Original Article

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Early-onset childhood absence epilepsy: is it a distinct entity?

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ABSTRACT – Childhood absence epilepsy (CAE) typically starts between four and seven years of age. Onset before three years is rare and has not been previously reported from North America. We retrospectively reviewed the electroencephalography laboratory database and paediatric neurology clinic records (from January 2000 to June 2009) at our institution in order to identify patients with absence seizures beginning before age three. Information was collected for age, gender, neurodevelopment, antiepileptic drugs (AEDs) used, seizure control, follow-up, and side effects. Of 12 patients identified, mean age at onset was 20.5 months (range: 11 months to two years; follow-up: six months to 11 years). Seven of 12 patients had normal neurodevelopment and five had speech delay. Four patients were seizure-free without AEDs, three were seizure-free with a single AED, and five still had seizures with multiple AEDs. Three patients had recurrences after medication withdrawal. Other previously published series have identified better seizure control than that reported here, however, 16% of the 130 patients so far documented are reported to have poorly controlled epilepsy, indicating that early-onset CAE is not a homogeneous condition. The debate as to whether early-onset CAE is a distinct epilepsy syndrome therefore continues. We believe that early-onset CAE may be a distinct epilepsy syndrome, with some features that overlap with those of typical CAE, as well as unique distinguishing features. Large prospective multicentric studies would be necessary to definitely resolve this matter.

Key words: absence seizures, early onset, childhood absence epilepsy

Childhood absence epilepsy (CAE) is an age-specific epilepsy syndrome classified as one of the idiopathic generalised epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). It is defined by episodes of unresponsiveness associated with bilaterally synchronous spike-and-wave discharges at 3 Hz with a normal background on EEG. CAE typically

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starts at four to seven years of age with a peak at around six or seven years, whereas juvenile absence epilepsy (JAE) presents at 11 to 12 years. The onset of absence epilepsy before the age of three years is rare and has not been previously reported in North America. Optimal treatment with antiepileptic drugs (AEDs) for this age group is also not known. Studies from Europe and South America have evaluated the significance of early-onset absence epilepsy, however, most of the data are contradictory (Cavazzuti *et al*., 1989; Aicardi, 1995; Darra *et al*., 1996; Covanis, 1998; Chaix *et al*., 2003; Fernandez-Torre *et al*., 2006; Shahar *et al*., 2007; Verrotti *et al*., 2011b; Caraballo *et al*., 2011; Giordano *et al*., 2011). The aim of this study was to assess the clinical relevance of early-onset absence epilepsy and to characterise seizure frequency, control, and prognosis in a cohort of patients with this condition.

Materials and methods

Approval was obtained from the Institutional Review Board of Drexel University College of Medicine, St. Christopher's Hospital for Children. A retrospective chart review was performed of the EEG database at St. Christopher's Hospital for Children, from January 2000 to June 2009, to identify patients with pure absence epilepsy that began before the age of three years. Absence seizures were defined as paroxysmal episodes of staring, unresponsiveness, or motor arrest with a concomitant electrographic 3-Hz spike-and-wave discharge on a normal EEG background. All EEGs were read and interpreted by an epileptologist. Clinical data of the patients identified were then reviewed and collected from the neurology clinic medical records. Data gathered included demographic variables such as age, gender, age at onset, diagnosis, and duration of follow-up. Information on seizure control, AEDs taken, response to treatment, side effects, and the presence or absence of developmental problems was also gathered for all the patients identified. Exclusion criteria included presence of other seizure types such as concomitant eyelid myoclonia, myoclonus, or generalised tonic-clonic seizures at initial presentation and during follow-up. This approach allowed us to identify patients with only pure absence epilepsy.

Results

Patient demographics, AEDs previously and currently taken, side effects, co-morbidities, and EEG findings are summarised in *table 1*.

Demographics

Twelve patients were identified with absence seizures beginning earlier than three years of age, including seven boys and five girls. The mean patient age at seizure onset was 20.5 months (range: 11 months to two years) with mean age at diagnosis of 3.1 years (range: 16 months to seven years). Follow-up ranged from six months to 11 years (mean: 4.8 years).

Clinical and EEG findings

All patients came to clinical attention because of episodes of staring and unresponsiveness and an initial EEG showing a 3-Hz spike-and-wave discharge lasting from 3 to 22 seconds with no asymmetry or focal abnormalities. Sleep was recorded during initial EEG for three of 12 patients, for the other children sleep was captured on subsequent routine or 24-hour ambulatory EEGs. Background activity was normal for age as part of the inclusion criteria. Five patients had a photoparoxysmal response and three showed occipital intermittent rhythmic delta activity on EEG. Neurodevelopment, as assessed by the Denver Development Screening test, was normal in seven patients (58%) and five patients (42%) had language delay, of whom four had mild speech delay and one had a moderate-to-severe language delay. Two children had a history of febrile seizures and one child's mother had a history of absence epilepsy.

