FULL-LENGTH ORIGINAL RESEARCH

Symptomatic and presumed symptomatic focal epilepsies in childhood: An observational, prospective multicentre study

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Summary

Objective: **To describe the clinical, neuropsychological, and psychopathologic features of a cohort of children with a new diagnosis of symptomatic or presumed symptomatic focal epilepsy at time of recruitment and through the first month. The selected population will be followed for 2–5 years after enrollment to investigate the epilepsy course and identify early predictors of drug resistance.**

Methods: **In this observational, multicentre, nationwide study, children (age 1 month–12.9 years) with a new diagnosis of symptomatic or presumed symptomatic focal epilepsy were consecutively enrolled in 15 Italian tertiary childhood epilepsy centers. Inclusion criteria were as follows: (1) diagnosis of symptomatic focal epilepsy due to acquired and developmental etiologies, and presumed symptomatic focal epilepsy; (2) age at diagnosis older than 1 month and <13 years; and (3) written informed consent. Children were subdivided into three groups: ≤3 years, >3 to 6 years, and >6 years. Clinical, electroencephalography (EEG), neuroimaging, and neuropsychological variables were identified for statistical analyses.**

Results: **Two hundred fifty-nine children were enrolled (116 female and 143 male). Median age: 4.4 years (range 1 month–12.9 years); 46.0% (n = 119) of children were younger than 3 years, 24% (61) from 3 to 6 years of age, and 30% (79) older than**

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6 years. Neurologic examination findings were normal in 71.8%. Brain magnetic resonance imaging (MRI) was abnormal in 59.9%. Children age ≤3 years experienced the highest seizure frequency in the first month after recruitment ($p < 0.0001$). Monotherapy in the first month was used in 67.2%. Cognitive tests at baseline revealed abnormal scores in 30%; behavioral problems were present in 21%. At multivariate analysis, higher chances to exhibit more than five seizures in the first month after epilepsy onset was confirmed for younger children and those with temporal lobe epilepsy.

Significance: In this prospective cohort study, an extensive characterization of epilepsy onset in children with symptomatic or presumed symptomatic focal epilepsies is reported in relation to the age group and the localization of the epileptogenic zone.

KEY WORDS: Childhood epilepsy, Focal symptomatic seizures, Cognitive function, Behavior impairment, Intractable epilepsy.

KEY POINTS

- The proportion of symptomatic or presumed symptomatic epilepsies (FS and FCE) in newly diagnosed focal epilepsies is about 80% (focal epilepsy about 60% of all epilepsies)
- In this observational, multicentre, nationwide study, a cohort (n = 259) of FS and FCE with onset in childhood was consecutively enrolled
- Almost half of FS and FCE begin before 3 years of age; the frequency of seizures at time of recruitment was higher when in older children ($p < 0.0001$)
- At time of recruitment, MRI abnormalities were found in 59.9%, abnormal neurologic examination in about 30% and, at cognitive evaluation in 30%

Incidence of childhood epilepsy is estimated to be between 0.5 and 0.7 per 1,000 persons per year.[1–5] Focal epilepsies are more frequent than generalized epilepsies (≥60%). The proportion of symptomatic or presumed symptomatic focal epilepsies is about 80%, and their onset is mainly in infancy.[3,4,6] Some authors have independently examined the natural course of disease in children with newly diagnosed epilepsy.[7–10] Remission, relapse, and intractability occur at variable rates during long-term follow-up. Intractability appears more frequently within 5 years after epilepsy onset, and in some cases it can be interrupted by long periods of remission.[6–8–12] In 2010, Dutch investigators described five outcome-related patterns over a 15-year follow-up period: stable-favorable, improving, variable, deteriorating, and stable-poor.[11]

Information regarding epilepsy prognosis is important for clinicians in counseling and managing children. Previous studies[13,14] found younger age at onset, magnetic resonance imaging (MRI) abnormalities, high seizure frequency, and focal slowing on electroencephalography (EEG) to be early predictors of intractability. Predicting intractability at seizure onset is extremely important, especially in children, because severe epilepsy carries a higher risk of cognitive impairment.[13,14] Children with drug-resistant epilepsy (DRE) experience greater difficulties in terms of social, educational, and occupational integration.[9]

