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Risk Factors for Seizure Recurrence After Antiseizure Medication Withdrawal in Children With Childhood Absence Epilepsy

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Research Article

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Abstract

Objective

To explore the potential predictive risk factors for seizure recurrence in children with childhood absence epilepsy (CAE) following antiseizure medication withdrawal.

Methods

A retrospective study was performed on 82 pediatric patients diagnosed with CAE at the Department of Pediatrics, Qilu Hospital of Shandong University. All patients maintained a 2-year seizure-free period after standardized antiseizure treatment and discontinued medication for a minimum of 6 months. Subjects were stratified into a recurrence group and a non-recurrence group according to the presence or absence of recurrent seizures after drug tapering and discontinuation. Univariate analyses, chi-square tests, and binary logistic regression models were applied to identify potential predictive risk factors for seizure recurrence relapse.

Results

Among the 82 enrolled children with CAE, 17 patients experienced seizure recurrence, corresponding to an overall recurrence rate of 20.73% (17/82). Logistic regression analysis demonstrated that interictal electroencephalogram (EEG) abnormalities, comorbid attention-deficit hyperactivity disorder (ADHD), and EEG abnormalities after medication withdrawal were potential predictive risk factors for seizure recurrence in children with CAE (all $P < 0.05$).

Conclusion

Interictal EEG abnormalities, comorbid ADHD, and post-withdrawal EEG abnormalities independently elevate the risk of seizure relapse after medication withdrawal among children with CAE. Clinicians should closely monitor patients presenting these high-risk indicators and establish individualized management protocols at an early stage to reduce the likelihood of seizure recurrence.

1. Introduction

For symptoms at presentation, physical exams and lab results.Childhood absence epilepsy (CAE) is an idiopathic generalized epilepsy (IGE) syndrome predominantly characterized by typical absence seizures, with complex pathogenesis involving multiple genetic variants and disrupted cerebral network function[1][2][3][4]. Children with CAE typically present with brief episodes of impaired awareness described as "staring spells". The hallmark electrographic feature is diffuse, generalized spike-and-wave discharges at

a frequency of 2.5–5.5 Hz[5]. Current clinical management of CAE relies on antiseizure medications (ASMs), which yield satisfactory seizure control for most patients. Nevertheless, a subset of children experience seizure relapse after complete drug withdrawal. This retrospective analysis aimed to identify clinical variables predictive of post-discontinuation seizure recurrence in CAE patients. Early recognition of these potential predictive risk factors may assist clinicians in optimizing timing for medication tapering and provide evidence-based guidance for therapeutic decision-making, highlighting substantial clinical value for prognosis stratification.

2. Materials and Methods

2.1 Study Population

A total of 82 pediatric patients with CAE diagnosed at the Department of Pediatrics, Qilu Hospital of Shandong University between April 2017 and April 2023 were included in the study. The age at onset ranged from 4 to 10 years.

Inclusion Criteria [5]:

1. Children with CAE were aged 4–10 years at diagnosis and presented with typical absence seizures.
2. All CAE patients underwent 3-hour video electroencephalography (vEEG) monitoring covering wakefulness and sleep states. Standardized hyperventilation and photic stimulation were performed in each subject, and typical absence seizures were captured during monitoring with generalized 2.5–5.5 Hz spike-and-wave discharges on EEG.
3. Enrolled children completed brain magnetic resonance imaging (MRI), computed tomography (CT), electroencephalography (EEG), and other relevant auxiliary examinations, and received standard treatment with anti-seizure medications (ASMs).
4. No obvious abnormalities were identified on brain MRI other auxiliary examinations in enrolled patients.
5. Antiseizure medication withdrawal was permitted only for enrolled children who remained seizure-free for more than 2 years after the last seizure under standard treatment, with no recurrence of typical absence seizures on EEG, and with a medication tapering period longer than 6 months.
6. All patients were followed up for at least 1 year, with routine EEG examinations scheduled at 1 month, 6 months, and 12 months after complete withdrawal of anti-seizure medications.All EEG abnormalities included in the analysis occurred before the first seizure recurrence.Children with seizure recurrence during medication withdrawal should undergo EEG examination immediately.

Exclusion criteria:

1. Presence of any of the following seizure types: prominent myoclonic seizures, prominent eyelid myoclonia, myoclonic-absences, atonic seizures, tonic seizures, atypical absence seizures, focal impaired awareness seizures.
2. Diffuse background abnormalities on EEG.
3. Age at onset inconsistent with the inclusion criteria.
4. Moderate to severe intellectual disability.
5. Cognitive stagnation or decline. Low cerebrospinal fluid (CSF) glucose and/or pathogenic variants in *SLC2A1* (testing is not required in most cases but is strongly recommended for patients with microcephaly and/or mild intellectual disability)

Relapse was defined as the reappearance of typical absence seizures after medication withdrawal in children, excluding myoclonic seizures, generalized tonic-clonic seizures and other seizure typesPatients were divided into a non-relapse group (n = 65) and a relapse group (n = 17) based on whether they had experienced a relapse. The non-relapse group consisted of 20 male and 45 female, with a mean age at onset of (6.34 ± 1.35) years; the relapse group consisted of 7 male and 10 female, with a mean age at onset of (6.33 ± 1.54) years.