Antiepileptic drugs taken

Initial monotherapy included ethosuximide for nine children, valproate for one, topiramate for one, and levetiracetam for another. The second AED used was valproate for six children, ethosuximide for two, and levetiracetam for one. In all, ethosuximide was used for 11 patients, valproate for seven, levetiracetam for four, and lamotrigine and topiramate each for one patient. Ethosuximide is typically the first AED used for uncomplicated childhood absence epilepsy in North America.

Clinical course and response to AEDs

Seven of 12 patients (58%) were seizure-free. Four of these seven were no longer taking medication having completed a seizure-free period of greater than two years and remained seizure-free, although one child continued to show a photoparoxysmal response on EEG but did not have recurrence of any epileptic seizures for 18 months following AED taper. The remaining three children were seizure-free with a single AED (two are currently taking valproate and one

Table 1. Patient demographics, AEDs and side effects, co-morbidities, and EEG findings.

Age at onset/ Age at diagnosis	First AED	Second AED	Current AED regimen	Seizure control	Recurrence	Normalised EEG on Rx	Neuro-development	Co-morbidity	Side effects	Duration of therapy/ Duration of follow-up
11 m/2 y	ETX		ETX	No	N/A	No	Language delay	ADHD	None	Ongoing/2.3 y
1 y/18 m	ETX	VPA	VPA	Yes	N/A	No	Normal	None	Rash (ETX)	Ongoing/3 y
16 m/16 m	TPM	ETX	None	Yes	No	Yes	Language delay	Premature	Mood (TPM)	2 y/3 y
16 m/19 m	ETX	VPA	None	Yes	Yes (VPA tapered off)	No	Language delay	ADHD	None	8 y/9 y
1.5 y/2.5 y	VPA		VPA	Yes	Yes	No	Normal	ADHD	None	Ongoing/6 y
2 y/7 y	ETX	LEV	LEV, ETX	No	N/A	No	Language delay	Febrile seizures	None	Ongoing/5 y
2 y/6 y	ETX	VPA	LEV, LTG	No	N/A	No	Normal	None	None	Ongoing/11 y
2 y/5 y	ETX	VPA (seizure free but SE)	LEV	Yes	No	No	Normal	None	None	Ongoing/3.5 y
2.5 y/3 y	ETX		None	Yes	Yes twice	Photo-paroxysmal response	Normal	Febrile seizures	None	6 y/7 y
2 y/2 y	ETX	VPA	None	Yes	No	Yes	Normal	None	None	3.5 y/4 y
2 y/4 y	ETX	VPA	VPA	No	N/A	No	Language delay	Autism	Rash (ETX)	Ongoing/2 y
2 y/2 y	LEV	ETX	None	No	N/A	No	Normal	None	None	4 m/parents stopped ETX

ETX: ethosuximide; VPA: valproate; LEV: levetiracetam; LTG: lamotrigine; TPM: topiramate; ADHD: attention deficit hyperactivity disorder; y: years; m: months; N/A: not applicable; SE: side effects.

levetiracetam) but all continued to show brief paroxysms of irregular generalised 3-Hz spike-and-wave discharges on EEG. Interestingly, one of these children had an allergic reaction to ethosuximide as initial AED at age 19 months. The parents elected not to treat the seizures, however, a year and a half later, because of an increase in frequency and duration of absences, valproate treatment was initiated and she has been seizure-free since. Three patients had seizure recurrence within three to four months after completing a two-year seizure-free period with a single AED. One of the three patients had two failed attempts to wean off ethosuximide after two years of seizure freedom but a third medication taper was successful and she has remained seizure-free for 18 months since. For the second patient, ethosuximide was successfully tapered and the third child remains on valproate treatment.

The remaining five patients (42%) continued to show clinical and/or electroencephalographic absence seizures; two on monotherapy with ethosuximide or valproate, one on a combination of ethosuximide and levetiracetam, and another on a combination of levetiracetam and lamotrigine. The fifth patient is currently on no medication although she was briefly taking levetiracetam with no response and ethosuximide with a good response, but the parents decided not to continue treatment and she still has seizures.

None of the twelve patients developed any other seizure types during follow-up.

Discussion

We report the first series from North America on the outcomes of children presenting with pure CAE before the age of three years. Several studies have been performed in Europe and South America attempting to classify early-onset absence seizures and determine whether they represent a distinct entity from traditional CAE and JAE. The results are variable and the outcomes are summarised in *table 2* (Cavazzuti *et al*., 1989; Aicardi, 1995; Darra *et al*., 1996; Covanis, 1998; Chaix *et al*., 2003; Fernandez-Torre *et al*., 2006; Shahar *et al*., 2007; Caraballo *et al*., 2011; Verrotti *et al*., 2011b; Giordano *et al*., 2011).