No prospective study has evaluated the outcome of children with symptomatic (FS) or presumed symptomatic focal epilepsies (FCE). Only retrospective studies of surgical series evaluated early predictors of drug resistance in children with medically treated FS and FCE.[15] No study has compared long-term outcomes of different therapeutic strategies (pharmacologic vs. surgery) in children. In addition, there is an ongoing debate regarding the timing of surgery in drug-resistant focal epilepsy, characterized by periods of remission and relapse.

More recently, attention has been increasingly directed to psychopathologic comorbidities in children with new or recent-onset epilepsy.[16–18] However, only a few prospective studies have focused on prevention of psychiatric comorbidity in subjects with drug-resistant focal epilepsy.[19]

We carried out a multicentre, nationwide, prospective study that analyzed the early clinical, neuropsychological, and psychopathologic features of a cohort of children with newly diagnosed symptomatic or presumed symptomatic focal epilepsies. The cohort is being followed to investigate the course of epilepsy and to identify predictors of drug resistance at 2 and 5 years after seizure onset in order to assess the best treatment strategy for drug-resistant patients.

METHODS

Children with newly diagnosed symptomatic or presumed symptomatic focal epilepsies were consecutively recruited in 15 Italian tertiary centers for pediatric epilepsy. Inclusion criteria were the following: (1) diagnosis of symptomatic epilepsy due to acquired and developmental etiologies, and presumed symptomatic focal epilepsy; (2) age at first diagnosis of epilepsy >1 month and <13 years; and (3)

written informed consent from caregivers. Children were excluded if they had (1) paroxysmal clinical manifestations not clearly classifiable as focal epilepsy; (2) idiopathic focal epilepsy; or (3) evidence for progressive immunologic or neurodegenerative disorders or dysmorphogenetic/genetic syndromes.

We excluded from the study all patients whose characteristics—that is, family history of epilepsy, frequent febrile seizures or febrile status, multifocal interictal EEG abnormalities or diffuse slow background activity—were suggestive of genetic etiology, specifically for PCDH19-related epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, epilepsy with variable foci, familial temporal lobe epilepsy or autosomal dominant lateral temporal lobe epilepsy.

The initial assessment included the following: (1) neurologic examination every 6 months for the first 2 years and annually for the next 3 years; (2) an initial video-EEG recording, while awake and asleep, as soon as possible after seizure onset and then repeated recordings according to clinical needs of each patient; (3) at least one 1.5 T (all centers) or 3 T (four centers) MRI study tailored on the basis of individual electroclinical features, within 6 months from initial diagnosis; and (4) neuropsychological assessment before starting medical treatment. The protocol was approved by the ethics committee of the promoting academic institution (University-Hospital of Padua) and the other participating centers.

Each center enrolled all children who met the inclusion criteria for 2 years after the first patient was recruited. Written informed consent was obtained from the parents and from children able to understand the implications of the study. Patients were enrolled from May 2010 to December 2013. Treatment decisions were made according to clinical practice, and were not influenced by the study.

Patients with symptomatic or presumed symptomatic focal epilepsies[20,21] were subdivided into three subgroups (i.e., frontal, temporal, and posterior localization) on the basis of the clinical manifestations and, when available, ictal electroclinical correlations during video-EEG studies.

Cognitive assessment was performed during the same session of the neurologic examination using standardized tests, namely the Wechsler intelligence scales (Wechsler Intelligence Scale for Children—Third Edition [WISC-III] or Wechsler Preschool and Primary Scale of Intelligence – Third Edition [WPPSI-III][22,23] and the Griffiths Mental Development Scales (GMDS).[24] In a minority of patients (10%), other scales were administered (Raven Progressive Matrices, Bayley Scales, Leiter-R, and Brunet-Lézine).

