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Early clinical and EEG findings associated with the outcome in childhood absence epilepsy

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ABSTRACT

Objectives: The objective of this study was to investigate several clinical electroencephalogram (EEG) findings possibly predicting the early response to antiepileptic drugs (AEDs) and the late outcome in children with clinical EEG features fitting the syndromic diagnosis of childhood absence epilepsy (CAE).
Methods: In 117 untreated patients with typical absences, we analyzed clinical EEG features, and resting EEG activity using partial directed coherence to calculate out- and inflow of cortical oscillations in different regions of interest.
Results: Absences began before 4 years in 12.0%, at 4–9.5 years in 71.8%, and at 10–13 years in 16.2% of the cases. Valproate was started in 91 patients and ethosuximide in 27. With one of AEDs, 77.8% reached seizure control, while the remaining patients needed to switch to the alternative AED. Only 5.9% patients remained drug-resistant. Absences with simple automatisms were the only feature associated with a lack of response to the first AED. Connectivity analysis of resting EEGs showed increased frontal outflow in patients compared with controls, which was significantly greater in the nonresponders to the first AED than in responders.
Among the 91 patients followed for 61.2 ± 31.7 months, 14.2% relapsed after a seizure-free period, without differences between the responders to the first or second AED.
Conclusions: The assessment of electroclinical features provided only minimal prognostic indices. The enhanced outflow of frontal oscillations suggests a circuitry dysfunction significantly greater in the nonresponder to the early treatment.
Seizure relapses were rare and comparable in patients who reached seizure freedom with first or second AED, indicating that the resistance to one AED does not influence the outcome.

1. Introduction

The operational classification of seizures [1] indicates that generalized onset nonmotor seizures include typical, atypical, myoclonic, and eyelid myoclonic absences. Typical absences present with an abrupt loss of contact that occurs synchronously with spike-and-wave (SW) discharges on electroencephalograms (EEGs) at an almost stable frequency near to 3 Hz, whereas atypical absences usually show a more gradual loss of contact and the frequency of SW complexes is <2.5 Hz [2,3]. The occurrence of multiple daily typical absence seizures associated with 2.5–3.5 Hz-generalized SW discharges indicates the syndromic diagnosis of childhood absence epilepsy (CAE) [4]. In the presence of a typical EEG clinical presentation, we included also patients younger than four years or 10 to 12 years old.

Although the prognosis in patients with CAE is generally benign, remission rates vary widely [5–7]. Indeed, various papers on the topic of CAE report variable unfavorable prognostic factors including a lack of response to initial treatment [8], a nontypical early or late age at onset [9], or the presence of a photosensitive trait [10]. Moreover, borderline EEG findings have been also reported as unfavorable, for instance discharges with multiple spikes or with irregular frequency [11,12] or short duration [13].

Probably, some of the previous studies included patients with some deviation with respect to the presentation of typical CAE [12].

We performed the present study to understand if antiepileptic drug (AED) resistance actually exists in patients with CAE without any clinical or EEG deviation from typical presentation and observed from the onset, before starting AED treatment.

We evaluated if the resistance to the first AED could really predict a worse outcome.

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To explore if the lack of a prompt response to AED may reside on a different circuitry rearrangement, we also compared the EEG connectivity pattern in a patient subset of responders and nonresponders to the first AED, based on methods that we already applied in a previous study on patients with typical absences [14].

2. Materials and methods

2.1. Patient selection

We reviewed the cases of all of the patients presenting with typical absences associated with the EEG pattern of bilateral, synchronous 2.5–3.5 Hz SW complexes. We included patients diagnosed between 1991 and 2017 at the Fondazione IRCCS Istituto Neurologico Carlo Besta (Milan) and between 2002 and 2017 at the University Hospital of Sassari. Patients did not receive drug treatments and, after the onset of AEDs, were followed up in the same centers.

On the basis of the clinical history and clinical EEG observation, we selected only those patients in whom typical absences occurred several times a day as isolated symptom, not associated with other seizure types or with signs of delayed psychomotor development, behavioral problems, or abnormal cognitive functioning. We included patients who had, during their first awake EEG recording, at least two absences associated with ictal SW discharges. In all of the patients, the EEG recording was made without sleep deprivation; it lasted 30–40 min and included 3 min of hyperventilation and stimulus trains of intermittent light stimulation at frequencies ranging from 1 to 40 Hz. Some patients underwent to a separate recording of an EEG during nap, performed in the early afternoon.

