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Long term outcome in children affected by absence epilepsy with onset before the age of three years

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ABSTRACT

Objective: The goal of this study was to define the long-term outcome of absence epilepsy presenting before the age of 3 years.
Methods: We retrospectively studied the medical records of 40 children from eight neuropediatric centers in Italy with respect to the personal and family histories of epilepsy or febrile seizures, time of follow-up, cognitive functions, treatment, and outcome.
Results: Forty patients were enrolled in this study. They all fulfilled the criteria for absence epilepsy with 3-Hz spike–wave complexes on the EEG, normal neurological examination, and no other seizures types. Seizure onset occurred between 24.1 and 36.0 months. There was a family history of epilepsy in 28%, and of febrile seizures in 13%. Thirty-three patients were treated with valproic acid (VPA), mostly used in monotherapy (26 patients) or in association with ethosuximide. At final follow-up, 33 patients were seizure free and 29 had normal EEGs. Thirty-four patients had a normal intelligence quotient (IQ), whereas 6 had a decreased IQ, mainly associated with poor control of seizures.
Conclusion: In our series, absence seizures presenting before the age of 3 appeared to have quite a good long-term clinical prognosis; the neuropsychological outcome was comparable to that of childhood epilepsy presenting after 3 years of age.

1. Introduction

Absence seizures (previously known as "petit mal") are brief generalized epileptic seizures clinically characterized by impairment of consciousness, with a typical EEG pattern of generalized, bilateral, synchronous, symmetrical spike–wave discharges of 3–4 Hz (>2.5 Hz). The International League Against Epilepsy (ILAE) Commission on Classification and Terminology of Epilepsies and Epileptic Syndromes in 1989, and the later update proposal in 2001, defined, within the group of idiopathic generalized epilepsies (IGEs), two distinct epileptic disorders: (1) Childhood absence epilepsy (CAE) has its onset between the ages of 3 and 12 and peaks at 5–7 years. CAE is the archetypal childhood epileptic syndrome of absence seizures. (2) Juvenile absence epilepsy (JAE), occurs at ages 11–12 years and manifests mainly as severe typical absence seizures. The classification of IGEs is controversial and it is still unclear whether absences of CAE and JAE represent two different subsyndromes or a spectrum of the same syndrome [1–6].

In recent years, some authors have reported the rare occurrence of absence epilepsy with early onset (EOAE), prior to the age of 3, that seems to have clinical manifestations and EEG features similar to those of CAE and JAE syndromes [6–15]. The global prognosis of EOAE appears less favorable than that of CAE, but in most of these studies heterogeneous forms of EOAE are described [16].

To better define the long-term outcome, a multicenter study was carried out by collecting different cases of children with onset of pure absences before the age of 3 years.

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2. Methods

2.1. Selection of patients

We included patients with the following criteria: onset of absence seizures before the age of 3, bilateral and symmetric 3-Hz spike–wave generalized discharges, and normal background activity. We excluded from the survey patients presenting at the onset with epileptic manifestations different from absence seizures (except for febrile seizures) or clinically manifesting focal seizures or myoclonic jerks and patients with abnormal neurological examination at the first evaluation or with a personal history of brain abnormalities diagnosed by imaging studies.

2.2. Demographics

We retrospectively studied the medical records of 40 children coming from eight pediatric neurology departments to collect uniform data on patients with clinical and EEG features of absence seizures, observed before the age of 3 years. For each patient, personal and family histories of epilepsy or febrile seizures were documented, along with time of follow-up, cognitive function, treatment used, and outcome.

Patients were followed for a period of 2.1–14.9 years (mean ± SD, 6.7 ± 3.8), and all patients underwent periodical clinical and EEG evaluations; furthermore, a final EEG was obtained for all patients together with an examination of cognitive function to verify remission and control of seizures. Patients were defined as seizure free when their caregivers reported, in two consecutive clinical evaluations, the absence of significant critical events.

At the last visit cognitive functions were evaluated using the Wechsler Intelligence Scale for Children—Revised (WISC-R) in children who had reached school age and the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R) in children younger than school age. Final outcome of seizures was also evaluated, during the last visit, in all patients.

Informed consent was obtained from the parents/guardians of the recruited children, and the study was approved by the ethics committee of each institution.

3. Results

Clinical characteristics of the 40 patients of the present study are summarized in Table 1.