The cognitive profile was considered to be in the mean range when the intellectual (WISC scales) or developmental (Griffiths Scales) quotients were >85, borderline between 85 and 70, and pathologic <70.

The psychopathologic profile was evaluated by administering the Child Behavior Checklist (CBCL)[25] and the Youth Self Report questionnaires on behavior (YSR)[25] to parents and children >11 years-old, respectively. The first assessments were carried out strictly before reaching a steady-state after the administration of the first antiepileptic drug.

Statistical analysis

The general description of the patients' characteristics at epilepsy onset was provided through absolute and relative frequencies. The following variables were selected for analysis: sex, familiarity, perinatality, neurologic examination, occurrence of neonatal seizures, seizure frequency, secondary generalization, occurrence of status epilepticus, seizure semiology, EEG findings, video-EEG recorded seizures, MRI, polytherapy versus monotherapy, type of antiepileptic drugs, cognitive profile, and psychopathologic profile. Patients were subdivided into three groups based on age at seizure onset (≤3 years, >3 to 6 years, and >6 years). The frequency of each variable among the three groups was compared by separate chi-square tests, or Fisher's exact tests, as appropriate. The presence of specific associations across variables was examined by additional chi-square (or Fisher's exact) tests. When available, mean scores in cognitive cohorts were analyzed using the *t*-test. In all statistical analyses, the significance level was set at 0.05 and tests were two-tailed. The analyses were performed by using the SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

The final sample of newly diagnosed symptomatic or presumed symptomatic focal epilepsies (FS and FCE), at the end of the 2-year enrollment period, included 259 patients (117 female 142 male). The three age groups were represented as follows: 119 (46.0%) ≤ 3 years, 61 (24%) >3 to 6 years, and 79 (30%) >6 years old. Median age at seizure onset was 4.4 years (standard deviation [SD] 3.8 years, range 1 month–12.9 years). Analysis of age distribution revealed a higher prevalence of FS and FCE in children younger than 3 years (Fig. 1).

Table 1 summarizes the characteristics of patients at the time of recruitment and through the first month.

A family history of epilepsy or febrile seizures was present in 25% of children (n = 64), including 4 with a family history of both FS and epilepsy; in 11 patients, family history was not known (adopted children). In 12% of cases (n = 31), neurologic disorders were present in the first month of life, following common transient metabolic disorders (hypoglycemia and hypocalcemia) or hypoxic–ischemic disorders; 8.9% (n = 23) of the children had neonatal seizures. At onset, neurologic examination was normal in 71.8% (n = 186).

Seizure frequency, that is, the number of seizures in the first month after recruitment, was ≤5 in 49.8% of patients (n = 129) and >5 in 50.2% (n = 100). Children younger than 3 years had a higher seizure frequency, whereas a

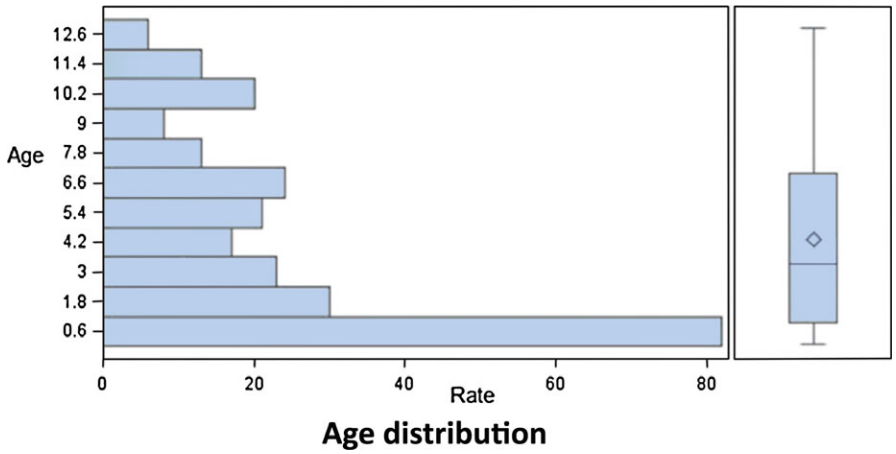

Figure 1.
Age distribution. The left panel shows the age distribution for the sample (N = 259). The right panel shows the distribution relative to the median age (4 years and 5 months).
Epilepsia © ILAE

