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Prognostic implications of persistent interictal epileptiform discharges on antiseizure medication withdrawal in patients with epilepsy in five-year remission

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ABSTRACT

Purpose: Whether patients with epilepsy in long-term remission and interictal epileptiform discharges (IEDs) can stop antiseizure medication (ASM) remains a challenging topic even though multiple studies have investigated ASM withdrawal. This study aimed to estimate seizure relapse and its risk factors in patients with epilepsy in five-year remission and persistent IEDs.

Methods: Patients with epilepsy and persistent IEDs were prospectively recruited from the Affiliated Nanjing Brain Hospital of Nanjing Medical University from Dec.1, 2010 to Dec.30, 2019. All enrolled patients achieved seizure remission for over five years and were divided into the ASM withdrawal and continuous treatment groups according to their personal preference. Seizure outcomes and 24 h video electroencephalogram findings were obtained through clinical visits or telephone interviews every three months until March 31, 2021. The cumulative recurrence rate and its diversity between the ASM withdrawal and continuous treatment groups were tested using Kaplan–Meier analysis. Multivariate Cox regression analysis was performed to explore the independent predictors for seizure recurrence. Relapsed patients were further monitored for their seizure control and prognosis.

Results: A total of 83 patients with epilepsy in five-year remission and persistent IEDs were enrolled in this study, including 41 (49.4%) in the ASM withdrawal group and 42 (50.6%) in the continuous ASM treatment group. During the follow-up with a median time of 36.8 months (range from 18.7 to 104.6 months), the seizure relapse in off-medication patients (43.9%, 18/41) was higher than that in on-medication patients (21.4%, 9/42; $P = 0.031$). In the multivariate analysis model, independent predictors for seizure recurrence were structural-metabolic epilepsy or unknown cause (*HR* = 6.185, 95% *CI* 1.166–32.805) and multiple seizure types (*HR* = 2.807, 95% *CI* 1.051–7.502). ASM withdrawal was not found to be an independent risk factor for seizure recurrence. Of 27 patients with seizure recurrence, 25 were given reinstitution or continuous ASM therapy, whereas two chose sustained observation without medication. At the end of the follow-up, 70.4% (19/27) of recurrence patients were completely free from seizures for at least one year again, and only one patient developed refractory epilepsy.

Conclusion: For patients with epilepsy in five-year remission and persistent IEDs, drug withdrawal may be a rational choice after the individualized assessment of benefits and risks. Furthermore, the independent risk factors for the seizure relapse were structural-metabolic epilepsy or an unknown cause, and multiple seizure types. Finally, patients with epilepsy relapsing after ASM withdrawal could achieve seizure remission again after ASM retreatment.

1. Introduction

Antiseizure medication (ASM) therapy remains the main treatment of epilepsy at present, with 65%–85% of patients with epilepsy becoming seizure-free after receiving appropriate medication treatment [1]. Up to 88% of patients suffer from one or more ASM adverse effects, such as memory impairment and depressed mood [2], resulting in decreased quality of life. Consequently, ASM discontinuation may be

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considered in patients with epilepsy, whose seizures have been completely controlled for a prolonged remission period, typically two to five years without interictal epileptiform discharges (IEDs) [3,4]. Moreover, previous studies have shown that IEDs were a predictive risk factor for seizure relapse and recommended the continuation of medication when making decisions leading to ASM withdrawal [5,6]. To date, ceasing ASMs in the long-term seizure-free patients combined with persistent IEDs remains a controversial topic. Additionally, questions on how long the seizure-free period of these patients should be before the decision is made to withdraw ASMs are present. Thus far, answers to these questions remain widely elusive.

The most common risk factors for seizure relapse are remote symptomatic causes and neurologic examination abnormalities. However, IEDs as a risk factor have yet to be fully studied in the ASM discontinuance literature. The 2013 Italian Guideline on ASM withdrawal recommended the reasonable gradual cessation of ASMs in seizure-free patients if persistent IEDs is the only potential prognostic predictor (level of evidence II, strength of recommendation B) [7]. However, seizure recurrence and its predictive risk factors in these patients remain unclear.