3.1. Medical history and clinical findings

Forty children fulfilling the inclusion criteria were selected for this survey. Patients were not quite equally distributed between males and females (17 girls and 23 boys), and age of onset was between 12.0

Table 1
Clinical characteristics at the onset of epilepsy and cognitive outcome of 40 patients with early-onset absence epilepsy.

Patient	Sex	Clinical history		Onset	Therapy	Outcome			
		Family history of seizures	Personal history of febrile seizures	Age at onset (months)	Treatment	Current age (years)	Seizure free	EEG	IQ
1	M	Febrile	–	36	VPA	5.9	Yes	Normal	Normal
2	M	–	–	24	VPA	13.8	Yes	Normal	Normal
3	M	–	–	14	Not treated	15.8	Yes	Normal	Normal
4	F	–	–	14	VPA → CLB	4.0	Yes	Normal	IQ = 69
5	M	–	–	36	LTG	13.2	Yes	Normal	Normal
6	F	–	–	12	VPA	15.9	Yes	Normal	Normal
7	F	Epilepsy	–	18	Not treated	9.0	Yes	Normal	Normal
8	F	–	–	14	VPA	13.3	Yes	Normal	Normal
9	F	Febrile	–	28	VPA	5.1	Yes	Occasional spike-wave complexes	Normal
10	F	–	–	35	VPA	5.3	Yes	Rare spike-wave complexes during HPV	Normal
11	F	Epilepsy	–	30	VPA	7.3	Yes	Normal	Normal
12	M	Febrile	–	32	VPA → ESM	7.1	Yes	Occasional polyspikes	Normal
13	M	Epilepsy	+	30	VPA	10.7	Yes	Normal	Normal
14	M	–	–	22	VPA	12.1	Yes	Normal	Normal
15	F	Epilepsy	–	36	ESM	6.4	Yes	Normal	Normal
16	M	–	–	35	VPA → ESM	8.5	No	Occasional widespread spike–waves	IQ = 71
17	F	–	–	27	VPA → LEV	8.8	No	Rare focal spikes	Normal
18	M	Epilepsy	+	24	VPA	15.8	Yes	Occasional spike–wave complexes	Normal
19	M	–	+	30	VPA	15.7	Yes	Occasional spike–wave complexes during HPV	Normal
20	M	–	–	18	VPA	8.9	Yes	Rare spikes and slow waves	Normal
21	F	–	–	36	VPA	9.9	Yes	Occasional focal spikes	Normal
22	F	Epilepsy	+	28	ESM	8.6	Yes	Normal	Normal
23	M	–	+	19	VPA	7.5	No	Occasional focal spikes	IQ = 62
24	M	–	–	24	ESM	10.3	Yes	Normal	IQ = 70
25	F	Epilepsy	+	30	VPA	9.6	No	Normal	Normal
26	F	Epilepsy	–	34	VPA	11.1	Yes	Normal	Normal
27	M	-	–	28	VPA → LTG	10.8	No	Normal	Normal
28	M	–	+	18	VPA	8.3	No	Occasional spike–wave complexes	IQ = 70
29	M	–	–	20	VPA → ESM	14.0	No	Normal	IQ = 68
30	F	–	+	25	VPA	6.7	Yes	Normal	Normal
31	M	–	–	26	VPA	7.7	Yes	Normal	Normal
32	F	–	+	22	VPA	6.3	Yes	Normal	Normal
33	F	Febrile	–	21	LEV	4.3	Yes	Normal	Normal
34	F	Febrile	–	22	VPA → CLB	3.9	Yes	Normal	Normal
35	M	–	–	36	VPA	5.5	Yes	Normal	Normal
36	M	Epilepsy	–	30	VPA	5.8	Yes	Normal	Normal
37	M	–	+	27	VPA	4.6	Yes	Normal	Normal
38	M	Epilepsy	+	32	VPA	6.4	Yes	Normal	Normal
39	M	Epilepsy	+	30	VPA	6.8	Yes	Normal	Normal
40	M	–	+	33	VPA	6.0	Yes	Normal	Normal

Note. HPV, hyperventilation; ESM, ethosuximide; CLB, clobazam; VPA, valproate; LTG, lamotrigine; LEV, levetiracetam; TPM, topiramate.

and 36.0 months (26.4 ± 7.1), with a prevalence of onset between 24.1 and 36.0 months (60% of patients) (Fig. 1).

Eleven of forty patients (28%) had a positive family history of epileptic seizures; furthermore, 5 of 40 patients (13%) had a family history of febrile seizures, and 13 of 40 (33%) had a personal history of febrile seizures.