Patients with onset age lower than 4 years or in a higher age range (10–12.5 years) with respect to that of typical CAE and patients with SW discharges lasting less than 4 s were also included when all other clinical and EEG features fitted the inclusion in CAE.

The other EEG criteria to select the patients were the presence of normal background activity and the recording of repeated SW discharges with a frequency ranging from 2.5 to 3.5 Hz, without presence of polyspike components and without any feature suggesting a focal origin or an atypical SW course. At our early observation, the neurological and cognitive evaluations were based on clinical judgment, while a formal cognitive evaluation was performed using Wechsler Preschool and Primary Scale of Intelligence or Wechsler Intelligence Scale for Children tests during the follow-up, in the event of any deviation from the normal cognitive development or behavior. The study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and it was performed in agreement with the protocols approved by the Ethical Committee of the Fondazione IRCCS Istituto Neurologico Carlo Besta.

2.2. Clinical EEG data collection

The following data obtained at the time of our earliest clinical observation were collected: 1) family history for epilepsy, 2) previous febrile seizures, and 3) age at the time of seizure onset.

The video-EEGs were recorded in a dimly lit room by means of 19 Ag/AgCl surface electrodes, placed according to the 10–20 International System, and acquired by means of a computerized system (sampling frequency: 256 Hz; bandpass filter: 1–120 Hz; 12 dB/octave; Micromed S.p.A., Mogliano Veneto, Treviso, Italy). All of the EEG signals were recorded using a montage with a common reference electrode that allowed offline mathematical data reformatting. Based on the examination of the video-EEG recordings, we separated the subgroup of patients with absences with simple automatisms [15]. The patients with preponderant myoclonic components suggesting possible eyelid myoclonia or myoclonic absences were excluded.

Two expert neurophysiologists (LC and MSD), who were blinded to the patients' classification, visually inspected the EEGs, and categorized 1) the dominant background frequency, 2) the presence of interictal SWs, 3) the presence of occipital intermittent rhythmic EEG delta activity (OIRDA), 4) the number and mean duration of ictal discharges occurring during an awake recording of about 30 min, 5) the mean SW frequency within the discharges, 6) the slowing of SW frequency during the discharges, 7) the amplitude asymmetries of the discharges, and 8) the presence of photoparoxysmal responses.

The presence and duration of interictal SWs and the occurrence of absences during drowsiness and spindle sleep were evaluated in the patients who underwent a nap EEG recording before starting treatment.

After assessing the six-month response to the first AED, the population was divided into responders and nonresponders. The judgment of resistance to the AED was always made in the presence of adequate drug daily dose together with plasma drug levels corresponding to the high part of the therapeutic range. Indeed, plasma drug levels were consistently monitored in all patients according to the standard procedures in the two epilepsy centers.

We subsequently evaluated the duration of follow-up, seizure recurrence, and the duration of AED treatment.

2.3. EEG connectivity analysis

We included in this evaluation only patients and controls aged 5.5–9.5 years. We selected this age range since younger children may physiologically present more immature connectivity pattern and because our previous study on connectivity was performed in patients with typical absences and controls in this age range.

We excluded any recordings without sufficiently long artifact-free epochs or signs of unstable vigilance. The analysis therefore involved 35 patients (20 females, aged 7.4 $\pm$ 1.9 years) and 17 healthy controls (eight females, aged 7.6 $\pm$ 1.5 years).

The patients' interictal EEGs (i.e., eyes-closed EEG samples without any epileptiform activity) and the controls' resting EEGs were visually inspected by an expert neurophysiologist (SF) in order to select suitable 30-s, artifact-free EEG epochs at least 1 min far from any spontaneous ictal SW discharge. In the preprocessing phase, the EEG data were normalized by subtracting the mean value and dividing the result by the standard deviation. Subsequently, the resting EEG of each subject was divided into about 60 nonoverlapping epochs of 1 s each. These epochs were considered as multiple realizations of the same statistical process, and their multivariate autoregressive (MVAR) coefficients were estimated using the Levinson–Robinson–Wiggins algorithm [16]. Eleven electrodes F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, and O2 were selected for the connectivity analysis. The following regions of interest (ROIs) were considered for subsequent analyses: frontal (F), central (C) and parieto-occipital (PO). Electrodes in the temporal regions were not considered since temporal cortex is known to have a marginal involvement into absence epilepsy. After estimating the MVAR model, partial directed coherence (PDC) was calculated as previously described [14]. A summary of the methods for the PDC calculation is reported as Supplementary material.

