

SHORT COMMUNICATION

Early-onset absence epilepsy: *SLC2A1* gene analysis and treatment evolution

S. Agostinelli^a, M. Traverso^b, P. Accorsi^c, F. Beccaria^d, V. Belcastro^e, G. Capovilla^d, S. Cappanera^f, A. Coppola^g, B. Dalla Bernardina^h, F. Darra^h, M. Ferretti^b, M. Eliaⁱ, D. Galeone^j, L. Giordano^c, G. Gobbi^k, F. Nicita^l, P. Parisi^m, M. Pezzella^b, A. Spaliceⁿ, S. Striano^g, E. Tozzi^o, A. Vignoli^p, C. Minetti^b, F. Zara^b, P. Striano^b and A. Verrotti^a on behalf of the collaborative group of Società Italiana di Neurologia Pediatrica (SINP)

^aDepartment of Pediatrics, University of Chieti, Chieti; ^bPediatric Neurology and Muscular diseases Unit, "G. Gaslini" Institute, Genoa; ^cChild Neuropsychiatry, Spedali Civili, Brescia; ^dDepartment of Child Neuropsychiatry, C. Poma Hospital, Mantova; ^eDepartment of Neuroscience, Sant'Anna Hospital, Como; ^fDepartment of Pediatric Neurology, Ospedali Riuniti, Ancona; ^gDepartment of Neurological Sciences, Federico II University, Naples; ^hUnit of Child Neuropsychiatry, University of Verona, Verona; ⁱDepartment of Neurology, Oasi Institute for Research on Mental Retardation and Brain Aging, Troina; ^jChild Neurology, Children's Hospital Giovanni XXIII, Bari; ^kDepartment of Child Neuropsychiatry, Maggiore Hospital, Bologna; ^lDepartment of Pediatrics, University of Rome "La Sapienza", Rome; ^mChild Neurology, II Faculty of Medicine, "La Sapienza" University, Rome; ⁿChild Neurology Unit, Department of Pediatrics, "La Sapienza" University, Rome; ^oDepartment of Child Neuropsychiatry, University of L'Aquila, L'Aquila; and ^pEpilepsy Center, University of Milan, Milan, Italy

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Background and purposes: To determine the prevalence of *SLC2A1* mutations in children with early-onset absence epilepsy (EOAE) and to investigate whether there were differences in demographic and electroclinical data between patients who became seizure-free with anti-epileptic drug (AED) monotherapy (group I) and those who needed add-on treatment of a second AED (group II).

Methods: We reviewed children with EOAE attended different Italian epilepsy centers. All participants had onset of absence seizures within the first 3 years of life but otherwise conformed to a strict definition of childhood absence epilepsy. Mutation analysis of *SLC2A1* was performed in each patient.

Results: Eighty-four children (57 in group I, 27 in group II) fulfilled the inclusion criteria. No mutation in *SLC2A1* was found. There were no statistical differences between the two groups with regard to F/M ratio, age at onset of EOAE, early history of febrile seizures, first-degree family history for genetic generalized epilepsy, duration of AED therapy at 3 years after enrollment, use of AEDs at 3 years, failed withdrawals at 3 years, terminal remission of EOAE at 3 years, and 6-month follow-up EEG data. Mean duration of seizures/active epilepsy was significantly shorter in group I than in group II ($P = 0.008$).

Conclusions: We demonstrate that in a large series of children with rigorous diagnosis of EOAE, no mutations in *SLC2A1* gene are detected. Except for duration of seizures/active epilepsy, no significant differences in demographic and electroclinical aspects are observed between children with EOAE who responded well to AED monotherapy and those who became seizure-free with add-on treatment of a second AED.

Introduction

Childhood absence epilepsy (CAE) is a well-recognized prototype of genetic generalized epilepsy (GGE) with typical absence seizures (TAS), which manifest with transient impairment of consciousness associated with bilateral, regular, symmetric and

Correspondence: S. Agostinelli, Department of Pediatrics, University of Chieti, Via dei Vestini 5, 66100 Chieti, Italy (tel.: +39 0871 358020; fax: +39 0871 574831; e-mail: sergio_agostinelli@yahoo.it).



generalized 3–4 Hz spike-waves on electroencephalogram (EEG) [1]. According to the strict criteria proposed by Panayiotopoulos, the onset of CAE must be limited between 4 and 10 years of age with a peak at 5–7 years [2]. Although lower age at onset compatible with CAE is uncertain, clinical series of children with TAS starting from a few months to 3 years of age have been reported [3–5]. It is possible that early-onset absence epilepsy (EOAE) is a distinct syndrome within the spectrum of GGE showing electroclinical features, response to therapy and prognosis, similar but not identical to CAE. In the majority of cases, a good anti-epileptic drug (AED) response with rapid disappearance of seizures is obtained with monotherapy, while in some children, add-on of another AED is needed [4,5].

