

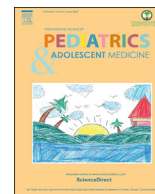
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Childhood absence epilepsy: Electro-clinical manifestations, treatment options, and outcome in a tertiary educational center

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ABSTRACT

Purpose and Background: To evaluate the electro-clinical manifestations and outcomes of children with absence epilepsy at a tertiary center in Saudi Arabia.**Methods:** This retrospective study reviewed the medical and EEG records of patients who were diagnosed to have CAE as per the International League Against Epilepsy (ILAE) definition for CAE. The study was conducted in the pediatric neurology clinic of King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia, between January 2000 and December 2019. Patients who did not meet (ILAE) criteria, lost follow-up, and those who did not receive treatment at KKHU were excluded. Data regarding the patient's disease, electro-clinical manifestations, anti-seizure medication response, and outcomes were collected.**Results:** A total of 35 patients, with an average age at diagnosis of 7 ± 2.1 y, were included in the study; among them, 51.4% were female and approximately 48.6% presented with a family history of epilepsy. Regarding clinical features, all patients experienced staring and altered awareness, 94.2% had less than 20 spells per day at the time of diagnosis, and 65.7% were provoked by the hyperventilation test. Regarding EEG findings, all patients had bilateral, symmetrical, and synchronous discharges in the form of regular 3 Hz spike-and-wave complexes, and 94.3% had a generalized initial ictal discharge. Also, 22.8% had eye fluttering with electrographic seizures. Ethosuximide (ESM) was used as the drug of choice in 45.7% of the patients. Regarding clinical outcomes, 94.3% had their disease clinically controlled, and 80% had a normalized EEG after few months of starting anti-seizure medication. Finally, 37.2% experienced complete remission of epilepsy after 3–5 y; however, one patient developed juvenile myoclonic epilepsy.**Conclusion:** This study described the electro-clinical manifestations of patients with childhood absence epilepsy and outcomes. Furthermore, early diagnosis and prompt treatment of childhood absence epilepsy improve treatment outcomes.© 2021 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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1. Introduction

Childhood absence epilepsy (CAE), also known as petit mal seizures, is a common pediatric epilepsy syndrome, accounting for approximately 10–17% of all childhood epilepsies, with an annual incidence of 8 per 100,000 in healthy school-aged children (a peak around 6–7 years) [1,2]. Additionally, being female and having a first-degree relative with a history of seizures increases the risk of CAE [3,4]. Typical absence seizures manifest as transient impairment of awareness, staring, blinking, and less commonly, various forms of automatism. Seizures are often activated by

hyperventilation (HV), with a mean duration of 9–10 s, occurring multiple times per day. Approximately 25% of seizures last for less than 4 s, and approximately 10% last longer than 20 s [5–7].

Electroencephalography (EEG) should be performed with intermittent photic stimulation (IPS) while the patient is sleep-deprived and hyperventilated to increase the likelihood of identifying an absence seizure. The characteristics of CAE on EEG are bilateral, symmetrical, and synchronized 3 Hz spike-wave complex discharges during the attack, which begin and end abruptly. Interictal findings are mostly normal; however, occasional generalized spike-wave discharges or focal abnormalities are common. This finding represents an EEG marker for CAE [5,8–10]. Treatment usually includes different anti-seizure medications, including ethosuximide (ESM), valproic acid (VPA), lamotrigine (LMT), and levetiracetam (LEV); among which, ESM is the recommended first-line therapy [11,12]. Early diagnosis and appropriate treatment lead to an excellent prognosis of CAE [13]. Most patients experience remission without major sequelae by early puberty; however, some children may develop persistent cognitive or psychiatric comorbidities [14–18]. Additionally, some patients are at risk for developing another type of seizure, such as juvenile myoclonic epilepsy [6]. Researchers have investigated CAE; however, information regarding electro-clinical manifestations and outcomes of patients with CAE remain unclear. Therefore, this study aimed to investigate the electro-clinical manifestations and outcomes of patients in Saudi Arabia.

2. Materials and methods

2.1. Study design

This retrospective study reviewed the charts of children with CAE who were followed up in the pediatric neurology clinic of King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia, between January 2000 and December 2019, which is a tertiary center; however, it accepts referral from general pediatric and university employee health clinic.