2.4. Statistical analysis

Clinical and EEG features were evaluated using bivariate logistic regression after dividing the patients in two groups according to the positive or lacking response to the first AED. The influence of a positive/negative response to a first AED on later seizure recurrence was assessed using the Mantel–Cox test.

The EEG connectivity datasets were statistically analyzed using repeated measures analysis of variance (RMANOVA) at a significance level of 5%; the sphericity assumption was evaluated using Mauchley's test, with the Greenhouse–Geisser correction of the degrees of freedom being applied when appropriate. Therefore, for each EEG frequency band (delta, theta, alpha, beta, and gamma) and graph index (out- and in-degree, out- and in-strength), a RMANOVA was made separately in order to evaluate the effects of the between-group factor (responders

or nonresponders to the first AED and "controls") and the effect of ROIs (F, C and PO) as within-group factor.

When RMANOVA showed a significant main effect, a post hoc analysis was made using Bonferroni's correction for multiple comparisons.

3. Results

The study involved 117 patients who started to experience absence seizures at a mean age of 6.9 ± 2.8 years (range: 2–13 years): 14 (12.0%) before the age of four years, 84 (71.8%) between the ages of four and 9.5 years, and 19 (16.2%) between the ages of 10 and 13 years. Their mean age at the time of the first EEG recording was 7.2 ± 2.7 years.

Thirty-six of the patients (30.0%) had relatives with epilepsy or febrile seizures, and eight (6.7%) had previously experienced typical febrile seizures.

Seizures were classified as absences with simple automatisms in 26 (22.2%). The duration of the ictal events was similar in patients with or without automatisms (7.4 ± 3.1 vs 8.5 ± 5.2 s), similar was also the number of recorded ictal events during the first awake EEG.

We assessed the early response to first AED after 6 months of treatment. Ninety patients received valproate (VPA) as their first AED, and 27 received ethosuximide (ESM). The choice of ESM, as first-line AED, increased slightly, from 21.7% of patients observed before 2001, to 33.3% of the 44 patients observed between 2001 and 2010, and to a similar percentage (32.2%) of the 45 patients observed after 2010. We did not find any correlation between clinical and EEG findings at the time of the early observation and drug choice.

Ninety-one patients (77.8%) became seizure-free shortly after starting their first AED, whereas 26 needed to switch to another AED. The percentage of nonresponders to VPA or ESM was similar, 21.9% and 22.2%. The nonresponders to VPA were switched to ESM and vice versa.

3.1. Responders and nonresponders to the first AED, clinical, and EEG features

Table 1 shows the distribution of the clinical and EEG characteristics of the first AED responders and nonresponders; there was no significant difference in the distribution of putative clinical or EEG "risk factors" capable of distinguishing the two groups.

Mean age at onset was similar in the responders and nonresponders to the first AED, and the patients not responding to multiple AEDs fell into different age groups (Fig. 1). Namely, among the 14 patients with onset before four years of age, only two did not become seizure-free with the first AED.

Considered as a whole, the patients with simple absences more frequently showed a complete response to the first AED than those with absences associated with simple automatisms (p = 0.044).

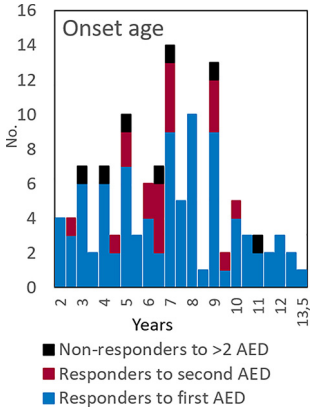

Fig. 1. Age at the time of onset of absences by response to AEDs.

At the time of our earliest observation, 38 patients underwent EEG nap recordings: 30 responders to their first AED (32.9%) and eight nonresponders (30.7%). The recordings during drowsiness and spindle sleep (and slow sleep when reached) showed a physiological pattern in all cases; none of the children reached a Rapid Eye Movement sleep stage. There was no significant between-group difference in the various measures of sleep SW discharges or the presence of absences during drowsiness (Table 2), even though the latter occurred in a larger percentage of responders.

