Childhood Absence Epilepsy – A Review of Treatment Strategies and Perspectives for the Future

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Abstract

Childhood absence epilepsy (CAE) is one of the most common forms of paediatric epilepsy. However, there is still a gap between the prevalence of CAE in paediatric epilepsies and the paucity of available data regarding its therapeutic management. Only nine randomised controlled trials have been published in the field over the past four decades, with many suffering from major methodological limitations. A recent large randomised double-blind controlled trial reported that ethosuximide and sodium valproate are the most effective anti-epileptic dugs in CAE and that cognitive performance appears to be better with ethosuximide than with sodium valproate. Although lamotrigine also demonstrated anti-absence properties in the same trial, it proved to be significantly less efficacious than ethosuximide or sodium valproate. Despite these recent advances, several questions, including long-term outcomes, management of refractory CAE and treatment duration, remain unanswered and further studies are required to refine therapeutic decisions.

Keywords

Childhood absence epilepsy, anti-epileptic drug

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Childhood absence epilepsy (CAE) is one of the most common forms of paediatric epilepsy, accounting for between 10 and 17 % of all cases of childhood onset epilepsies.[1] CAE is defined by age-related onset, clinical and electrographical characteristics, and a presumed genetic aetiology.[2] The syndrome typically begins at between four and eight years of age in an otherwise healthy child. Typical absence seizures are characterised by brief loss of awareness associated with bilateral, synchronous symmetrical 3 Hz spike-waves on a normal background of electroencephalographic (EEG) activity.[2] Although CAE is usually considered to be a benign form of epilepsy, the remission rate varies across studies from 21 to 95 %.[3,4] About 15 % of patients could progress to juvenile myoclonic epilepsy, favoured by risk factors such as absence status before or during anti-epileptic drug (AED) treatment, development of tonic-clonic or myoclonic seizures after onset of treatment, or abnormal background on initial EEG.[5] In addition, it has been shown that affected children, including those who are seizure free, can develop both psychosocial and educational difficulties.[6] Neuropsychological deficits include lower scores at measures of general cognitive functioning and memory performances, with selective involvement of nonverbal memory and delayed recall.[7] These difficulties could reflect the impact of either seizures or of a neurodevelopmental susceptibility, AEDs or a mixture of these factors. In this context, therapeutic decisions should balance the anti-epileptic efficacy and tolerability of AEDs, with a specific attention to their impact on cognition.

What do Anti-epileptic Drug Trials Show?

Despite the increasing number of AEDs that have been licensed for the treatment of seizure disorders over the past 20 years, only a few have been evaluated in the treatment of CAE. Consequently, valproic acid (VPA) and ethosuximide (ESM) have been used as first-line agents for the treatment of absence seizures for over 40 years.[8] Over these four decades, only nine randomised controlled trials (RCTs) have been published in the field,[9–17] with many suffering from major methodological limitations. RCTs are separated into four classes according to the rating scale of their level-of-evidence,[18] the highest being class I. To be classified as class I or II, monotherapy AED trials should fulfil:

- a double-blind randomised controlled design;
- efficacy as primary outcome;
- a treatment duration ≥24 weeks;
- a sufficient sample size to show non-inferiority of no worse than a 20 % relative difference in efficacy;
- study exit not forced by a predetermined number of treatment-emergent seizures; and
- an appropriate statistical analysis.

Based of this rating scale, the level of evidence for each AED can be determined; with the highest value (level A and B) implying that at least one class I and/or II study is available. Furthermore, quality assessment of RCTs in CAE should also consider the clinical relevance of the primary efficacy endpoint. Indeed, patients with CAE can

demonstrate both electro-clinical absence seizures and isolated generalised spike and wave bursts on EEG without clinically detectable absences. Importantly, cognition might be impaired during so-called infra-clinical absences and clinicians often face the issue as to whether they should revise treatment when such EEG discharges persist while clinically detectable absences are fully controlled. In this context, RCTs should assess the disappearance of both spontaneous and hyperventilation-triggered EEG discharges.