3.2. Treatment

All patients were treated with antiepileptic drugs (AEDs) except two (patients 3 and 7) whose seizures were controlled and whose EEG features normalized without therapy a few months from onset. Thirty-one of 38 patients were on monotherapy, and 7 of 38 patients required duotherapy. Duration of therapy ranged from 1.4 to 12.1 years (4.2 ± 2.6). Thirty-three of 38 patients were prescribed valproic acid (VPA) as the drug of first choice in the dosage range 20.2 to 34.6 mg/kg/day. Twenty-six patients received VPA in monotherapy, and 7 patients in duotherapy. In patients who continued to have seizures while taking VPA, ethosuximide was the most frequently used drug of second choice. Other AEDs used are listed in Table 1.

Valproic acid monotherapy was effective in controlling seizures in 23 of 26 patients. In only one patient (patient 23), who was found to have an intelligence quotient (IQ) below the normal range at the end of follow-up, VPA monotherapy was not effective either in controlling seizures or in normalizing EEGs. Therefore, among all 31 patients in monotherapy, seizures were controlled in 90% and EEG features were normalized in 23. However, only 43% (3/7) of patients in bitherapy were seizure free at the end of the follow-up, and EEG normalization was achieved in 71% (5/7) of these patients.

3.3. Epilepsy and cognitive outcome

During follow-up, none of the patients developed generalized tonic–clonic seizures or myoclonic–astatic seizures. At the end of the follow-up 33 of 40 patients (83%) were seizure free, with normalization of the EEG in 29 of 40 (73%). At the end of follow-up, cognitive function was found to be normal in 34 patients (Table 1). In only 6 patients were cognitive skills found to be below the normal range according to the WISC-R or WPPSI-R, and 4 of the 6 were not seizure free at the end of the follow-up period.

4. Discussion

4.1. Epidemiology and clinical features of pure early-onset absence epilepsy

Early-onset absence epilepsy is rare, accounting for less than 1% of children with epilepsy onset before the age of 3 years [15,16]; in this retrospective study we analyzed the long-term outcome of children with EOAE and their response to AEDs. After a review of the literature on EOAE, we were able to identify only 44 published cases. The first patients were reported by Cavazzuti et al [17], who described a series of 12 children with typical EOAE, and in 1989, the same authors [7] reported a video/EEG study of an infant who presented with typical absence seizures at the age of 6.5 months. In 1980, De Marco [8] described a case of very early petit mal epilepsy, and in 1986, Robaszewska [18] described an 18-month-old infant with recurrent absence seizures. In 1995, Aicardi [9] reported 5 children with absence seizures, but only one case was affected by typical EOAE. Moreover, Darra et al. [10] recognized 6 cases of typical EOAE, and in 1998, Covanis [11] analyzed the EEGs and clinical correlates of 7 children with EOAE. Thereafter, Chaix et al. [16], in analyzing a personal series, reported another 2 children who were affected by EOAE. More recently, 3 more children with EOAE and with normal neurological examinations were described by Fernandez-Torre et al. [14]. Shahar et al. [6] reviewed many early studies about EOAE and added 8 new patients with normal psychomotor development. Finally, in 2007, Titomanlio et al. [15] described two siblings with EOAE and mild mental retardation.

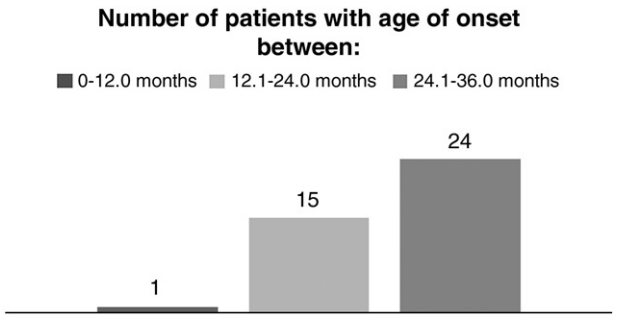

Fig. 1. Distribution of the onset-age expressed in months.

In our study there was a nearly equal distribution between males and females, not demonstrated in previous surveys, because of the small numbers of patients studied. Lack of sex preponderance might be a characteristic of EOAE, in contrast to the pattern generally seen in CAE, but it is not possible to draw a firm conclusion from a relatively small retrospective study.