Seven patients (5.9% of the study population) did not respond when switching to the second AED and continued to have absence also after the third AED. The small number of patients resistant to multiple AEDs prevented a statistical comparison; however, in these "resistant" patients, we did not find any particular EEG or clinical feature, except for the presence of absences with automatism in four of them, a larger proportion with respect to the remaining patients (20.0%).

3.2. Connectivity analysis

3.2.1. Out- and in-degrees

Repeated measures analysis of variance indicated a significant interaction between the groups (responder and nonresponder patients and controls) and the out-degree measured on different ROIs in alpha ($F(3,46) = 7.9$; $p = 0.001$) and beta ($F(3,46) = 4.0$; $p = 0.024$) bands, but not significant interaction for in-degree.

The post hoc comparison showed that the out-degree values were significantly higher on the frontal ROI in both the alpha and beta bands in the responders (alpha: $t(33) = 2.65$, $p = 0.012$; beta: $t(33) = 2.7$, $p < 0.010$),

Table 1
Clinical and EEG data in responders and nonresponders to the first AED.

	Responders to first AED	Nonresponders to first AED	ExpB	Sig.	Confidence interval
	N = 91	N = 26		p	95% CI
Clinical findings (n = 117)					
Family history of epilepsy	31 (34.0%)	8 (32.3%)	0.790	0.631	0.302–2.067
Previous febrile seizures	7 (7.6%)	2 (8.0%)	0.972	0.973	0.183–5.152
Absences with simple automatisms	14 (15.4%)	12 (46.1%)	0.395	0.040	0.160–0.975
Age at seizure onset (years)	6.9 ± 2.9	6.7 ± 2.1	0.977	0.767	0.835–1.142
EEG findings (n = 117)					
Background (Hz)	8.6 ± 1.4	8.6 ± 1.3	0.992	0.963	0.719–1.371
Interictal SWs	66 (75.5%)	16 (69.2%)	0.852	0.742	0.329–2.207
Posterior slow waves	24 (26.4%)	9 (34.6%)	0.677	0.412	0.266–1.720
No. of ictal SW discharges	4.7 ± 4.1	5.6 ± 3.6	1.048	0.355	0.949–1.158
SW frequency (Hz)	2.9 ± 0.3	2.9 ± 0.2	1.186	0.847	0.211–1.158
Mean discharge duration (s)	8.6 ± 5.0	6.9 ± 2.1	0.909	0.107	0.810–1.021
Slight slowing in SW frequency	35 (38.5%)	13 (50.0%)	0.625	0.294	0.260–1.502
Asymmetric SW amplitude	3	1			
Photoparoxysmal responses	5	1			

Table 2
EEG findings during sleep.

Sleep EEG recordings at the onset	Responders to first AED	Nonresponders to first AED	ExpB	Sig.	Confidence interval
	N = 30	N = 8			
SW discharges during drowsiness	29 (96.7%)	7 (87.5%)	4.143	0.335	0.230–74.352
Duration of SW discharges during drowsiness	9.0 ± 5.3 s	6.3 ± 3.5 s	0.881	0.217	0.720–1.077
SW discharges during slow sleep	27 (90.0%)	8 (100.0%)	4.787	0.999	0.000
Duration of SW discharges during slow sleep	5.3 ± 3.5 s	4.0 ± 1.5 s	0.858	0.388	0.639–1.152

and in the alpha band in the nonresponders ($t(27) = 5.7$, $p < 0.001$) (Fig. 2, A and B) in comparison with controls.

Nonresponders compared with responders showed significantly higher out-degree values on the frontal ROI in alpha band ($t(32) = 3.5$; $p = 0.002$).

3.2.2. Out- and in-strength

Repeated measures analysis of variance revealed significant interactions between out-strength measured on different ROIs in alpha ($F(3,47) = 3.8$; $p = 0.030$), and beta ($F(3,47) = 14.0$, $p < 0.001$) bands, but not significant interaction for in-strength.