Most of the studies that evaluated AEDs in CAE did not fulfil the quality criteria required to be classified as a class I or II study. Indeed, until 2010, all available RCTs were classified as class III studies according either to open-label design (n=4) or to inadequate treatment duration despite double-blind design (n=4).

Among the four open-label studies, two of the studies compared VPA and ESM[10,15] and the other two studies compared VPA and LTG[9,11] (see *Table 1*). Patients were between four and fifteen years old. Sample sizes were limited, comprising between 20 and 38 patients and the duration of the follow-up ranged from 12 months to four years. No difference was observed between VPA and ESM: the seizure-free rate ranged from 40.0 to 70.0 % with VPA compared with 57.1 to 80.0 % with ESM. Similarly, the two studies that compared VPA and LTG showed similar seizure-free rates with either drug. At the one-year follow-up, between 52.6 and 66.6 % of patients were controlled by LTG compared with between 68.4 and 80.0 % with VPA. However, these two latter studies also suggested that VPA efficacy was faster than that of LTG. Indeed, at one month, 52.6 to 60.0 % of patients treated with VPA were seizure free compared with 0.0 to 5.3 % of patients treated with LTG; whereas at three months, seizure freedom was observed in 63.1 to 73.3 % of patients taking VPA versus 36.8 to 53.3 % taking LTG. Even at one year, the non-significant differences observed between drugs exceeded a relative difference of 20 %, suggesting that an adequate sample size would have resulted in showing statistically and clinically relevant superiority of VPA over LTG.

Among the four short-term double-blind controlled studies, one study compared VPA and ESM[16] and the other three studies were placebo-controlled trials that compared either gabapentin (GBP),[17] LTG[13] or levetiracetam (LEV)[12] with placebo (see *Table 2*).

Sato and colleagues compared VPA and ESM in a randomised double-blind response-conditional crossover study.[16] Sixteen naïve and 29 drug-resistant patients aged three to 18 years with absence seizures were included. They received either VPA with placebo for six weeks followed by ESM with placebo for six weeks or the same regimen in the reverse order. However, patients who were responders during the first treatment period were not crossed over to the alternative treatment. At the end of the first period of the crossover, there was a trend toward a non-significant higher seizure-free rate with VPA (40.9 %) than with ESM (34.8 %). However, when both treatment periods were included in the analysis, the probability of response to VPA was 37.3 ± 3.5 versus 38.3 ± 3.4 % to ESM.

Frank and colleagues compared LTG with placebo in a randomised double-blind response-conditional study.[13] Forty-five patients aged two to 16 years with newly diagnosed CAE entered an open-label dose escalation of LTG. LTG was slowly titrated in accordance with the clinical response of the patient until either the patient achieved seizure freedom or the maximal dose of 15 mg/kg/day had been reached. Patients who became seizure free could enter the four-week

Table 1: Open-label Studies

Study	Anti-epileptic Drugs		Number of Patients		Patient Characteristics as Defined by Inclusion Criteria		Trial Characteristics		Seizure-free Rate (%)	
	Group 1	Group 2	Group 1	Group 2	Epileptic Syndrome	Age (Years)	Trial Duration (Months)	Primary Outcome	Group 1	Group 2
Callaghan et al., 1982[10]	ESM	VPA	14	15	Drug-naïve CAE	4–15	18–48	Complete or partial (50 to 90 %) remission of seizures confirmed by 6 hours telemetry and observation by parents and teachers	57.1	40.0
Martinovic, 1983[15]	ESM	VPA	10	10	Drug-naïve 'simple absences'	5–8	12–24	Number of seizures per day as observed by parents	80.0	70.0
Coppola et al., 2004[11]	VPA	LTG	19	19	Drug-naïve CAE and JAE	3–13	12	Lack of clinically observed seizures since the previous visit and lack of electroclinical seizures during ambulatory 24-hour EEG testing and a video-EEG session with hyperventilation	68.4	52.6
Basu et al., 2005[9]	VPA	LTG	15	15	Drug-naïve CAE and JAE	5–14	12	No clinical and EEG evidence of seizure	80.0	66.6

CAE = childhood absence epilepsy; EEG = electroencephalographic; ESM = ethosuximide; JAE = juvenile absence epilepsy; LTG = lamotrigine; VPA = sodium valproate.