lower frequency was more often reported in older children ($p < 0.0001$). Status epilepticus (≥30 min) had been experienced by 10.8% children (n = 28), whereas 26.3% (n = 68) exhibited focal seizures with secondary generalization. The first interictal EEG (awake and asleep) was abnormal in 94.6% and showed focal epileptiform discharges in 45.7% of cases (n = 118), equally distributed in all age groups.

Ictal electroclinical features allowed classification of the different types of focal epilepsy in about 70% of patients (n = 179). In 44.0% (n = 114) of children, seizures were captured on the first video-EEG; the probability of recording seizures was higher in children younger than age 3 years ($p = 0.0002$). Based on electroclinical features, no group emerged from statistical analysis ($p = 0.81$); the frontal (63 patients) and the temporal (63 patients) groups were equally represented, and the posterior group (53 patients) was nearly equally represented. The number of seizures observed at onset was >5 in the temporal and frontal groups and ≤5 in the posterior group ($p = 0.002$). No correlation was found between cognitive alterations, seizure frequency, and electrographic abnormalities. At the time of recruitment, no treatment was started in 18.9% of cases (n = 49, of which 19 symptomatic and 30 probably symptomatic), due to low seizure frequency and/or parental refusal. One third of these children started antiepileptic drug (AED) treatment during the following 6 months. At the onset of epilepsy, monotherapy gained seizure control in 67.2% (n = 174). Polytherapy was used in 13.9% of children (n = 36) in whom seizures continued despite administering two antiepileptic drugs in the first month. The most widely used AEDs were carbamazepine (35.5%), valproic acid (20.5%), levetiracetam (10.4%), vigabatrin (8.9%), benzodiazepines (6.6%), phenobarbital (6.2%), and phenytoin (4.6%). Other drugs, such as oxcarbazepine, topiramate, and adrenocorticotropic hormone (ACTH) treatment were rarely used. Seizure intractability (persistence of seizures despite the use of two or more antiepileptic drugs with adequate, tolerated, and appropriately chosen schedules in the first month of diagnosis) required a more frequent use of polytherapy in the younger group. The chi-square test revealed that most of children treated with monotherapies had frontal lobe epilepsy (50/174), whereas most of children treated with polytherapies had temporal lobe epilepsy (15/36); the posterior epilepsy (22/49) and the undetermined group (16/49) were more often without treatment ($p < 0.0001$).

Brain MRI was performed at onset in almost all patients (247/259) and was abnormal in 59.9% (n = 154), uncovering malformations of cortical development (including tuberous sclerosis) in 21.4%; tumors (5.8%); vascular diseases, that is, cavernoma (10.5%), and sequelae results (i.e., stroke or encephalitis) or scars (posttraumatic lesions) (3.9%). Additional MRI abnormalities (18.3%) included those not otherwise classified (i.e., hypoxic ischemic encephalopathy and minor or not specific abnormalities such as ventricular dilatation). Frontal lobe epilepsy (n = 46) was frequently observed in the group of children with abnormal MRI findings, even if the difference with respect to temporal lobe (n = 34) and posterior region (n = 28) epilepsy was not significant ($p = 0.065$).

Clinical data on cognitive development (normal or pathologic) at recruitment were available for 245 children (95% of the total sample). Overall, standardized scores in cognitive tests were obtained on 183 children (71.0%); 38.2% of them were assessed using the Wechsler scales and 47.5% using the Griffiths Scales. The standardized assessment of the cognitive profile, revealed that 62.3% of children (114/183) were within the mean range, 11.4% were borderline, and 26.3% were impaired.