Out-strength in the beta band was greater on the frontal ROI in the responders ($t(35) = 3.7$; $p = 0.001$) and the nonresponders to the first AED ($t(29) = 3.0$; $p = 0.005$) in comparison with controls. Moreover, out-strength was lower in both patient groups on the parieto-occipital ROIs, ($t(29) = 2.4$; $p = 0.024$ and $t(29) = 3.1$, $p = 0.004$) (Fig. 2, C and D), but the difference survived after Bonferroni's correction in the nonresponders only.

3.3. Follow-up

The mean follow-up was 74.9 ± 38.1 months.

The seven patients in whom seizures recurred also when treated with the second AED (5.9% of the study population) continued to experience absences without any protracted seizure-free period when treated with lamotrigine or levetiracetam, and all remained on AED treatment until the last observation.

Nineteen of the remaining 110 patients were followed up for less than one year, and did not experience any recurrence during stable AED treatment. The mean follow-up of the 91 patients followed for more than one year was 61.2 ± 31.7 months, which was similar in responders to the first AED (n = 74: 59.3 ± 30.9 months) and in those requiring a second AED to reach seizure freedom (66.9 ± 45.0 months).

Patients who had absences with simple automatisms had not significantly different late recurrence with respect to those with simple absences (17.8% vs 12.7%).

Patients with onset in the lower (<4 years) age range did not have late recurrence; patients with onset in the higher age range (10–12.5 years) had percentage of late recurrence similar to that of subjects with the more typical onset age of CAE (20.0% vs 15.8%) (see e-Table 1 for details).

The treatment was withdrawn in 37 of these 91 patients (41.9% of the responders to the first AED and 31.6% of those who responded to the second AED). The timing of the decision to withdraw was slightly later in patients who did not respond to first AED than in those who responded (Mantel–Cox logrank test: 3.974; $p = 0.046$) (Fig. 3).

During the course of the follow-up, seizures recurred after a seizure-free period in 13 patients (14.2%), without any significant difference between the responders and nonresponders to the first AED (12.3% and 23.5%). They also recurred in a similar percentage of patients discontinuing or continuing the treatment (14.8% and 13.5%), although they recurred earlier in the patients trying to taper the AEDs (Kaplan–Mayer; Mantel–Cox: 6.096; $p = 0.014$). Ten patients with recurring seizures had absences, and three had isolated generalized tonic–clonic seizures; all became again seizure-free when they resumed the AED treatment, or its daily dose was adjusted.

At the time of the last observation, only three of the 91 patients followed up for more than one year showed mild cognitive impairment and five mild behavioral problems (5.5%). Cognitive impairment occurred more often in the patients who needed a second AED to become seizure-free (17.3% vs 2.7%; Fisher's exact test, $p = 0.043$). Logistic regression analysis of the putative risk factors for seizure recurrence during the follow-up that were already recognizable at the time of our first observation did not reveal any further statistically significant factor.

Two of the seven patients who did not respond to the second AED were lost to follow-up after one year; the other five were followed up for 78–244 months. Comparison of this small group with the remaining

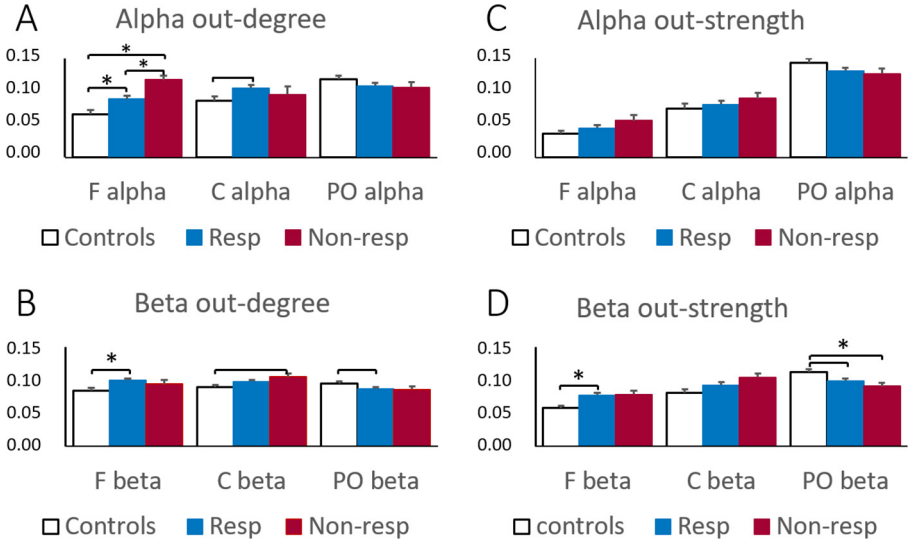

Fig. 2. Out-degree (A and B) and out-strength (C and D) in different ROIs (F = frontal, C = central, PO = parieto-occipital) in healthy controls and patients responding or not responding to first AED. The bars indicate significant differences, and the asterisks the significant differences that remained after Bonferroni's correction.