Table 2: Short-term Double-blind Controlled Studies

Study	Anti-epileptic Drugs		Number of Patients		Patient Characteristics as Defined by Inclusion Criteria		Trial Characteristics			Seizure-free Rate (%)	
	Group 1	Group 2	Group 1	Group 2	Epileptic Syndrome	Age (Years)	Study Design	Trial Duration (Weeks)	Primary Outcome	Group 1	Group 2
Sato et al., 1982[16]	ESM	VPA	23	22	Drug-naïve and drug-resistant absence seizures	3–18	Response-conditional cross-over study	12	Reduction in seizure frequency as judged by 12 hour EEG telemetry	34.8*	40.1*
Trudeau et al., 1996[17]	GBP	PCB	15	18	Newly diagnosed CAE	4–16	Parallel group	2	Reduction in seizure frequency as judged by 24 hour EEG telemetry	6.7	22.2
Frank et al., 1999[13]	LTG	PCB	15	14	Newly diagnosed typical absence seizures	3–15	'Responder-enriched' study design	4	Complete seizure freedom as assessed by conventional hyperventilation testing with EEG recording	62.0	21.0
Fattore et al., 2011[12]	LEV	PCB	38	21	Newly diagnosed CAE and JAE	4–16	Parallel group	2	Freedom from clinical seizures on days 13 and 14 and from EEG seizures during a standard EEG recording with hyperventilation and intermittent photic stimulation on day 14	23.7	4.8

** Seizure-free rate at the end of the first period of the crossover. CAE = childhood absence epilepsy; EEG = electroencephalographic; ESM = ethosuximide; GBP = gabapentin; JAE = juvenile absence epilepsy; LEV = levetiracetam; LTG = lamotrigine; PCB = placebo; VPA = sodium valproate.*

double-blind period and were randomly allocated either to LTG maintenance or to placebo. Twenty-nine patients were randomised. Sixty-two per cent of patients who received LTG remained seizure free in comparison with 21 % with placebo (p<0.02).

GBP was compared with placebo during a two-week double-blind trial in newly diagnosed CAE.17 Eighteen patients were randomly allocated to placebo and 15 to GBP. At the end of the double-blind period, four patients were responders in the placebo group compared with only one in the GBP group (p=0.344, Fisher's exact test).

LEV was evaluated in a two-week placebo-controlled trial in children and adolescents with newly diagnosed absence seizures.[12] The patients were randomised and received either LEV of up to 30 mg/kg/day (38 patients) or placebo (21 patients). Ninety-two per cent of randomised patients suffered from CAE and 8 % from juvenile absence epilepsy. After a follow-up of two weeks, nine of the patients treated with LEV (23.7 %) and one with placebo (4.8 %) were responders (p=0.08). During long-term open-label follow-up, 17 patients were seizure-free with LEV treatment after one year follow-up whereas 34 became seizure-free with another AED (27 children with VPA, six children with ESM and one child with a combination of both).

Overall, the informative value of these open-label studies and short-term double-blind RCTs remained limited. Indeed, their main conclusions were that VPA, ESM and LTG were efficacious in CAE whereas GBP and LEV did not prove more efficacious than placebo. However, whether one of the first three should be preferred as first-line therapy remained an open question because none of the studies was powered enough to formally investigate the relative efficacy of one drug (VPA, ESM or LTG) over the others. Indeed, a meta-analysis of studies comparing ESM and VPA remained inconclusive.[19] Similarly, the treatment guidelines edited by the International League against Epilepsy in 2006 concluded that "VPA, ESM and lamotrigine (LTG) may be considered as candidates for initial monotherapy in CAE", without hierarchy between these three drugs.[18] Importantly, beyond the issue of anti-epileptic efficacy, these studies also poorly addressed the effectiveness of AEDs, which combine both long-term efficacy and tolerability. Indeed, safety issues and specifically cognitive outcomes, were not adequately addressed.