When comparing neuroimaging and cognitive findings, a significant association emerged: 70% of children with abnormal MRI and 52.8% of those with normal MRI had an abnormal cognitive development before treatment was started ($p = 0.012$). Children exhibiting MRI abnormalities obtained significantly lower values in the total developmental quotient (DQ) on the Griffiths Development Mental Scales (negative MRI: mean 96.8, SD 16.5; positive MRI: mean 85.4, SD 18.9; $t_{62} = 2.99$, $p = 0.004$).

Table 1. Characteristics of patients at time of epilepsy onset

			Age at seizure onset			
			≤3 years	>3–6 years	>6 years	p-Value
Total sample	259		119 (46)	61 (24)	79 (30)	
Sex F:M, n (%)	259	116:143 (44.8:55.2)	59:60 (49.6:50.4)	27:34 (44.3:55.7)	30:49 (38.0:62.0)	0.25
Family history, n (%)	259					
No		180 (69.5)	83 (69.7)	36 (59.0)	61 (77.2)	0.22
Febrile seizure		23 (8.9)	10 (8.4)	9 (14.8)	4 (5.0)	
Epilepsy		41 (15.8)	17 (14.3)	11 (18.0)	13 (16.5)	
Febrile seizure + epilepsy		4 (1.5)	2 (1.7)	2 (3.3)	0 (0.0)	
Unknown		11 (4.3)	7 (5.9)	3 (4.9)	1 (1.3)	
Perinatality, n (%)	259					
Normal		224 (86.5)	104 (87.4)	47 (77.1)	73 (92.4)	0.10
Neurologic disorders		31 (12.0)	13 (10.9)	13 (21.3)	5 (6.3)	
Unknown		4 (1.5)	2 (1.7)	1 (1.6)	1 (1.3)	
Neurologic examination, n (%)	259					
Normal	259	186 (71.8)	77 (64.7)	40 (65.6)	69 (87.3)	0.001
Abnormal		73 (28.2)	42 (35.3)	21 (34.4)	10 (12.7)	
Neonatal seizures, n (%)	259	23 (8.9)	11 (9.2)	5 (8.2)	7 (8.9)	ns
Number seizures ≤5 vs. >5, n (%)	259	129:130 (49.8:50.2)	36:83 (30.3:69.7)	41:20 (67.2:32.8)	52:27 (65.8:34.2)	<0.0001
Secondary generalization, n (%)	259	68 (26.3)	26 (21.8)	17 (27.9)	25 (31.6)	0.29
Status epilepticus, n (%)	259	28 (10.8)	11 (9.2)	10 (16.4)	7 (8.9)	0.27
Electroclinical features, n (%)	259					
Frontal		63 (24.3)	28 (23.5)	15 (24.6)	20 (25.3)	0.81
Temporal		63 (24.3)	26 (21.9)	15 (24.6)	22 (27.8)	
Posterior		53 (20.5)	23 (19.3)	12 (19.7)	18 (22.8)	
Unknown		80 (30.9)	42 (35.3)	19 (31.1)	19 (24.1)	
EEG[a], n (%)	258					
Negative		11 (4.3)	5 (4.2)	3 (4.9)	3 (3.8)	0.72
Focal		118 (45.7)	54 (45.9)	22 (36.1)	42 (53.2)	
Lobar		55 (21.3)	22 (18.6)	17 (27.9)	16 (20.3)	
Multilobar		4 (1.6)	2 (1.7)	1 (1.6)	1 (1.2)	
Multifocal		61 (23.6)	29 (24.6)	16 (26.2)	16 (20.3)	
Diffused		6 (2.3)	3 (2.5)	2 (3.3)	1 (1.2)	
Unknown		3 (1.2)	3 (2.5)	0 (0.0)	0 (0.0)	
Seizures recorded during v-EEG, n (%)	259	114 (44.0)	69 (58.0)	20 (32.8)	25 (31.6)	0.0002
MRI, n (%)	257					
Negative		103 (40.1)	45 (37.8)	28 (45.9)	30 (39.0)	0.21
Tumor		15 (5.8)	5 (4.2)	5 (8.2)	5 (6.5)	
Cortical malformation		55 (21.4)	34 (28.6)	6 (9.8)	15 (19.5)	
Vascular disease		27 (10.5)	8 (6.7)	9 (14.8)	10 (12.9)	
Scars		10 (3.9)	3 (2.5)	3 (4.9)	4 (5.2)	
Other alterations		47 (18.3)	24 (20.2)	10 (16.4)	13 (16.9)	
Therapy, n (%)	259					
No		49 (18.9)	17 (14.3)	14 (22.9)	18 (22.8)	0.21
Monotherapy		174 (67.2)	84 (70.6)	40 (65.6)	50 (63.3)	
Polytherapy		36 (13.9)	18 (15.1)	7 (11.5)	11 (13.9)	
Drugs, n (%)						
Carbamazepine	259	92 (35.5)	39 (32.8)	24 (40.0)	29 (39.7)	0.66
Valproic acid	259	53 (20.5)	23 (19.3)	14 (23.3)	16 (22.0)	0.85
Levetiracetam	259	27 (10.4)	11 (9.2)	5 (8.3)	11 (15.0)	0.46
Vigabatrin	259	23 (8.9)	21 (17.6)	2 (3.3)	0 (0.0)	<0.0001
Benzodiazepines	259	17 (6.6)	7 (5.9)	5 (8.3)	5 (6.8)	0.83
Phenobarbital	259	16 (6.2)	12 (10.1)	3 (5.0)	1 (1.4)	0.03
Phenytoin	259	12 (4.6)	4 (3.4)	4 (6.7)	4 (5.5)	0.61
Oxcarbazepine	259	5 (1.9)	2 (1.7)	0 (0.0)	3 (4.1)	0.26
Topiramate	259	8 (3.1)	4 (3.4)	1 (1.7)	3 (4.1)	0.75
ACTH	259	4 (1.5)	4 (3.4)	0 (0.0)	0 (0.0)	0.09
Other drugs	259	5 (1.9)	2 (1.7)	2 (3.3)	1 (1.4)	0.67