2.2 Clinical Variable Assessment

Clinical data were systematically extracted from medical records, including gender, age at onset, age at medication withdrawal, presence of interictal EEG abnormalities, persistent typical absence seizures after 6 months of ASMstreatment, comorbid ADHD, ASM streatment duration ≥ 4 years, combined ASMs treatment, EEG abnormalities after medication withdrawal, and personal history of febrile seizures. All variables were analyzed for their association with post-withdrawal seizure recurrence.

2.3 Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were expressed as mean ± standard deviation. Categorical clinical variables were compared using chi-square tests. Variables with statistically significant associations in univariate analyses were entered into a binary logistic regression model to screen potential predictive risk factors for seizure recurrence relapse. A two-tailed P value < 0.05 was defined as statistically significant.

3. Results

3.1 Baseline Demographic Overview

Of the 82 CAE participants, 65 exhibited no seizure recurrence after drug withdrawal: 20 males (30.77% of non-recurrent patients) and 45 females (69.23%). Seventeen patients developed recurrent seizures, including 7 males (41.18% of recurrent patients) and 10 females (58.82%).

3.2 Comparison of Demographic Characteristics Between Groups

Demographic comparisons between the recurrence and non-recurrence groups are summarized in Table 1. No statistically significant intergroup differences were detected for gender distribution (P = 0.879), age at seizure onset (P = 0.318), or age at medication withdrawal (P = 0.294). Continuous age variables were analyzed via the Mann–Whitney U test.

Table 1
Demographic characteristics of patients with and without seizure recurrence

Characteristic	Recurrence Group (n = 17)	Non-recurrence Group (n = 65)	Total (N = 82)	Statistical Test	P-value
Gender				χ^2 Test	0.879
Male	7	20	27		
Female	10	45	55		
Age at onset	6.338 ± 1.541 Med:6.250 IQR:1.96	6.343 ± 1.347 Med: 6.330 IQR:1.67	6.342 ± 1.379 Med6.330 IQR:1.75	Mann–Whitney U test	0.318
Age at medication withdrawal	9.819 ± 1.543 Med:9.580 IQR:1.91	9.615 ± 1.729 Med:9.330 IQR:2.24	9.658 ± 1.685 Med:9.330 IQR:1.89	Mann–Whitney U test	0.294

Note: P < 0.05 indicates statistical significance.

3.3 Univariate Analysis of Risk Factors for Seizure Recurrence

Univariate association analyses demonstrated three variables significantly correlated with seizure relapse: interictal EEG abnormalities (P = 0.011), comorbid ADHD (P = 0.046), and post-withdrawal EEG abnormalities (P < 0.001). Full univariate comparisons are presented in Table 2.

Table 2
Univariate analysis of clinical factors associated with seizure recurrence

Clinical Factor	Non-recurrence (n)	Recurrence (n)	Total (n)	χ^2 Value	P-value
Interictal EEG				6.512	0.011*
Normal	48	7	55		
Abnormal	17	10	27		
Post-withdrawal EEG				15.580	< 0.001*
Normal	64	11	75		
Abnormal	1	6	7		
Comorbid ADHD				3.989	0.046*
Yes	3	4	7		
None	62	13	75		
History of febrile seizures				0.002	0.962
Yes	4	2	6		
None	61	15	76		
Combined ASMs treatment				3.369	0.066
Yes	19	9	28		
No	46	8	54		
Persistent absence seizures ≥ 6 month post ASMsinitiation				3.279	0.070
Yes	16	8	24		
None	49	9	58		
ASMs treatment duration ≥ 4 years				0.469	0.493
Yes	51	12	65		
None	14	5	17		

Note: P < 0.05 indicates statistical significance.

3.4 Binary Logistic Regression for Independent Predictors

All variables with P < 0.05 in univariate testing were incorporated into a binary logistic regression model to identify potential predictive risk factors for seizure recurrence. As shown in Table 3, interictal EEG abnormalities (OR = 4.788, 95%CI: 1.148–19.963, P = 0.032), comorbid ADHD (OR = 9.141, 95%CI: 1.375–

60.775, P = 0.022), and post-withdrawal EEG abnormalities (OR = 74.509, 95%CI: 5.963–931.048, P < 0.001) emerged as potential predictive risk factors for seizure recurrence in children with CAE.

Table 3
Binary logistic regression analysis of potential predictive risk factors for seizure recurrence

Variable	B	Standard Error	Wald χ^2	P-value	Odds Ratio (OR)	95% CI for OR
Interictal EEG abnormality	1.566	0.728	4.621	0.032*	4.788	1.148–19.963
Comorbid ADHD	2.213	0.967	5.241	0.022*	9.141	1.375–60.775
Post-withdrawal EEG abnormality	4.311	1.288	11.194	< 0.001*	74.509	5.963–931.048
Constant	−3.636	2.153	2.854	0.091	0.026	—

Note: P < 0.05 indicates statistical significance.

