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Long-term Prognosis of Childhood Absence Epilepsy

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ABSTRACT

Introduction: We aimed to investigate the long-term prognosis of childhood absence epilepsy (CAE), and identify factors associated with treatment outcomes.

Methods: Patients with a definitive diagnosis of CAE according to the International League Against Epilepsy 2021 criteria and with a minimum of 3-year follow-up duration were included. The children were divided according to the time of seizure control. Early seizure remission was defined as seizure freedom within 6 months after the treatment onset.

Results: Twenty-four patients with a mean age of 13.7 (9.4–22.0) were included in this study. At the final follow-up, all patients were seizure-free except for one case. Seizure freedom was achieved after initial treatment in a mean of 0.78 years. The treatment was ceased in 19 children (79.2%) after a mean of 3.2 years. Patients having absence seizures without motor components had a higher rate of early seizure remission (p=0.026). In 81.3% of the patients; all of whose repetitive post-treatment EEGs were devoid of any generalized spike-wave discharges and absence seizures; remission was established within 6 months or less (p=0.026).

Conclusions: CAE has a favorable prognosis with seizure control obtained in the majority of the cases and more than half of them were obtained within 6 months following the initiation of treatment. Moreover, having an absence seizure without motor components and repetitively normal post-treatment EEGs appear to be associated with a higher rate of early seizure remission.

Keywords: Absence epilepsy, child, electroencephalography, prognosis

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INTRODUCTION

Childhood absence epilepsy (CAE) is a well-defined idiopathic generalized epilepsy (IGE) syndrome with a high treatment response and a very good remission rate. Over time, stricter diagnostic criterias and proper anti-seizure medication (ASM) selection resulted in higher remission rates and improved outcomes (1,2).

Treatment outcomes and related factors have been poorly studied in homogenous groups of patients with CAE. In recent studies, the absence seizures without motor phenomena were related to worse treatment outcomes (3). Another interesting finding concerning prognosis was the duration of the seizures; patients whose shortest seizures were longer had better treatment outcomes (4).

Using the latest proposed definition of the International League Against Epilepsy (ILAE)(5), we aimed to investigate the long-term prognosis of CAE and identify electro-clinical factors associated with treatment outcomes.

Highlights

- **All cases except one (95.8%) were seizure free at the final follow-up.**
- **In more than half of the cases, seizure freedom was obtained within 6 months.**
- **Seizure freedom was achieved after initial treatment in a mean of 0.8 years.**
- **The treatment was ceased in 19 children (79.2%) after a mean of 3.2 years.**
- **Absence seizures without motor components associated with early seizure remission.**

METHODS

Study Design and Participants

Medical records of patients with epilepsy admitted to our tertiary pediatric epilepsy center between 2006 and 2022 were reviewed. Patients with a definitive diagnosis of CAE according to the ILAE 2022 criteria and with a minimum of 3 years follow-up duration were included (5). We have also included 23 patients from our previous study who had been monitored for at least three years (6). Exclusion criteria were previously presented (6).

Patients' clinical parameters, including age, gender, age of seizure onset, history of febrile convulsions, family history, ASM use, time to remission after initial treatment, duration of ASM use, duration of seizure freedom, and follow-up duration were evaluated.

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To investigate factors associated with the treatment outcome, we divided the children according to the time of seizure control. Seizure control was assessed using both the parents' reports and the EEG results. Early seizure remission was defined as seizure freedom within 6 months after the treatment onset and the rest of the patients were defined as the late remission group.

EEG Recordings

At least two video-EEG recordings of each child were made: one before treatment and one after treatment. EEG recording features and criteria for considering ictal discharges as a typical absence seizure were previously reported (6). Using the previously described method, the EEG analysis and the semiological characteristics of absence seizures were identified (6)

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows v. 21.0 (IBM Corp., Armonk, NY) was used in order to perform statistical analyses. Descriptive statistics were presented as numbers and percentages for categorical variables and mean, standard deviation, minimum and maximum for numeric variables. To demonstrate the normality of the distribution of quantitative data, the Shapiro-Wilk normality test was used. The Mann-Whitney U test was used to compare continuous variables that were not normally distributed, whereas the independent samples t-test was used to compare normally distributed continuous variables. Pearson's chi-square test and Fisher's exact test were used to compare categorical variables. The level of statistical significance was set at $p < 0.05$.

Ethical Considerations

The protocol was approved by the ethical committee of Clinical Research Ethical Committee of Istanbul University- Cerrahpaşa Medical Faculty (E-83045809-804.01-701585).