Continued

Table 1. Continued.

			Age at seizure onset			
			≤3 years	>3–6 years	>6 years	p-Value
Cognitive profile, n (%)	245					
Normal		143 (58.3)	57 (51.4)	37 (63.8)	49 (64.5)	<0.99
Pathologic		81 (33.1)	33 (29.7)	21 (36.2)	27 (35.5)	
Not applicable		21 (8.6)	21 (18.9)	0 (0.0)	0 (0.0)	
Psychopathologic profile, n (%)	141					
Normal		112 (79.4)	34 (87.2)	31 (72.1)	47 (79.7)	<0.24
Pathologic		29 (20.6)	5 (12.8)	12 (27.9)	12 (20.3)	

[a]EEG terminology: *focal*, epileptiform anomalies limited to a small area of one lobe; *lobar*, epileptiform anomalies limited to one lobe; *multilobar*, epileptiform anomalies present in two or more adjacent lobes; *multifocal*, epileptiform anomalies present in two or more spatially separated lobes; *diffuse*, synchronous and symmetrically epileptiform anomalies.

Table 2. Association between clinical variables and the number of seizures in the first month (dependent variables)

Variables (independent)	Fraction	Percentage (%)	p-Value	Un-OR	95% CI	Adj-OR	95% CI
Age							
≤3 years	83/119	70	0.0001	1 (ref.)		1 (ref.)	
3–6 years	20/61	33		0.21	0.11–0.42	0.17	0.08–0.35
>6 years	27/79	34		0.23	0.12–0.42	0.18	0.09–0.35
Electroclinical features							
Frontal	32/63	51	0.005	1.14	0.59–2.22	1.19	0.57–2.51
Temporal	42/63	67		2.33	1.16–4.66	3.02	1.38–6.63
Posterior	18/53	34		0.59	0.28–1.21	0.59	0.26–1.31
Unknown	38/80	48		1 (ref.)		1 (ref.)	
MRI							
Negative	50/103	49	0.67	1.15	0.70–1.90	–	–
Positive	79/154	51					
Cognitive profile							
Normal	69/143	48	0.87	1.15	0.62–1.86	–	–
Pathologic	40/81	49		1.07		–	–