In our series, 28% had a family history of epilepsy and 33% had a personal history of febrile seizures; these percentages are higher than those reported in literature, suggesting the possibility of a specific epileptic syndrome with putative familiar inheritance. In fact, only 7 of the 41 cases of EOAE ever discussed in the literature (17%) had a positive family history of epilepsy [8,13–16]. Genetic mutations associated with a family history of epilepsy were demonstrated in only one case: Audenaert et al. [13] identified a mutation of the *SCN1B* gene in a Belgian family in which febrile seizures, febrile seizures plus, and EOAE segregated. Genetic mutations were also pursued in another study [15], in which chloride channel (*CLCN2*), GABA(A) receptor γ_2 subunit (*GABRG2*), and neuronal nicotinic acetylcholine receptor α_4 subunit (*CHRNA4*) genes, previously identified in patients with CAE, were sequenced in a family in which two of the three siblings showed EOAE and mild mental retardation, but no mutations of the candidate genes were found. Furthermore, in differential diagnosis with IGE syndromes and EOAE, Glut-1 deficiency syndrome should be considered, as some authors have suggested that Glut-1 deficiency might occur in more than 10% of patients with EOAE [19]. These cases can be distinguished from other forms of EOAE by the recognition of meal-related episodes of mild confusion and unexpected difficulties in school or persistence of unusual EEG abnormalities, as well as improvement of EEG with introduction of a ketogenic diet [20,21]. In conclusion, it would appear that polygenic inheritance and multifactorial influences may cause a wide range of epileptic manifestations within EOAE, but they are rarely associated with pure absences [13–15].

Electroencephalographic abnormalities in our patients consisted of bilateral and symmetric 3-Hz spike–wave generalized discharges and normal background activity, a pattern also reported in previous descriptions of EOAE [6,7,11,14–16,22].

4.2. Treatment and clinical outcome

Valproic acid monotherapy represented the most frequently used AED treatment to control seizures in our sample, in agreement with other studies [6,9,11,13–16]. Use of ethosuximide as well as other AEDs as second-line therapy is also consistent with the literature [22,23]. In the present survey, control of seizures with AED was achieved in 83% of patients, suggesting a good response to VPA and a benign evolution for this subgroup of EOAE. Furthermore, the large majority of patients who still had EEG abnormalities at the end of follow-up showed only occasional spike–wave complexes, or rare focal spikes, as outlined in Table 1. Such a good response to VPA was

previously reported in EOAE and is also common in CAE; in fact, a benign long-term outcome in EOAE has been reported by many authors [6,8–10,13,14,24], in disagreement with some other surveys that consider EOAE a heterogeneous group of idiopathic epilepsies with a more unfavorable prognosis compared with CAE or JAE [7,11,15,16]. This worse prognosis is probably related to a major heterogeneity observed in these patients, if compared with the well-defined homogeneous group of patients described in the present study.

In particular, we excluded patients presenting at the onset with epileptic manifestations different from absence seizures (except for febrile seizures). Furthermore, we documented that none of the patients in our series developed generalized tonic–clonic seizures or myoclonic seizures, so defining a limited group within EOAE. The onset of epilepsy with myoclonic absences, in fact, usually occurs between 3 and 12 years of age, but some studies [14] emphasize that this type of epilepsy can occur in even younger children. Furthermore, some studies [7,14,16] have reported a possible occurrence, at onset or later, of generalized tonic–clonic seizures or myclonic seizures in children with EOAE.

4.3. Cognitive outcome

At the end of follow up, the neuropsychological outcome was normal in 34 of the 40 children in our study. Six had mild mental impairment and had a worse prognosis; four of them were still having seizures. Previous studies [9,11,15,16] had suggested that neurological development was poorer in patients with EOAE than in those with CAE, but our experience appears to contradict this view. Our clinical experience suggests that children with EOAE infrequently have a long-term risk of mild learning impairment, as is also demonstrated in IGE syndromes [25] and in CAE [26], but this risk is not greater than in CAE.

The better neuropsychological outcome of our patients is probably related to the strict inclusion criteria in the present study, defining a limited group with EOAE.

5. Conclusion

In summary, EOAE is characterized in our series by an electro-clinical course comparable to that of CAE, of which it represents a subsyndrome with earlier onset. Clinicians should be aware of the existence of this subgroup of children affected by EOAE, who, despite the early onset, generally have a good prognosis, in terms of both seizures and cognition.

Conflict of interest statement

None of the authors has any conflict of interest to disclose. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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