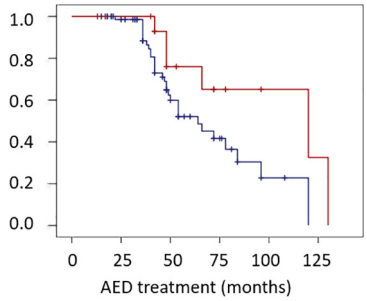

Fig. 3. Survival curves of AED treatment duration in the patients responding to their first AED (blue line) and those responding to the second (red line). The patients who did not respond to the second AED have been omitted because they all continued to be treated until the last follow-up observation.

patients showed that they more frequently developed cognitive impairment than the other patients who continued to be followed up (Fisher's exact test, $p = 0.028$).

4. Discussion

The aim of this study was to investigate the electroclinical features possibly associated with AED resistance in patients presenting with absence seizures fitting the syndromic classification in the category of CAE and to evaluate their follow-up outcome. To this aim, we examined a large group of otherwise healthy children diagnosed at seizure onset before starting AED treatment in two epilepsy centers in whom we were able to record and evaluate clinical EEG ictal events.

The patients started treatment with VPA or less frequently with ESM, both of which are considered the first-choice treatments for absence seizures [17], and there was no difference in the percentage of patients becoming seizure-free on either, thus suggesting that the chosen first drug did not influence the early response to treatment. The absence of any detectable relationship between drug choice and clinical EEG picture at the onset indicates that objective features did not determine the choice between the two drugs but attributable to the personal experience of the neuropediatrician, even more recent data indicate a superiority of ESM [18].

Most of the patients (77.8%) became seizure-free upon treatment with their first AED; while 16.2% did not respond to the first AED but became seizure-free when treated with their second AED: an overall positive response rate of 94.0%. The remaining 6.0% who continued to experience absences met the definition of drug resistance [19].

The proportion of patients who became seizure-free after treatment with their first or second AED is larger than that reported in some previous studies [11,20,21]. This was probably because of our restrictive inclusion criteria, since the rate of favorable outcomes was similar to that observed in patients who meet Panayiotopoulos's criteria for a diagnosis of CAE [12,22].

Our series included a small percentage of patients with an earlier (< 4 years) seizure onset than the classic age range for CAE syndrome [9]. We did not find that an early onset had a negative influence on the prognosis. This confirms that patients with typical absences, not associated with any feature of defective neuropsychological development, share the good prognosis and drug sensitivity of those with onset in more typical age range [23,24]. The same was found in patients in the higher age range, showing clinical and EEG features consistent with CAE. This "elder" patient group may however represent a specific population, worthy to be evaluated in the future, in comparison with patients with other "adolescent" syndromes presenting with absences (namely juvenile absence epilepsy).

4.1. Clinical and EEG features

Among the clinical and EEG features, we did not find any factor predictive of an early resistance to first AED, as well, we did not find factors characterizing the small number of patients who became resistant to multiple AEDs. Namely, the two "border" factors for CAE definition, which are atypical age of onset or shorter than 4-s SW discharges, showed no influence. The only clinical finding associated with a lack of response to the first AED was the presence of simple automatic movements during the absences [25]. To the best of our knowledge, the association of this finding with increased resistance to AED has not been reported in other studies [26]. We have no obvious explanation for this finding; however, we cannot exclude that a particular involvement of frontal regions may lead to automatic behavior. This would require a specific study in selected populations, since, in our study, the small number of patients with this absence type prevented further evaluation. Actually, in our series absence with automatisms were related to a lacking response to first AED, but not with a worse late outcome.

As clinical features, the visually assessed EEG features were similar in the responders and nonresponders to the first AED, and even the seven patients who became drug-resistant did not show any differences in terms of the duration or morphology of SW discharges.