Children between 4 and 10 years of age, who had CAE with a normal neurologic examination, brief and frequent absence epilepsy, and EEG ictal discharges of regular 3 Hz spike-and-wave complexes (based on the International League Against Epilepsy (ILAE) definition) who were followed up for at least one year, were included in the study. Children with other types of seizures and who did not meet (ILAE) criteria or lost follow-up were excluded. Terminal remission of seizures was defined as no seizures within a period of one year with no treatment. Cognitive development was assessed with each visit through school performance reported by parents. Patients with cognitive or behavioral difficulties were referred to other specialties for assessment and management.

2.2. Data collection

Data were collected from the patients' medical and EEG records which were encoded in an Excel sheet. Data included age at diagnosis and follow-up, school performance before and after treatment, clinical manifestations, EEG findings, and anti-seizure medications. Additionally, the clinical outcomes of each patient were reported.

2.3. Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). All numerical variables were analyzed and described as means and standard

deviations. On the other hand, categorical variables were analyzed as counts and percentages. Statistical significance was set at $P < .05$.

2.4. Ethical considerations

This study was approved by the Institutional Review Board of the College of Medicine, King Saud University, Riyadh, Saudi Arabia (IRB: No. E–20–4685); additionally, the study was conducted following the Declaration of Helsinki for human studies. Informed consent was waived due to the retrospective nature of the study. Confidentiality of the data was ensured for all participants.

3. Results

A total of 35 patients were included in the study. Information regarding the clinical manifestations, EEG findings, and outcomes of these patients are described below.

3.1. Demographics and clinical characteristics of patients

Among the 35 patients, 18 (51.4%) were females and 17 (48.6%) were males. The average age of onset was $7 (\pm 2.1)$ years, ranging from 4 to 12 years of age. Additionally, 12 patients (34.3%) were in kindergarten at the time of diagnosis; furthermore, 17 (48.5%) had good school performance before diagnosis. Finally, 25 patients (71.4%) experienced no decline in school performance after initiating the therapy.

Among the cohort, two patients (5.7%) had a history of febrile seizure, and 17 (48.6%) had a positive family history of epilepsy. Furthermore, one patient had learning disabilities while another had speech delay; the remaining patients had normal developmental history.

Different clinical manifestations were observed in this cohort, with most patients manifesting more than one feature. All patients had staring episodes and altered awareness, while seven patients (20%) had eye blinking. The descriptions of the episodes were evaluated. Among the cohort, 33 patients (94.2%) had less than 20 episodes per day at the time of diagnosis; additionally, 27 patients reported a duration of < 5 s per spell.

Furthermore, the HV test was performed in 27 patients (77.1%). Clinical seizures were provoked by HV in 23 patients (65.7%). [Table 1](#) summarizes the demographic and clinical characteristics of the patients.

3.2. Electroencephalography (EEG) features

EEG findings were reported for all patients. Thirty-four patients (97.1%) had normal background activity. Generalized interictal discharges (94.3%) were bilaterally symmetric and synchronous in the form of regular 3 Hz spike-and-wave complexes. Twenty-nine patients (82.9%) had a discharge duration of less than 10 s. Additionally, 22 patients (62.9%) experienced seizures during HV, while IPS provoked electrographic seizures with no clinical manifestations in three patients (8.6%). On the other hand, 17 patients (48.5%) had electrographic seizures with clinical manifestations, including eyelid fluttering, staring, eye blinking, altered awareness, and automatism ([Table 2](#)).

3.3. Anti-seizure medications (ASMs)

Most patients (16, 45.7%) were prescribed ESM, followed by VAP in 13 patients (37.2%). Additionally, 31 patients (88.5%) responded

Table 1
Demographics and clinical characteristics of the 35 patients.

