 (100%) patients who continued VPA achieved seizure freedom with normalization of EEG seen in 11 (78.6%) patients. No statistically significant difference in seizure

response rate was found between the two groups ($p=0.50$). In the subgroup of patients with typical EEG discharges at baseline, seizure freedom was reported in 20/21 (95.2%), while in the subgroup with non-typical EEG discharges it was 11/12 (91.7%) which was not statistically significant ($p=1$).

In the ESM group at 2-month study period, AED regimen was modified in 9 patients; in 8 patients ESM was switched to VPA (in 6 patients no seizure control + no normalization of EEG, in 2 patients seizure control but no normalization of EEG), and VPA was added to ESM in 1 patient (seizure control but no normalization of EEG). Table 4 shows response rates at 6-month study period in these patients. In the group of patients in which

ESM was switched to VPA, seizure control was achieved in 4 out of 6 patients (66.7%). Also, in the same group, EEG normalization was achieved in 6 out of 8 patients (75%). In 1 patient with persistent EEG abnormality without seizures, addition of VPA achieved normalization of EEG. In the VPA group at 2-month study period, ESM was added to 2 patients, but neither seizure control nor normalization of EEG were attained in both patients at 6-month study period. Small number of patients in which AED regimen was modified at 2-month study period precluded statistical analysis.

Overall, out of 44 patients in this study, 38 patients (86.4%) were seizure free at 6-month study period.

DISCUSSION

Staring spells, perioral automatisms and eyelid myoclonia are the most common clinical characteristics of typical absence seizures. Eyelid myoclonia may or may not occur concurrently with staring spells. Automatisms were predominantly recorded during hyperventilation in our patients which also has been reported in a previous study⁽⁶⁾. Several previous reports also suggest that automatisms may occur in all children with absence seizures particularly during longer seizures^(6,7). In our study 72.7% (32/44) patients had perioral automatisms, and 54.6% (24/44) had eyelid myoclonia.

Although a few have difficulty in achieving seizure control, as about two-thirds of children with CAE achieve complete remission, it is generally considered a pharmacoresponsive epilepsy⁽¹⁵⁻¹⁸⁾. In our study, 77.3% were seizure free at 2-month study period, and 86.4% (including patients whose AED regimen was modified at 2 months) were seizure free at 6-month study period. In a recent RCT study, freedom from failure for combined (ESM + VPA) cohort at 16-20 weeks⁽¹⁾ was 55.3%, and at 12 months⁽¹³⁾ was 44.7%. Similarly, in a community-based study, combined (ESM + VPA) remission rate (achieving and being in ≥ 1 -year remission by 2 years after diagnosis) of 57.6% was reported⁽¹⁸⁾.

In our study a positive drift towards effectiveness of both ESM and VPA was observed as early as within a few weeks after starting AED regimen. At 2-month study period, in the ESM group, no seizures were noted in 71.4%; while in the VPA group it was 87.5%. Also, at

6-month study period, out of 19 patients who continued ESM 89.5% patients had no seizures; while in the 14 patients who continued VPA 100% patients were seizure free. No statistically significant difference was observed in response rate between the ESM and VPA groups, both at 2-month and 6-month study period ($p=0.28$ and $p=0.50$ respectively). Similar equivalent efficacy of ESM and VPA in the management of CAE was reported in a recent NIH funded RCT for CAE treatment with ESM, LTG and VPA, where short term (16-20 weeks) and medium term (12 months) freedom-from-failure rates for ESM (53% and 45% respectively) versus VPA (58% and 44% respectively) were noted^(1,13). Also by 12 months after starting therapy, only 37% of all enrolled subjects were free-from-treatment-failure on their first medication. Almost two thirds of their subjects with treatment failure due to lack of seizure control at 12 months were in the LTG group, while the largest subgroup (42%) of the subjects discontinuing due to adverse events was in the VPA group (increased BMI after 6 months being the most frequent cause)⁽¹³⁾. In a community-based study, comparable efficacy of ESM (59%) and VPA (56%) for remission (achieving and being in > 1 -year remission by 2 years after diagnosis) was observed⁽¹⁸⁾.

In RCTs the choice and titration of AED regimen is per study protocol. However, in community practice decision regarding choice of AED is of the patients which is guided, but not controlled, by the treating physician, and AED titration is more flexible, both of which may alter the response rate. Also, in our study, ability to modify AED regimen due to failure to achieve seizure freedom at 2-month study period may have had a positive impact on the outcome at the 6-month study period when compared to the above studies.

Effect of genetic polymorphism is hypothesized to be exerting influence on effectiveness of AEDs in the treatment of CAE^(19,20) which may account for the variability in the outcome amongst CAE studies^(1,13,18,21,22).

Absence seizure is generated as a result of disruptions in thalamocortical pathways specifically involving T-type calcium channels which are coded by CACNA1G, CACNA1H, and CACNA1I⁽²³⁻²⁵⁾. Antiepileptic medications effective against CAE including ESM and VPA have been proposed to exert their effect at these channels^(24,26). In addition, action of P-glycoprotein (coded for by the

ABCB1 transporter gene), a drug efflux transporter located in the intestine and at the membrane of brain capillary endothelial cells, also may affect the response of AED20. A recent study on pharmacogenetics of AED efficacy in CAE showed that 4 common T-type calcium channel variants and 1 common ABCB1 transporter variant were associated with differential drug response of ESM, LTG and VPA, and suggested that this genetic profiling may also impact drug responsiveness in CAE⁽¹⁹⁾.

Non-typical EEG features have been proposed to be prognostic of poorer outcome in children with CAE⁽²⁷⁻²⁹⁾. A recent community based study⁽¹⁸⁾ reported that children with versus without non-typical EEG features were less likely to enter complete remission (50% vs. 71%, $p=0.03$). In that study first medication was ESM in 41 (69%) and VPA in 18 (31%), and non-typical EEG features at baseline were present in 17% in ESM group versus 61% in VPA group. In our study 14/28 (50%) patients in the ESM group and 6/14 (43%) patients in the VPA group had non-typical EEG features at baseline, and seizure freedom at 2-month study period in the ESM subgroup with typical EEG was 78.6%, and with non-typical EEG was 64.3%; with the same being 100% and 66.0% respectively in the VPA group. When combined (ESM + VPA), for the subgroup of patients with typical EEG activity at baseline, seizure freedom at 2-month study period was 87.5%, while for the non-typical EEG subgroup it was 65.0% ($p=0.15$), and the same being 95.2% and 91.7% respectively at 6-month study period.

CONCLUSIONS

- 1) The main limitation of our single-center retrospective data analysis study is a small sample size.
- 2) Although no statistically significant difference in the effectiveness of ESM and VPA in AED naive patients with CAE at 2-month and 6-month study periods was noted, our study did demonstrate trend towards (i) improved response after switching AED at 2 months, (ii) better response rate with VPA, and (iii) superior response in patients with typical EEG discharges at baseline.
- 3) A larger long-term CAE study is needed to (i) define role of serial EEGs in determining the impact on the outcome of switching AED at short term (2-3 months),

(ii) delineate drug resistance if continued seizure activity is noted at 6 months; and (iii) determine the significance of non-typical EEG characteristics at baseline, in relation to choice of AED and long-term outcome.

Conflict of Interests: The authors declare no conflict of interests.

This study was approved by Kaiser SCPMG Institutional Review Board.

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