RESULTS

Demographical and Clinical Features

Twenty-four patients with a mean age of 13.7±3.8 (9.4–22.0) were included in this study. Nine of them (37.5%) were female and 15 of them (62.5%) were male. The mean follow-up duration was 6.3±3.3 years (3–16). The mean number of EEGs recorded per patient was 4.3±1.6 (2–8). The demographical and clinical features of patients were demonstrated in Table 1.

Pre-treatment EEG Findings

Pre-treatment interictal EEG features were shown in Table 2. Occipital intermittent delta activity (OIRDA) was observed in 14 patients (58.3%), and all of these observed during hyperventilation (HV). Eight out of these 14 patients also had OIRDA during non-HV periods. Unilateral or asymmetric OIRDA was not detected in any of the recordings. Occipital intermittent delta activity preceded an absence seizure in 7 patients (29.2%), one of whom also presented OIRDA following an absence seizure.

All patients had more than one absence seizure during pre-treatment EEGs. Additionally, each patient had at least one absence seizure during HV. Pre-treatment ictal EEG and semiological findings were summed up in Table 3.

Treatment and Seizure Outcomes

Initial treatment was valproic acid in 20 patients (83.3%), ethosuximide in 1, and lamotrigine in 1 patient. Only two patients (8.3%) were treated with polytherapy (lamotrigine plus ethosuximide, valproic acid plus levetiracetam). At the final follow-up, all patients were seizure-free except for one case. Seizure freedom was achieved after initial treatment in a mean of 0.8±1.2 years (5 days to 4.5 years). The mean duration of seizure freedom was 5.4±3.4 years (6 months to 15.0 years). The treatment was ceased in 19 children (79.2%) after a mean of 3.2±1.4 years (1.4-6.6 years) of seizure freedom and they were followed up without ASM for a mean of 2.7±2.6 years (6 months to 10.0 years). Eighteen patients (75%) were seizure-free and without ASMs for at least 1 year before the final follow-up. There was no seizure relapse or progression into other IGE syndromes in any of the patients.

Post-treatment EEG Findings

First post-treatment EEGs were performed in a mean of 1.4 years (3 months to 4.5 years). In 19 patients (79.2%), generalized spike-wave discharges (GSWD) and absence seizures had resolved on all repetitive post-treatment EEGs. In three patients, GSWDs and absence seizures disappeared after 5 to 8 years. EEG abnormalities persisted in only two patients (8.3%). These two patients were represented in Case Vignettes. The presence of focal spike-wave discharges (FSWD) on pre-treatment and post-treatment EEGs were shown in Figure 1.

Focal spike-wave discharges were present in only 6 patients (25%) on post-treatment EEGs (4 centrotemporal-FSWD, 2 frontal-FSWD, 1 temporoparietooccipital-FSWD, and 1 central-FSWD). Four patients had FSWDs while asleep, and two had them both awake and asleep. Five of 6 patients also had FSWDs on pre-treatment EEGs, three of whom had formerly multifocal FSWD. Only one patient who didn't have any FSWDs previously had a centrotemporal-FSWD on post-treatment EEGs. In two patients, GSWDs resolved whereas, FSWDs continued (Figure 1).

Table 1. Demographical and clinical features

N=24	
Age (mean ± SD)(range), years	13.7±3.8 (9.4–22.0)
Age of seizure onset (mean ± SD)(range), years	6.7±2.1 (4.3–11.0)
Mean duration of absence seizure in pretreatment EEG, seconds	7.7±3.0 (4–13)
Mean duration of shortest absence seizure in pretreatment EEG, seconds	5.9±2.1 (4–10)
Mean duration of longest absence seizure in pretreatment EEG, seconds	9.3±4.3 (4–20)
Follow-up duration, years	6.3±3.3 (3.0–16.0)
History of febrile convulsion	2 (8.3%)
Family history of epilepsy	2 (8.3%)

SD: standard deviation

Table 2. Interictal EEG findings on pre-treatment EEGs

N (%)	Awake	Asleep	Total
FSWDs	**11 (45.8)**	**20 (83.3)**	**20 (83.3)**
Frontal-FSWDs	9 (37.5)	18 (75.0)	18 (75.0)
TPO-FSWDs	4 (16.7)	9 (37.5)	10 (41.7)
CT-FSWDs	3 (12.5)	3 (12.5)	3 (12.5)
Focal	9 (37.5)	13 (54.2)	13 (54.2)
Multifocal	2 (8.3)	7 (29.2)	8 (33.3)
GSWDs	**9 (37.5)**	**23 (95.8)**	**23 (95.8)**
GSWDs with symmetric onset only	7 (29.2)	10 (41.7)	10 (41.7)
GSWD with asymmetric onset only	-	1 (4.2)	1 (4.2)
GSWDs with both asymmetric and symmetric onset	2 (8.3)	12 (50.0)	12 (50.0)
Polyspikes	-	3 (12.5)	3 (12.5)
PPR	4 (16.7)	-	4 (16.7)