		Number of patients	Percentage
Gender	Male	17	48.6
	Female	18	51.4
School performance before treatment	Good	17	48.5
	Poor	6	17.2
Decline in school performance after treatment	Preschooler	12	34.3
	Yes	10	28.6
Developmental history	No	25	71.4
	Normal	33	94.2
	Learning disability	1	2.9
Family history of epilepsy	Speech delay	1	2.9
	Yes	17	48.6
Number of spells at diagnosis (per day)	No	18	51.4
	1–20	33	94.2
Duration of spell at diagnosis (seconds)	>20	2	5.8
	<5	27	77.1
	11–20	6	17.1
Provoked by hyperventilation (bedside)	>20	2	5.8
	Yes	23	65.7
	No	4	11.4
Clinical manifestation	Not done	8	22.9
	Staring and altered awareness	35	100
	Eye blinking	7	20
	Generalized tonic-clonic movement	4	11.4
	Myoclonic jerks	4	11.4
	Automatism	2	5.7

Table 2
EEG features.

		Number of patients	Percentage	
The seizure was recorded during	Hyperventilation	22	62.9	
	Awake state	6	17.1	
	Sleep	4	11.4	
	Intermittent photic stimulation	3	8.6	
Normal background activity	Yes	34	97.1	
	No	1	2.9	
The initial inter-ictal discharges	Generalized	33	94.3	
	Focal (fragments)	2	5.7	
	Yes	35	100.0	
Bilateral, symmetrical, and synchronous discharges of regular 3 Hz spike-and-wave	1–10 s	29	82.9	
	Duration of the generalize 3 Hz spike-and-wave discharges	11–20 s	1	2.9
	More than 20 s	5	14.2	
Electrographic seizures with clinical features (occurred in 17 patients = 48%) ²	Eye lid fluttering	8	22.8	
	Staring	4	11.4	
	Eye blinking	2	5.7	
	Altered awareness	2	5.7	
	Automatism	1	2.9	
	Electrographic seizures without clinical features	18	51.5	
Provocation by hyperventilation (during EEG recording)	Yes	22	62.9	
	No	8	22.9	
	Not done	5	14.2	
Provocation by photic stimulation (during EEG recording)	Yes	3	8.6	
	No	29	82	
	Not done	3	8.6	

to ASM monotherapy, while four had poor response and required additional ASM.

3.4. Outcome

The majority of the patients, 33 (94.3%), had their disease clinically controlled, and 28 patients (80%) had a normalized EEG after starting anti-seizure medication. Uncontrolled seizures or abnormal EEG findings were attributed to poor compliance with drugs. Twelve patients (34.3%) achieved complete remission of epilepsy after 1 y of discontinuing medications. However, most of the remaining patients had controlled clinical seizures for 2–3 y, with normal EEG, but required maintenance with ASM. Thirty

patients (85.6%) had good school performance, while five patients (14.9%) had poor school performance (Table 3).

4. Discussion

Few studies have investigated the electro-clinical features of CAE. Therefore, our study aimed to explore the electro-clinical manifestations and outcomes of CAE in a cohort of 35 children treated at a tertiary center.

We found a higher prevalence of CAE in female patients compared to male patients, with a mean age of 7 (±2.1) years. Additionally, we found that 48.6% of the patients had a family history of epilepsy and 5.7% had a history of febrile seizures, which

Table 3
Anti-seizure medications and outcome of the 35 patients.

		Number	Percentage
Monotherapy		31	88.6
Polytherapy		4	11.4
Anti-seizure medications	Ethosuximide	16	45.7
	Valproic acid	13	37.2
	Levetiracetam	2	5.7
	Ethosuximide and Levetiracetam	1	2.85
	Levetiracetam and Lamotrigine	1	2.85
	Ethosuximide, Levetiracetam, and Valproic acid	1	2.85
	Valproic acid and Lamotrigine	1	2.85
	Valproic acid	1	2.85
	Levetiracetam	1	2.85
	Ethosuximide	1	2.85
	Valproic acid and Levetiracetam	1	2.85
	No failure	31	88.6
	Clinically controlled seizure	Yes	33
No		2	5.7
Normalization of EEG (after few months of starting ASM)	Yes	28	80
	No	7	20
Complete remission of epilepsy	Yes	12	34.3
	No	23	65.7
Total duration from onset to final remission (for patient who had Complete remission of epilepsy)	3–5 years	11	31.4
	>5 years	1	2.9
School performance after one year of management	Still on ASM	23	65.7
	Good	30	85.6
	Poor	5	14.9

is consistent with the results of the study by Sadlier et al. [5] who found that 19% of their patients had a history of febrile seizures; these results indicate the genetic propensity of CAE. However, genetic testing is not a routine procedure for CAE; therefore, it was not included in this cohort. Additionally, a previous study found that HV induced seizures in 83% of children, and IPS induced absence seizures in 21% of children [5]. In this study, we observed that HV provoked seizures in two-thirds of the patients; however, IPS induced seizures less frequently.