4. Discussion

Idiopathic generalized epilepsies (IGEs) constitute a common group of epilepsy syndromes, accounting for 15%–20% of all epilepsy diagnoses[6][7]. The ILAE updated its classification framework for IGEs in 2017[8], and refined diagnostic definitions for four core absence-related IGE syndromes in 2022: CAE, juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone[5]. Among these, CAE represents the most prevalent subtype, responsible for 10%–15% of all pediatric epilepsy cases[9]. First-line ASMs for CAE include ethosuximide, valproate, and lamotrigine[6][10]. While modern ASMs achieve robust seizure control for most patients, post-withdrawal relapse remains a critical clinical challenge. Prior literature has identified multiple poor prognostic markers for CAE, including concurrent generalized tonic–clonic seizures, myoclonic absences, photosensitivity, onset age younger than 4 or older than 10 years, and a positive family history of generalized epilepsy[11]. Identification of these risk markers enables personalized timing of drug tapering and improves long-term therapeutic outcomes.

Interictal EEG abnormalities are widely validated as a robust predictive biomarker for seizure recurrence across epilepsy cohorts, consistent with the present study's findings. In our cohort, 27 children demonstrated abnormal interictal EEG recordings, of whom 10 experienced seizure relapse. Multivariate regression confirmed interictal EEG abnormalities as an potential predictive risk factors for seizure recurrence (OR = 4.788). Occipital intermittent rhythmic delta activity (OIRDA), a specific EEG variant, remains controversial regarding prognostic implications; several prior studies suggest OIRDA may correlate with favorable long-term outcomes rather than elevated relapse risk[12][13].

EEG abnormalities detected during or after medication tapering have gained increasing attention as prognostic indicators. Reported overall relapse rates after ASMsdiscontinuation range from 12% to 67% across epilepsy populations[14]. Abnormal electrographic findings during drug withdrawal are repeatedly associated with higher relapse likelihood[15]. A meta-analysis of 703 patients by Yao et al. demonstrated significantly higher recurrence rates among individuals with abnormal EEG during tapering[16]. In our sample, only 1 of 7 children with abnormal post-withdrawal EEG remained seizure-free, yielding an extremely elevated odds ratio for relapse (OR = 74.509). A strong association observed in this cohort that requires confirmation in larger prospective studies..

ADHD represents the most frequent psychiatric comorbidity in pediatric epilepsy populations[17]. A Chinese cohort study reported a 19.59% higher prevalence of ADHD among children with epilepsy relative to neurotypical peers[18]. Shared neurodevelopmental pathway dysfunction, secondary cognitive impairment related to chronic seizures and sleep disturbance, and behavioral side effects of ASMs are hypothesized to underlie CAE–ADHD comorbidity. The inattentive subtype predominates among dual-diagnosis patients. CAE itself impairs sustained selective attention; comorbid ADHD exacerbates inhibitory control deficits and persistent cognitive dysfunction. A prospective neuropsychological assessment documented baseline attention deficits in 36% of newly diagnosed CAE patients, implying shared genetic and circuit-level pathological mechanisms for both conditions[11][19]. Consistent with prior research by Asadi-Pooya et al., our regression model identified comorbid ADHD as a powerful independent predictor of seizure relapse (OR = 9.141)[20]. Attention deficits are frequently overlooked during routine CAE follow-up, even when absence seizures are fully controlled; standardized neurodevelopmental screening and combined behavioral-pharmacological interventions are recommended for dual-diagnosis patients][21].

Consensus has not been established regarding the prognostic impact of demographic and clinical variables including gender, age at onset, age at withdrawal, febrile seizure history, combined ASMs treatment, and prolonged treatment duration[16][20][22][23]. Some cohorts report higher relapse risk among female patients, consistent with the higher female predominance observed in CAE (60%–75% of all cases)[23][24][25][26]. Longer seizure remission duration prior to tapering and monotherapy status have been linked to reduced relapse risk in several longitudinal studies [27][28]. Verrotti et al. reported a 2.5-fold increased recurrence risk for children with a personal history of febrile seizures after ASMswithdrawal[22]. In the current analysis, no significant intergroup differences were observed for gender, onset age, withdrawal age, persistent absences after 6 months of treatment, polytherapy, febrile seizure history, or treatment duration ≥ 4 years (all $P > 0.05$).

In summary, interictal EEG abnormalities, comorbid ADHD, and abnormal EEG after medication withdrawal are three potential predictive risk factors for seizure recurrence in children with CAE after ASMsdiscontinuation. Clinicians should intensify surveillance for patients presenting these risk features. Limitations of this study include its single-center retrospective design, moderate sample size, the small number of relapse events among children with CAE leads to unstable estimates in the multivariable

model, limited scope of collected clinical variables, short post-withdrawal follow-up duration, and inherent recall bias associated with retrospective chart review, which may constrain generalizability and precision of effect estimates. Future prospective, large-sample, randomized controlled studies with extended follow-up are needed to validate our findings. Where feasible, statistical methods such as Firth logistic regression should be applied to provide more robust evidence for determining the optimal timing of ASM tapering and withdrawal in pediatric patients.

Declarations;The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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