Recently, mutations in *SLC2A1* gene leading to reduced function of glucose transporter type 1 (GLUT-1), the molecule transporting glucose across the blood–brain barrier, have been found in over 10% of subjects with absences starting before 4 years of age [6].

The purpose of this retrospective multicenter study was to determine the prevalence of mutations in *SLC2A1* gene in children presenting with our strict criteria for EOAE, rather than the previously used broad criteria, and to investigate whether demographic (age at onset, early history of febrile seizures, first-degree family history for GGE) and electroclinical features (treatment outcomes, 6-month follow-up EEG data) were different between patients who responded to monotherapy and patients who needed add-on therapy.

Methods

Patients and study design

We reviewed retrospectively the medical records of all children with a strict diagnosis of EOAE attended sixteen different Italian epilepsy centers between 2001 and 2009 for at least 3 years. The study was approved by the Ethics Committee of each institution. All parents gave informed consent.

Inclusion criteria were as follows: (i) onset within the first 3 years of age; (ii) daily TAS accompanied by bilateral, regular, symmetric and generalized 3–4 Hz spike-waves with normal background on EEG; (iii) normal development and neurologic examination at onset; (iv) no brain imaging abnormalities. Patients were not eligible if there were: (i) other seizures as generalized tonic-clonic seizures or myoclonic jerks before or during the absences; (ii) eyelid or perioral myoclonia, rhythmic massive limb jerking, and single or

arrhythmic myoclonic jerk of the head, trunk, or limbs; (iii) no impairment of consciousness during the 3–4 Hz spike-waves discharges; (iv) photic and other sensory precipitation of clinical seizures. These strict criteria utilized a different definition of EOAE to that used in the context of GLUT-1 deficiency syndrome, which included patients with onset of absences before 4 years of age, no evidence of a secondary cause for epilepsy, generalized spike-waves on EEG, and absence of atonic/tonic seizures [6].

We subdivided all patients into two categories according to their AED response: group I (children who responded well to the first AED monotherapy and became seizure-free) and group II (children who became clinically seizure-free with add-on treatment of a second AED, after the maximum-tolerated dose of the first AED had been achieved).

The two groups were compared with regard to the following aspects: sex; age at onset of EOAE; occurrence of febrile seizures (FS) prior to EOAE; first-degree family history of GGE; duration of seizures/active epilepsy; duration of AED therapy at 3 years after enrollment; number of patients receiving AEDs at 3 years; number of failed withdrawals at 3 years; terminal remission of EOAE at 3 years (defined as the time from the last seizure to 3-year follow-up); EEG data collected after 6 months from the EOAE onset; and occurrence of mutations in *SLC2A1* gene (mutation analysis of *SLC2A1* was performed on genomic DNA by direct sequencing).

Statistical analysis

Statistical analysis was conducted using SPSS Version 17.0 (SPSS Inc, Chicago, IL, USA). The results are expressed as means (SD) for continuous variables and as percentages for categorical variables. Comparisons of continuous data were performed with Student's *t*-test, and those of categorical data with the χ^2 test. Statistical significant was defined as a *P*-value <0.05.

Results

Eighty-four children (F/M ratio: 35/49) fulfilled the inclusion criteria. Mean age at onset was 25.5 ± 7.9 months. Twenty patients (23.8%) had a history of FS before the onset of TAS, and 29 (34.5%) had a first-degree family history of GGE. All children were treated with AEDs and after a follow-up period of 3 years, seizures were controlled in each patient with 59 children (70.2%) still on therapy. Mean terminal remission at 3 years was 2.7 ± 0.3 years. Mutations in *SLC2A1* were not identified in any subject.