CT: centrotemporal; FSWDs: focal spike-wave discharges; GSWDs: generalized spike-wave discharges; PPR: photoparoxysmal response; TPO: temporoparietooccipital.

Table 3. Ictal EEG and semiological findings on pre-treatment EEGs

Ictal EEG findings	N (%)
Bilateral synchronous symmetric onset only	9 (37.5)
Bilateral synchronous asymmetric onset only	1 (4.2)
Both bilateral synchronous symmetric and asymmetric onset*	10 (41.7)
Both focal and bilateral synchronous symmetric onset*/**	5 (20.8)
Ictal semiological findings	
Absence without motor components only	10 (41.7)
Absence with motor components only	7 (29.2)
Absence with and without motor components	7 (29.2)
Motor semiological findings	
Oral automatisms only	8 (33.3)
Mild clonic movements of the eyelids only	2 (8.3)
Extremity myoclonias only	1 (4.2)
Both oral automatisms and mild clonic movements of the eyelids	3 (12.5)

*In one patient, bilateral synchronous symmetric, asymmetric and also focal seizure onset was present. **Frontal seizure onset was found in two patients, and TPO seizure onset was in two. One patient had both frontal and TPO seizure onset.

Early Seizure Remission

Early seizure remission was obtained in fifteen children (62.5%). There was no association between early seizure remission and gender, seizure onset age, history of febrile convulsion, family history of epilepsy, mean duration of absence seizures, mean duration of shortest and longest absence seizures, having absence seizures with motor components, or having seizures both with and without motor components, bilateral synchronous symmetric seizure onset, bilateral synchronous asymmetric seizure onset or focal seizure onset, presence of FSWDs, presence of FSWDs both during the awake and asleep, presence of GSWDs and asymmetric GSWDs, presence of GSWDs both during the awake and asleep, presence of OIRDA. However, patients having absence seizures without motor components had a higher rate of early seizure remission compared to patients who had concomitant motor phenomena (81.3% vs 28.6%) (p=0.026). Moreover, in 81.3% of the patients, all of whose repetitive post-treatment EEGs were devoid of any GSWDs and absence seizures, remission was established within 6 months or less (p=0.026).

Case Vignettes

Patient 1 was a female with a seizure onset age of 6. She had no history of febrile convulsions and epilepsy in her family. Ictal findings in pre-treatment EEG demonstrated both bilateral synchronous symmetric and asymmetric (with left hemisphere predominance) seizure onset. The duration of absence seizures ranged between 10 to 13 seconds. There were both absences with oral automatisms and absences without motor components. She had bilateral independent frontal FSWDs during sleep. She had symmetrical GSWDs while awake, however, both symmetric and asymmetric GWSDs were arising while asleep. She was treated with valproic acid. After 4.5 years of treatment, the EEG revealed symmetrical GSWDs during both awake and asleep periods. Furthermore, an absence seizure without motor components was observed during HV. This was the only patient without seizure remission after 4.5 years of follow-up.

Patient 18 is a male with no history of febrile convulsions and family history of epilepsy. He had a seizure onset age of 10. He only had bilateral synchronous symmetric seizure onset on pre-treatment EEG. His absence seizures lasted 4 seconds, and they were accompanied by oral automatisms and mild clonic movements of the eyelids. He had bilateral independent frontal FSWD during sleep. Bilateral OIRDA was observed during both HV and non-HV periods. During sleep, both symmetric and asymmetric GWSDs were found. He was treated with lamotrigine and ethosuximide, and seizure freedom was obtained after 4.5 years. His EEG in the first year of the treatment revealed bilateral OIRDA, GWSDs during both awake and asleep periods, and bilateral independent frontal FSWDs during sleep. After 5 years of treatment, his final EEG displayed GWSDs during both awake and asleep periods, as well as bilateral independent frontal FSWDs during sleep.