In order to evaluate a further possibly predictive EEG feature, we made a PDC-based connectivity analysis of resting awake EEG epochs. This evaluation was performed in a more restricted patient group, with classical onset age, comparable with the patient group included in our previous study [14] and a control group of healthy subjects.

The results obtained in the present study confirm a prominent involvement of frontal cortical regions and are in line with those obtained with different imaging analyses [27–29]. The main evidence was an increased outflow from the frontal regions in the alpha band and beta band, suggesting that oscillations occurring in resting condition in frontal cortex have an increased influence over other regions in patients with typical absences. Both responders and nonresponders to the first AED had a similar profile in comparison with controls, but the nonresponders had a significantly higher frontal outflow toward other regions compared with both controls and patients who became seizure-free after treatment with their first AED. This may suggest a quantitatively stronger dysfunctional role of the frontal cortex in generating absences with some degree of resistance to AED. The small number of truly AED-resistant patients (i.e., those resistant to two or more AEDs) prevented any further comparison.

4.2. Long-term outcome

Thirteen of the patients who achieved remission after treatment with their first or second drug relapsed with absences or isolated generalized tonic–clonic seizures after a seizure-free period of at least one year. This relapse occurred in both treated patients and in those whose treatment had been tapered. Furthermore, a lack of response to the first AED did not affect the probability of seizure relapse, but simply delayed AED withdrawal. The relapsed seizures responded to the resumption of the AED or its dose adjustment, thus confirming the essentially benign nature of the epilepsy albeit with a small risk of relapse. A recent study that prospectively evaluated a large population with typical absences, to assess the long-term outcome in CAE, found that the tonic–clonic seizures occur as late as 5–10 years after the onset of the syndrome [13]. The length of our patient follow-up varied and so we cannot exclude the later occurrence of seizures, but it is probably enough to detect an occasional seizure relapse and reasonably excludes an evolution toward true AED-resistant epilepsy.

Three of our seven AED-resistant patients showed mild cognitive impairment during the follow-up, unnoticed at the time of our earliest observation. The association between refractory absence seizures and cognitive impairment has been reported in a previous study [30] and been attributed to the repetition of the seizures or the adverse effects of the drugs used to treat them. In our patients, the multiple AED resistance did not develop during the follow-up, but became evident during the first year of follow-up, without seizure-free periods, therefore

suggesting that an unidentified mechanism could lead to both absences and developmental defect.

In our study, the only factor that slightly influenced the response to the first AED was the presence of simple automatisms during absences; moreover, absences with automatisms characterized four out of the seven patients who were truly resistant to two AEDs; conversely, they did not negatively affect the late outcome.

4.3. Conclusions

Our study performed in a quite large series of patients with typical absences and EEG pattern confirms a good prognosis, which appears to be independent from the chosen drug (VPA or ESM), but also from the "apparent" early resistance, with a lacking control with the first AED. Indeed, the proportion of late seizure relapse was similar in all patients, regardless of whether they responded to the first or second AED and no one developed late resistances to AED.

The clinical and EEG features were unable to discriminate between responders and nonresponders to first AED. The few patients who showed drug resistance also to the second AED had recurrent seizures from the onset, suggesting a still unidentified mechanism of poor drug responsivity.

Our connectivity measures confirmed a stronger outflow of cortical oscillations, in alpha and beta bands, occurring on frontal regions toward other cortical regions, in patients with absences with respect to controls. The strongest outflow found in patients who did not respond to first AED can hypothetically represent the mechanism of increased resistance to treatments, but the demonstration needs more selective and extensive studies.

4.4. Limitations

Our population is rather large, bearing in mind the restrictive inclusion criteria; nevertheless, we cannot exclude that the negative results obtained by comparing some clinical or EEG features in responders and nonresponder to first AED could be affected by the anyway limited subject number. This is certainly true for the few patients who developed a multiple AED resistance since the small number prevented any statistical comparison.

Actually, we did not find obvious elements justifying the choice of the first AED and the preponderant use of VPA. This limitation derives from the nonrandomized nature of the study therefore consenting the subjective choice of the pediatrician firstly observing the child.

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Declaration of Competing Interest

The authors declare no conflicts of interest to disclose.

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