In this context, the National Institutes of Health-funded study published in the *New England Journal of Medicine* in 2010 by Glauser and colleagues is momentous[14] (see *Table 3*). Indeed, this large multicentre double-blind RCT, which compared ESM, VPA and LTG in children with newly diagnosed CAE, addressed most of the limitations of previous studies:

- it enrolled a large population, homogeneous in age distribution, seizure type and EEG criteria;
- the dose regimen was flexible, adapted to clinical and EEG responses; and
- a clinically relevant primary endpoint was used, defined by the proportion of patients who remained on treatment and were free from both clinical and EEG seizures at the final assessment.

Four-hundred and fifty-three children were randomised with a median age of seven years five months: 156 were assigned to ESM, 149 to LTG and 148 to VPA. Dosage was increased every one to two weeks over a

Table 3: Characteristics and Results of the Randomised Controlled Trial Reported by Glauser et al., 2010[14]

	Number of Patients	Freedom from Treatment Failure (%)	Lack of Seizure Control (%)	Intolerable Adverse Events (%)	Cognitive Outcomes		
					Baseline IQ	Attentional Difficulties (Defined as a CPT Index >0.60) (%)	
						Baseline	Last Follow-up
ESM	156	53	14	24	93.1 ± 16.1	34	33
VPA	148	58	12	24	93.1 ± 14.3	42	49
LTG	149	29	47	17	95.6 ± 14.5	30	24
ESM versus VPA (p value)	–	ns	ns	ns	ns	ns	0.03
ESM versus LTG (p value)	–	<0.001	<0.001	ns	ns	ns	ns
VPA versus LTG (p value)	–	<0.001	<0.001	ns	ns	ns	<0.001

CPT = Conners' continuous performance test; ESM = ethosuximide; IQ = intelligence quotient; LTG = lamotrigine; ns = non-significant p-value; VPA = sodium valproate.

16-week period until the patients were seizure free or demonstrated treatment side effects. At each study visit, efficacy evaluation used a standardised protocol: if the parents did not report any clinical seizure, up to two five-minute trials of bedside hyperventilation were performed, eventually completed by a one-hour video-EEG monitoring if no seizure was observed. The children were considered free from seizures only if no spike-wave burst lasting three or more seconds was detected on the EEG. The highest allowable daily doses were 60 mg/kg for ESM, 60 mg/kg for VPA and 12 mg/kg for LTG. Overall, 209 children (47 %) achieved the primary outcome at week 16 or week 20. Treatment failures were related to lack of seizure control in 109 patients (24 %) and intolerable side effects in 97 (22 %). The freedom-from-failure rate was similar in ESM and VPA groups (53 and 58 %, respectively). By contrast, LTG effectiveness was significantly lower with a freedom-from-failure rate at 29 %. The odds ratio with ESM versus LTG was 2.66 (95 % confidence interval [CI], 1.65–4.28) and 3.34 (95 % CI, 2.06–5.42) with VPA versus LTG. The secondary endpoint was attentional dysfunction. Attention was evaluated with the Conners' Continuous Performance Test (CPT) before randomisation and at the end of the treatment period. Although ESM and VPA did not differ for the primary outcome, the children on VPA demonstrated greater incidence of neuropsychological impairment. Thus, 49 % of patients on VPA had attentional difficulties, defined as a CPT index >0.60, in comparison with 33 % in the ESM group (odds ratio, 1.95 [95 % 1.12–3.41], p=0.03) and with 24 % in the LTG group (odds ratio, 3.04 [95 % CI 1.69–5.49], p<0.001). However, in this study, VPA wastitrated up to 60 mg/kg/day whereas in several European countries, the highest recommended dose of VPA is 30 mg/kg/day. Therefore, the question arises as to whether or not a lower ceiling dose might have improved tolerability without comprising efficacy. Moreover, attentional difficulties (defined as a CPT index >0.60) occurred at baseline with a higher frequency in the VPA cohort (42 %) than in the ESM (34 %) or LTG (30 %) cohorts. In addition, although the impact of VPA on the CPT remained statistically significant after adjusting for baseline differences, its effect size proved to be limited (an increase in the rate of attentional dysfunction from 42 to 49 %) and of uncertain clinical significance.