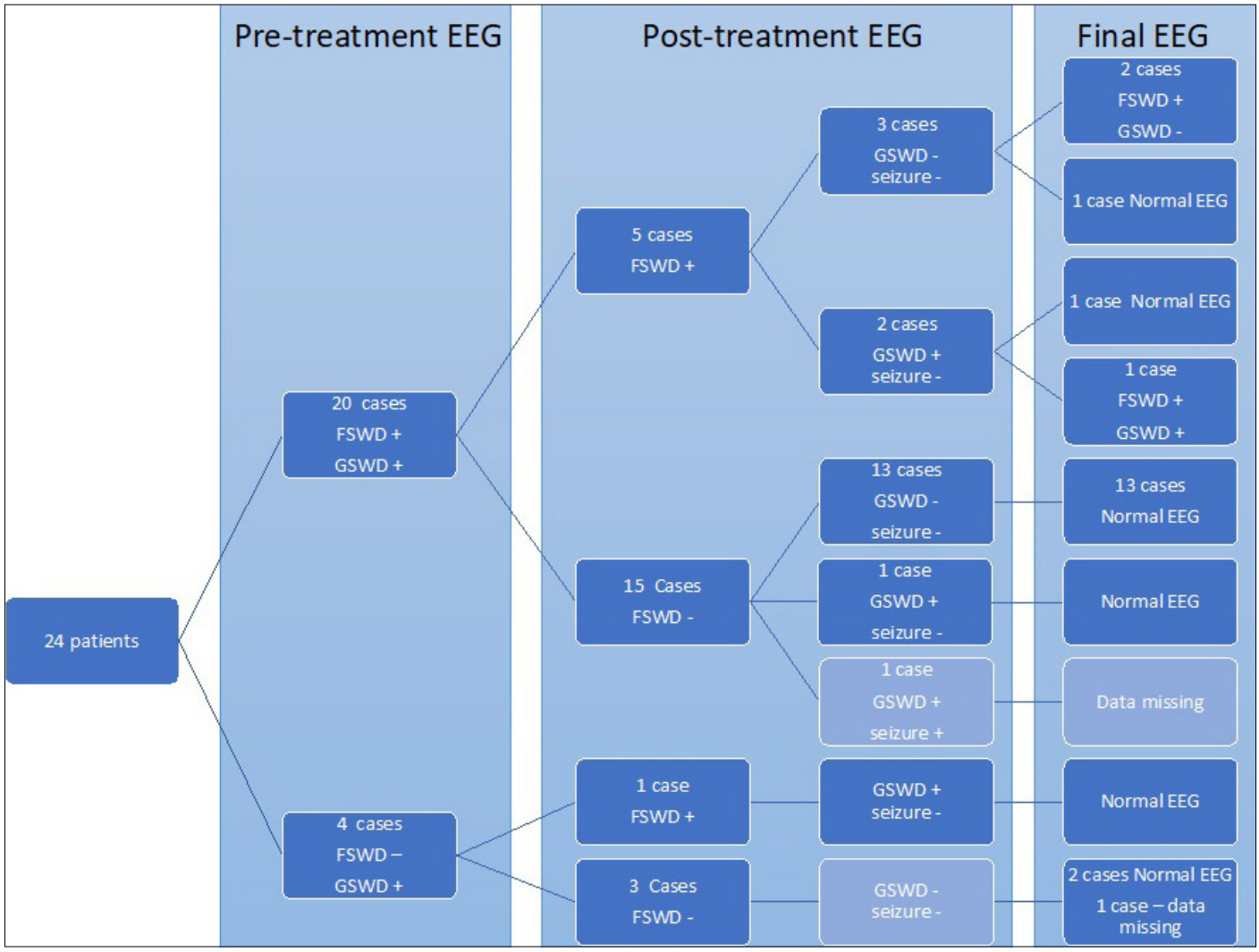

Figure 1. Presence of FSWDs on pre-treatment and post-treatment EEGs (FSWDs: focal spike-wave discharges; GSWDs: generalized spike-wave discharges; *Two patients had only one EEG after the onset of treatment).

DISCUSSION

Several studies were conducted to evaluate the prognosis of patients with CAE. Since the diagnostic criterias change over time, the data in the literature are variable and heterogeneous. Here, we presented the clinical features and prognosis of 24 patients with CAE, applying the latest definition of ILAE (5).

The mean age of seizure onset was found to be 6.7 which is in accordance with the peak age of onset of 6–7 (7). The range for age of seizure onset was 4.3–11 years-of-age in our series. The typical age at onset was 4–10 in the literature, however, a broader range of 2–13 years-of-age was also reported (5).