Table 1 Comparison of demographic and electroclinical features between the two groups

	Group I (n = 57)	Group II (n = 27)	P-value
F/M ratio	24/33	11/16	0.906
Age at onset (months)	24.8 ± 7.6	26.7 ± 8.4	0.193
Personal history of febrile seizures (%)	14 (24.6)	6 (22.2)	0.814
First-degree relatives with GGE (%)	19 (33.3)	10 (37.0)	0.739
Duration of seizures/active epilepsy (months)	2.0 ± 0.6	2.4 ± 0.5	0.008
Duration of AED therapy at 3-year follow-up (years)	2.5 ± 0.7	2.8 ± 0.4	0.138
Patients using AED at 3-year follow-up (%)	39 (68.4)	20 (74.1)	0.597
Failed withdrawals during 3-year follow-up (%)	6/18 (33.3)	2/7 (28.6)	0.649
Terminal remission at 3-year follow-up (years)	2.8 ± 0.4	2.6 ± 0.3	0.077
6-month follow-up EEG data			
Normal (%)	43 (75.4)	21 (77.8)	0.814
Generalized 3–4 Hz spike-wave complexes (%)	7 (12.3)	4 (14.8)	0.748
Generalized epileptiform discharges (%)	4 (7.0)	1 (3.7)	0.549
Focal epileptiform discharges (%)	3 (5.7)	1 (3.7)	0.754
<i>SLC2A1</i> mutations (%)	0	0	–

AED, anti-epileptic drug; GGE, genetic generalized epilepsy.

Group I included 57 patients (67.9%) and group II 27 patients (32.1%). In group I, 41 children (71.9%) were treated with valproate (mean dose, 27.9 ± 7.1 mg/kg/day), 10 (17.5%) with ethosuximide (mean dose, 25.1 ± 3.5 mg/kg/day) and 6 (10.6%) with lamotrigine (mean dose, 3.2 ± 1.5 mg/kg/day). In group II, 16 patients (59.3%) received valproate (mean dose, 24.5 ± 8.1 mg/kg/day) + ethosuximide (mean dose, 21.8 ± 6.1 mg/kg/day), 8 (29.6%) valproate (mean dose, 27.9 ± 5.4 mg/kg/day) + lamotrigine (mean dose, 3.8 ± 1.3 mg/kg/day), and 3 (11.1%) valproate (mean dose, 24.1 ± 7.3 mg/kg/day) + levetiracetam (mean dose, 27.2 ± 5.3 mg/kg/day). The mean time between the start of the first and second AED was 1.8 ± 0.7 months.

No significant differences in demographic and electroclinical variables, except for mean duration of seizures/active epilepsy ($P = 0.008$), were observed between the two groups (Table 1).

Discussion

This study demonstrates that in a large series of children with rigorous diagnosis of EOAE, no mutations

in *SLC2A1* gene are detected. *SLC2A1* mutations are not found in EOAE *per se* but are part of the underlying condition (GLUT-1 deficiency syndrome). Application of our strict criteria leads to a group of children with homogeneous disease characteristics and prognosis. Reasonably, in patients with newly suspected EOAE who are in accordance with these proposed criteria, it is advisable not to assess the *SLC2A1* gene mutations.

All children of this study were treated with AEDs and became seizure-free with an elevated terminal remission of epilepsy at 3 years (2.7 ± 0.3 years). Such a good response was mainly obtained in monotherapy (67.9%) with valproate, ethosuximide, or lamotrigine. Nevertheless, in nearly one-third of cases, seizures cessation could be achieved only with a combination of two AEDs. These two categories of patients showed similar demographic and electroclinical aspects, except for duration of seizures/active epilepsy, which appeared significantly shorter in children treated with AED monotherapy than in those who became seizure-free with add-on therapy of a second AED, after the maximum-tolerated dose of the first AED had been achieved. These findings are in line to those reported in children with CAE [7].

Although this is not an epidemiological study, the large number of patients with EOAE observed over a 7-year period could lead to reconsider the real prevalence of this epilepsy. In a previous study, we had observed that children with TAS starting within the first 3 years of life represented about 3.5% of all subjects with TAS observed in a 15-year period [4].

Among our patients, there was a slight male preponderance, in contrast to the pattern generally seen in CAE [7]. In our series, 34.5% had a first-degree family history for GGE, and 23.8% had a history of FS before the onset of TAS. These high percentages may suggest the possibility of a specific epileptic syndrome with putative familiar inheritance.

In conclusion, our study suggests that children who conform to our strict diagnostic criteria for EOAE do not have a high risk of *SLC2A1* gene mutations. This is significantly different to previous reports using a broad definition of EOAE. Our patients present a homogeneous prognosis with complete absence seizures control on AED treatment and epilepsy remission similar to those reported in CAE. These findings also demonstrated that, as long as the other parts of CAE definition are fulfilled, age of onset has little effect on prognosis; therefore, strict-definition EOAE may be included as a part of CAE.

Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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