The comparison between the cognitive profile and medical treatment revealed that children with a normal cognitive profile were more often treated with monotherapy or not treated (98/143 and 31/143 respectively; p = 0.03). Children on AEDs were evaluated before starting treatment and obtained significant lower values on the Wechsler Total Scale compared with children receiving no treatment (no therapy: IQ 102.2, SD 14.7; mono- or polytherapy: IQ 86.2, SD 20.7; $t_{60} = 2.51$, p = 0.015).

With multivariate analysis, higher chances to exhibit more than five seizures in the first month after epilepsy onset was confirmed for younger children and those with temporal lobe epilepsy (Table 2). A psychopathologic profile was evaluated in only 141 patients (54.4%) at seizure onset and revealed various symptoms (social cognition, communication, and behavioral problems) in 20.6% of children (n = 29).

Discussion

Anticipating epilepsy prognosis is a major factor influencing treatment strategy and possibly long-term outcome.

This is the first prospective study on a select cohort of patients with newly diagnosed symptomatic and presumed symptomatic focal epilepsy.

Previous studies assessing the course of newly diagnosed epilepsy, either focal or generalized, revealed unexplained fluctuations of remission and relapse (recurrence of seizures after remission) in about one third of patients.[7,9] Intractability appears more frequently within 5 years after epilepsy onset, and in some cases is interrupted by long remissions. The long-term impact (20–45 years) of childhood-onset epilepsy and its treatment was analyzed by Sillanpää et al.,[7,8] who highlighted how both presumed symptomatic (72%) and symptomatic (47%) epilepsies could face up to 10-year remission periods, and likewise with the idiopathic group (95%). Berg et al.[7] recently observed that sizable heterogeneous groups of patients did not enter a prolonged remission, irrespective of epilepsy severity, demonstrating that between complete remission and relentless intractability, there is a spectrum of seizure outcomes. In these cases, chronic DRE could be linked to cognitive impairment with repercussions lasting a lifespan.[7]

We evaluated a select population of symptomatic or presumed symptomatic focal epilepsies (FS and FCE) with onset in childhood (1 month–13 years) in order to assess clinical course as a preliminary step to better implement treatment strategies in patients at higher risk of drug resistance.

In this initial report, at the time of recruitment (time 0), through the first month, we describe the characteristics of FS and FCE at onset. Seizures in FS and FCE often started before the age of 3 years (46%). In younger children (≤3 years) the frequency of seizures at onset was higher than in older children ($p < 0.0001$).

Polytherapy was more frequently needed in the younger age group as a consequence of the higher number of children with resistant seizures. Predictors of higher seizure frequency in the first month after enrollment were younger age and ictal semiology suggestive of temporal lobe epilepsy. Neurologic evaluation revealed abnormalities in 28.2% of all children, more often in those younger than 6 years ($p = 0.001$). In the same group, intellectual disability represented a major feature.

Using a prospective design, our study confirms that in children with seizure onset before 3 years of age, in particular in those with abnormal EEG and/or MRI findings and/or cognitive profile, drug resistance is highly probable and carries a high risk of having an unfavorable impact on the global neurodevelopment.[28] Alternative therapeutic strategies to pharmacology may be advised in the early stages, as shown recently by Reinholdson et al.,[29] who through a prospective, population-based, longitudinal study, described the outcomes of 47 children having undergone ablative surgery when younger than 4 years of age. Most children had seizure onset within the first year of life, and the median age at surgery was 2 years and 1 month. Two thirds of the children exhibited neurodevelopmental abnormalities, but in about 50%, a favorable seizure outcome was achieved after surgery, and improvements remained consistent over time.[29] DRE in such young children suggests earlier consideration of possible surgical treatment. Presurgical evaluation is facilitated by the recording of seizures during the first EEG, as observed in our study ($p = 0.0002$).