We obtained seizure control in 95.8% of the children, similar to the rate reported by Grosso et al (8). No relapses occurred either in our study or the study of Grosso et al. (8). This data is consistent with previous suggestions that absence seizures disappear with age in more than 90% of the cases (7). Furthermore, we found that seizure control was obtained within 6 months in 62.5% of children. The rate of obtaining seizure control within 6 months of treatment was stated as 70.2%(9) and 83%(10) in the literature. However, seizure relapses were detected during the long-term follow-up in both studies.

In our study, the treatment was ceased in 79.2% of the children. These children were seizure-free for a mean of 3.2 years (1.4–6.6) when the treatment was halted. The rate of cases without treatment at final follow-up was reported as 81–82% in previous studies (8,9). The higher rates in these studies could be explained by their cohorts' older mean age and/or longer follow-up duration. In another study, ASM was discontinued in 61% of cases, and 17% of these patients had seizure recurrences. However, cases with generalized tonic-clonic seizures were also included in this cohort (11). The mean treatment duration was reported as 2.2 and 3.5 years in the literature (8,12) which are similar to our findings (3.6 years).

Previous research used various definitions for terminal remission. Trinka et al. reported a seizure freedom rate of ≥2 years, with or without treatment, as 43%(13). Sinclair et al. stated that 76% of their patients were seizure-free 2 years after the initiation of ASMs (10). In the study of Callenbach et al. (9), 83.7% of the cases had no seizures for more than 5 years. Grosso et al. (8) and Martínez-Ferrández et al. (12) defined terminal remission as at least 1 year without seizures and ASMs. Terminal remission rates were 78.8% and 82% in these studies, respectively. In our study, the terminal remission rate of at least 1 year without seizure and ASMs was 62.5%. Since remission of this syndrome is age-dependent, our cohort being relatively younger compared to these studies could explain this rather lower rate of remission. For example, in another study, the remission rate was 49.4% with a mean follow-up duration of 5.5. years (2).

The GSWDs and absence seizures disappeared on all post-treatment follow-up EEGs in 79.2% of the cases. At the final follow-up, GSWDs

persisted only in two patients (8.3%). The FSWDs were present in 83.3% of patients during their pre-treatment EEGs. However, in 75% of them, these focal findings resolved following the onset of treatment. Previous literature reports that 48.6% of the patients had normal EEGs at the 6th month mark of treatment, moreover, 5.4% of patients only had focal abnormalities (9). In another study, it was stated that 22.7% of patients still had abnormal EEG findings at the final follow-up (12). However, the characteristics of abnormal EEG findings weren't defined in this study. This rate is comparable with our data that 83.3% of the cases had normal EEGs at the final follow-up.

We also analyzed the electroclinical factors that may potentially affect the treatment outcome in CAE. In our cohort, a higher rate of early seizure remission was found to be associated with having absence seizures without motor components. On the other hand, Kessler et al. reported that patients having absence seizures with pause/stare and eye involvement but no motor automatisms (face automatisms, hand automatisms) had worse treatment outcomes (3). However, we could not separately investigate the effects of motor components on treatment outcomes due to the limited study size. Dlugos et al. associated the treatment success with the longer duration of the individual's shortest seizure (4). However, we were not able to demonstrate such an association in our study. One of the reasons for this discrepancy may lay in the slight difference in the inclusion criteria; we defined absence seizures as GSWDs lasting ≥4 seconds accompanied by a clinically detectable absence seizure, whereas Dlugos et al used a slightly shorter minimum of 3 seconds.

Finally, two patients had persisting EEG abnormalities and late or no seizure remission. Both of them had absences accompanied by motor components. These were consistent with our findings that having absence seizures without motor components and repetitively normal post-treatment EEGs were associated with early seizure remission. In their pre-treatment EEGs, bilateral independent frontal FSWDs, and, both symmetric and asymmetric GWSDs were found during sleep. However, since these features were present in the majority of the patients, we cannot claim that they point toward a worse prognosis.

There are several limitations of this study. The study's retrospective nature and small sample size make it difficult to draw firm conclusions. Moreover, a formal neuropsychological evaluation was not performed.

CONCLUSION

This study confirms that CAE has a favorable prognosis with seizure control obtained in the majority of the cases and more than half of them were obtained within 6 months following the initiation of treatment. Moreover, having an absence seizure without motor components and repetitively normal post-treatment EEGs appear to be associated with a higher rate of early seizure remission. More studies using the latest diagnostic criteria with a larger number of patients are required to delineate the electroclinical features that influence the treatment outcome.

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