What Could be Recommended in Daily Practice and What Information is Missing?

As detailed above, some evidence is available to guide first-line therapy in newly diagnosed CAE:

- ESM and VPA are the most effective AEDs in this clinical setting;
- cognitive performances might be better with ESM than with VPA, justifying the use of the former as first-line therapy;
- although LTG has anti-absence properties, it proved to be less efficacious than both ESM and VPA in CAE; and
- no other AED has demonstrated efficacy in CAE, including GBP, which was found to be inefficacious.

Moreover, AEDs known to potentially aggravate other idiopathic generalised epilepsy syndrome, such as carbamazepine, oxcarbazepine or phenytoine,[20] should be avoided. However, several questions remain unanswered and future studies are required to refine therapeutic decisions.

One of the main issues is the long-term outcome. Indeed, the longest follow-up in studies with robust methodology was 20 weeks,[14] whereas RCTs with longer follow-up have used open-label designs or small sample sizes.[9–11,15] This limitation underlies several questions. About 15 % of children with CAE will progress to juvenile myoclonic epilepsy and/or suffer generalised tonic-clonic seizures at adolescence.[5] ESM has been shown to be inefficacious to suppress generalised tonic-clonic seizures.[21] In this context, the comparative incidence of generalised tonic-clonic seizures between ESM andVPA cohorts will be of particular interest. Similarly, although several RCTs, including the Glauser study,[14] enrolled patients with juvenile absence epilepsy, the preference of ESM over VPA in this specific syndrome should be questioned by the frequent co-existence of generalised tonic-clonic seizures. Another issue is related to chronic side effects. Specifically, long-term cognitive and educational outcomes are required. Similarly, several psychiatric co-morbid disorders have been reported in CAE.[22] In this context, potential positive or negative impacts of AEDs on psychological status might be important to consider for treatment selection and should be monitored during follow-up. In addition, whether some major chronic effects of VPA, such as weight gain, might emerge as troublesome during long-term follow-up, remains to be investigated. Similarly, for the small percentage of females who will need to continue treatment during adolescence and adulthood to ensure seizure freedom, optimisation of therapy should also take into consideration the available information about the comparative effects of individual drugs on foetal and post-natal development.

In most studies, the responder rates varied between 40 and 60 %, highlighting the fact that a significant proportion of patients will require second-line monotherapy and eventually polytherapy. Evidence-based data about the management of refractory CAE are lacking.[23] According to the similar efficacy of ESM and VPA in newly diagnosed CAE, switching from one to the other in case of treatment failure seems to be the most reasonable choice. When patients fail to respond to both ESM and VPA, the probability of achieving seizure freedom with LTG monotherapy is likely to be low. In this context, the combination of AEDs might be proposed, with particular interest in the association of VPA/LTG, which showed some evidence of a positive pharmacodynamic interaction.[24] Despite the paucity of data, LEV[25] and zonisamide[26] have also been proposed in the treatment of refractory absence seizures. A ketogenic diet[27] and vagal nerve stimulation[28] might be discussed as alternative non-pharmacological therapies.

Whatever the therapeutic choice, one of the main remaining grey areas in the management of CAE is the issue of treatment duration. About 12 to 19 % of children with CAE suffer from seizure recurrence after the withdrawal of AEDs.[29,30] As for other epileptic syndromes,[31] a delay of two years seizure freedom is usually retained before starting to taper AEDs. This general recommendation might be modulated by the specific characteristics of the epileptic syndrome, such as the presumptive link between the dynamic of CAE and that of brain development, as well as by the presence of individual risk factors, including absence status before or during AED treatment, development of tonic-clonic or myoclonic seizures after onset of treatment and abnormal background on initial EEG.[5] However, we still lack precise and robust data to guide us on the optimal treatment duration in patients with CAE.

Conclusion

Despite the major impact of the recent study reported by Glauser and colleagues,[14] there is still a gap between the prevalence of CAE in paediatric epilepsies and the paucity of available data on its therapeutic management. Beyond the recommendation of preferring ESM as a first-line therapy in newly diagnosed CAE, most of the other issues still require further investigation. ■

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