The question remains of how and when to treat older children and those who do not enter prolonged remission.

As observed in previous pediatric surgical series,[30] the majority of children in our study had frontal and temporal lobe epilepsies, whereas posterior focal epilepsy was less frequently seen, and an epileptogenic zone was not clearly identifiable in one third of patients.

We found MRI abnormalities more frequently (~60%) in children with frontal lobe epilepsy, although the difference with temporal lobe and posterior region epilepsy was not significant.

From a pharmacologic point of view at onset, our study points out to some novel findings that might be useful for clinical practice. Frontal lobe epilepsy was more easily controlled by monotherapy than the temporal lobe epilepsy. Posterior epilepsy and the group of undetermined focal epilepsy showed a lower frequency of seizures at onset, and these two groups were more often without treatment ($p < 0.0001$). This finding might explain the higher prevalence of temporal lobe epilepsy in pediatric surgical series. However, no study has prospectively analyzed the development of drug resistance and cognitive outcome in children with focal symptomatic epilepsy in relation to the identified epileptogenic zone (frontal, temporal, and posterior) and the undetermined one. Our planned follow-up study will provide more data on this point also in relation to age groups.

Few data are available on the cognitive profile in drug-resistant patients at epilepsy onset, and studies are typically designed to evaluate the cognitive profile postsurgery.[26–34] Previous studies, mostly retrospective, revealed that children with drug-resistant focal epilepsy score lower on IQ tests, and in particular regarding to memory.[33,35] Moreover, in children with epilepsy, high rates of comorbid learning disabilities, psychiatric and behavioral difficulties, and psychosocial problems occur (26–28%).[36–38]

In our study, at the time of recruitment, we found a high percentage of children with normal cognitive profile.

However, children who had epileptiform EEG discharges and abnormal MRI findings more often required polytherapy for controlling seizures and exhibited delayed cognitive development (70%).

No correlation was found between the number of seizures in the first month after enrollment (less or more than five seizures) and the cognitive evaluation ($p < 0.87$).

Younger children with MRI abnormalities obtained significantly lower values on the total DQ ($p = 0.004$). Moreover, one third of the children with cognitive problems also had negative MRI ($p = 0.021$).

The cognitive profile and developmental scales can be useful in the evaluation of newly diagnosed epilepsies, in particular in relation to the possible periods of remission and relapse, and the choice of the best treatment in patients with MRI abnormalities and drug resistance. It is also important to consider alternative treatment strategies to AEDs for children with severe focal epilepsy to preserve their neurologic development and cognitive skills.[29,35,39]

We expect our observational study will delineate the evolution of symptomatic and presumed symptomatic focal epilepsy, particularly in age-related groups.

Some authors found higher scores on the CBCL in children with chronic seizures, compared to those with other chronic diseases like asthma[40] and juvenile rheumatoid arthritis. It could be argued that psychiatric comorbidities are associated with childhood-onset epilepsy and may persist during seizure remission, accounting for the poor psychosocial outcome (employment, educational attainment, socioeconomic status, and quality of life).[16,17] Recently, different authors have highlighted the importance of using

well-established dimensional measures (i.e., Child Behavior Checklist) at the onset of epilepsy[37] and appropriate monitoring over time.[17,19] It has been reported that >15% of children with newly diagnosed epilepsy have behavioral and related disorders, and 10.7% are in the clinical range for attention problems.[16]

In our study, only about half of the children were evaluated for psychopathologic problems at epilepsy onset, and 21% of them exhibited various symptoms (social cognition, communication, and behavior problems). Because of the frequency and severity of emotional and behavior problems in children with newly diagnosed epilepsy, a comprehensive evaluation and treatment of psychiatric problems are mandatory. However, this information could not be obtained in the group of children younger than 3 years of age due to the nonapplicability of the test. We are hopeful that follow-up data will provide new insights to improve the management of drug-resistant symptomatic and presumed symptomatic focal epilepsies in the short and long term and contribute to the identification of the timing for successful surgery.

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Disclosures

None of the authors has any relevant conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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