We found different clinical manifestations in our patients, with most presenting with more than one feature. All patients presented with staring and altered awareness; on the other hand, eye blinking, generalized tonic-clonic seizures, myoclonic movement, and automatism were less frequently reported symptoms, which is consistent with a previous study [7].

Based on the information taken from parents and notes from the chart during the follow-up, we found that, the most of patients had <20 spells per day at the time of diagnosis with two-thirds reporting a duration of <5 s per spell. However, no previous study has reported similar findings.

Similarly, Sadleir et al. [5] demonstrated a regular 3-Hz generalized spike-and-wave on the EEG; however, approximately only half of their patients presented generalized interictal discharges while most of our patients presented with this finding.

Additionally, 82% of patients presented with electrographic seizures with clinical features lasting for an average duration of 9.4 s. The clinical features are comprised of an arrest of activity, followed by eyelid fluttering, then eye opening and staring, altered awareness, and automatisms. On the other hand, 48% of the patients had electrographic seizures, with clinical features lasting less than 10 s, including eyelid fluttering followed by staring, altered awareness, and less commonly, automatism and eye blinking. In addition, most seizures were recorded during HV and less commonly with IPS, which is consistent with the previous study [5].

Three anti-seizure medications are commonly used as first-line agents for CAE: ESM, VPA, and LTG [19]. Among them, ESM is the recommended first-line therapeutic agent for most children with CAE [11].

Glauser et al. provided class I evidence for the use of ESM as the optimal initial treatment for CAE. Additionally, they found that ESM and VPA were more effective initial monotherapy agents for CAE compared to LTG [12].

Similarly, Berg et al. assessed the long-term progression of patients according to the initial treatment administered (VPA or ESM). Their study revealed that patients treated with ESM maintained a higher rate of full remission compared to those treated with VPA [20]. In our study, most patients responded to a single ASM; particularly, most used ESM as the first-line therapeutic agent, which showed a high rate of seizure control and remission; this was followed by VPA. These findings are consistent with those of previous studies.

The terminal remission rate for CAE is high; however, the methodology and definition used in each study affect the result. In this study, terminal remission was defined as a period of one year with no seizures without treatment. We found a modest terminal remission rate (34.3%) compared to previous literature [13]. This discrepancy in results can be attributed to heterogeneity between the studies in inclusion criteria, methods, follow-up length, and outcome definitions. Regarding the total duration of the disease, a universally accepted criteria for treatment duration remains controversial; generally, a period of 1–2 y without seizures and normal EEG readings is recommended [21]. In our study, most of the patients had complete remission from epilepsy after 3–5 y; however, a small group had epilepsy for more than five years, similar to previous literature [22]. This indicates the necessity of adequate long-term follow-up, despite the good prognosis of CAE, especially in patients with an initially poor response. Early diagnosis and prompt treatment improve the prognosis and outcomes of patients with CAE. According to a case series, approximately 38% of patients with CAE can develop psychosocial, academic, or professional problems [23]. In our study, most patients had good school performance; the patients with poor school performance were already performing poorly before diagnosis, while the remaining participants were in kindergarten.

This study has some limitations. First, it is a retrospective study with a small sample size and conducted at a single center; therefore, the generalizability of the results may be limited. Second, genetic testing was not performed. There was no formal and proper neuropsychological assessment for the group of patients with learning disabilities.

5. Conclusion

Absence epilepsy is a common childhood epilepsy syndrome. Early diagnosis and prompt management help improve patient outcomes. Future prospective studies with a larger sample size are warranted to better understand the electro-clinical features and treatment outcomes of the disease.

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Declaration of competing interest

There are **no** conflicts of interest to declare.

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Visual abstract

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