In the last year alone, there have been three large series of patients with "pure" early-onset CAE; two multicentre studies from Italy each with 40 and 33 children (Verrotti *et al*., 2011b; Giordano *et al*., 2011) and one from South America with 11 children (Caraballo *et al*., 2011). Our patient population is similar in that these were children who had only absence seizures, did not develop any other seizure type during follow-up, and had normal EEG background features. However, 9/11 (82%) patients in Caraballo's series, 33/40 (82%) in Verrotti's cohort and 28/33 (85%) patients in Giordano's paper were described as seizure-free compared to only 58% in our group of children. One reason for this discrepancy could be that both EEG and clinical status were used in our study to determine seizure freedom, *i.e*. seizures were classified as ongoing seizures if they were captured on EEG. The discrepancy could also be due to the relatively low use of valproate and high use of ethosuximide as first line AED in our population. In North America, there is some hesitation on the part of both physicians and patients to use valproate in young children because of the risk of hepatotoxicity. However, the success rate of valproate and ethosuximide for the treatment of CAE in North America is similar, ranging from 49% (Sato *et al*., 1982) to 53%-58% (Glauser *et al*., 2010). Therefore, a lower level of valproate treatment in our group can not be the only explanation for the difference reported by Caraballo *et al*. (2011), Giordano *et al*. (2011) and Verrotti *et al*. (2011b). Finally, it is possible that there is geographically-determined heterogeneity in the therapeutic response of CAE to valproate treatment, with a response of 89% in Europe (Mazurkiewicz-Beldzinska *et al*., 2010) and 74% in China (Huang *et al*., 2009), whereas in North America the response has consistently been less than 60% (Sato *et al*., 1982; Glauser *et al*., 2010).

Some rare conditions such as paroxysmal dyskinesia and glucose transporter (Glut-1) deficiency syndrome have been shown to be associated with early-onset absence seizures (Guerrini *et al*., 2002; Hirsch, 2004). We did not evaluate our patients for Glut-1 deficiency as the constellation of typical clinical features associated with Glut-1 deficiency, including developmental delay, ataxia, hypotonia, and infantile seizures, was not present in any of our patients.

Clinicians should be aware that absence epilepsy can occur in children below the age of three years. Including the present series, approximately 130 patients with this type of epilepsy have been reported in the literature, indicating the relative rarity of this epileptic disorder. Early-onset absence epilepsy is thought to represent less than 1% of epilepsies with onset at less than three years (Chaix *et al*., 2003; Caraballo *et al*., 2011).

While the majority of patients had good seizure control with conventional AEDs, 21 had poorly controlled disease (Chaix *et al*., 2003; Verrotti *et al*., 2011b; Giordano *et al*., 2011, and the present series), indicating that this is not a homogeneous condition. Our study also shows that there are some patients who do not have a uniformly good outcome with regards to seizure control and intellectual outcome. The unique vulnerability of the developing brain in the early years of childhood, as well as genetic heterogeneity and

Table 2. Outcomes associated with early-onset absence seizures based on the literature.

Study	Number of patients	Age at onset	Drugs used	Outcome	Comments
Cavazzuti *et al*., 1989	1	6.5 m	Nitrazepam	Well controlled	
Aicardi, 1995	1	<2 y	VPA	Well controlled	
Darra *et al*., 1996	6	<3 y	Not specified	Well controlled	
Covanis, 1998	7	<3 y	VPA	Well controlled	
Chaix *et al*., 2003	10	<3 y	VPA, ETX, CLB, LTG, TPM	5/10 with persistent seizures on polytherapy	Tapering of an AED in one patient resulted in recurrence.
Fernandez-Torre *et al*., 2006	3	<3 y	VPA, ETX	Well controlled	One patient had a myoclonic absence seizure. Treatment with ETX resulted in better seizure control for one patient.
Shahar *et al*., 2007	8	<3 y	VPA, LTG	Well controlled	Treatment with LTG resulted in seizure control for two patients. Three patients relapsed after VPA withdrawal.
Caraballo *et al*., 2011	11	<3 y	9/11-no medication	9/11 seizure-free	Two patients had persistent absence and generalised tonic-clonic seizures.
Verrrotti *et al*. 2011b; Caraballo *et al*., 2011	40	<3 y	VPA, ETX	33/40 (82%) seizure-free	
Giordano *et al*., 2011	33	<3 y	VPA, ETX, LTG, LEV	28/33 (85%) seizure-free	
This study	12	<3 y	VPA, ETX, LTG, LEV	7/12 (58%) seizure-free	Tapering of AEDs in three patients resulted in recurrence.

VPA: valproate; ETX: ethosuximide; LTG: lamotrigine; CLB: clobazam; TPM: topiramate; LEV: levetiracetam; y: years; m: months.

geographically-determined epigenetic differences, might account for the different clinical response to AEDs seen in different cohorts.

However, the debate over whether early-onset CAE is a distinct epilepsy syndrome continues. Whereas Verrotti *et al*. (2011a) believe that this is the case, Giordano *et al*. (2011) argue that early-onset CAE should be considered a continuum within the wide spectrum of idiopathic generalised epilepsies. In agreement with Verrotti *et al*. (2011a), we believe that early-onset CAE may be a distinct epilepsy syndrome with some features that overlap with those of typical CAE, as well as unique distinguishing features. Large prospective multicentre studies would be necessary to definitively resolve this matter. □

Disclosure.
None of the authors has any conflict of interest to disclose.

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