Therefore, this prospective study was designed to investigate seizure recurrence and its risk factors in patients with epilepsy in five-year remission and persistent IEDs. Relapsed patients were further monitored for their seizure control and prognosis. Our findings could provide better evidence regarding ASM withdrawal in patients with persistent IEDs.

2. Materials and methods

The Hospital Institutional Review Board and the Ethics Committee of Nanjing Brain Hospital affiliated to Nanjing Medical University approved the study (application number: 2020–KY008–01). Upon admission, all participating patients were requested to sign an informed consent form if they agreed that their information could be used in this study.

2.1. Patients

Patients with epilepsy who had undergone ASMs therapy during a five-year seizure-free period and persistent IEDs were recruited from neurology clinics of the Nanjing Brain Hospital affiliated to Nanjing Medical University between Dec. 1, 2010 and Dec. 30, 2019. In this study, the term "persistent IEDs" was defined as IEDs findings presented in every 24 h video electroencephalogram (VEEG) monitoring, which was performed at least once a year for more than three consecutive years. IEDs findings were determined in all enrolled patients both during the seizure-free period and at subsequent follow-up visits. IEDs abnormalities in these patients were characterized by focal, multifocal, or generalized sharp waves; spikes; spike-wave complexes; and polyspike-wave complexes, with or without accompanying slow waves. Patients were diagnosed as epilepsy according to the practical clinical definition of epilepsy by the International League Against Epilepsy (ILAE) [8]. Classifications of seizures and epilepsy were determined based on the ILAE 2010 classification [9,10]. Following the ILAE treatment guidelines [11], all patients received proper and standard ASM treatment by monotherapy or polypharmacy, the dosage of which was based on individual condition and drug recommendation. A brain 3.0 T-MRI scan, 24 h VEEG, and hematological, hepatic, and renal function tests were performed in each patient deemed eligible for the study.

The exclusion criteria were as follows: (1) patients with refractory epilepsy or benign epilepsy syndrome, such as Lennox-Gastaut syndrome, West syndrome, benign epilepsy with centrotemporal spikes (BECTs), and genetic epilepsy with febrile seizures plus (GEFS+); (2) patients with underlying malignancy, progressive degenerative disease, or serious systemic illness; (3) patients who underwent epilepsy surgery; (4) pregnant or lactating women; (5) patients with uncertain history of seizures; and (6) patients in poor compliance with medications and follow-up visits.

2.2. Methods

Patients with epilepsy meeting all the inclusion and exclusion criteria above were enrolled. The risks and benefits of drug withdrawal were discussed with all eligible patients and/or their caregivers. All patients signed an informed consent. After patients achieved seizure-free status for at least five years, they were then stratified into two cohorts depending on whether they accepted or refused ASM withdrawal. The ASM doses were slowly tapered off for at least six months. For those taking multiple ASMs, one drug was reduced first, and the other drugs were gradually reduced for at least eight weeks when the first drug had been completely discontinued. A few patients with a low-dose ASM (*e.g.*, taking valproate 0.5 g/day) had a withdrawal period of three months.

All patients were followed up every three months until the end of the study period on March 31, 2021, through telephone or outpatient services. Data on seizure recurrence, seizure-free survival and 24 h VEEG monitoring were collected. Follow-up sessions were continued for relapsed patients after their therapy reinstitution or ASM adjustment. A minority chose to withhold medication because of only one episode and after weighing the benefits and risks.

2.3. Variables

A database was built to record all patient information during the follow-up period. Demographic data and relevant predicted factors were collected as follows: (1) gender; (2) age at seizure onset (years); (3) age at enrollment (years); (4) etiology of epilepsy: idiopathic epilepsy called genetic, symptomatic epilepsy called structural-metabolic, and cryptogenic called epilepsy of unknown cause; (5) seizure type: classified as generalized (including tonic-clonic, tonic, clonic, absence, and myoclonic seizures), focal (with or without impairment of consciousness, or focal to bilateral tonic-clonic seizure), or multiple types based on history; (6) number of seizure types: number of different subtypes described above; (7) epilepsy syndromes; (8) neuroimaging findings: abnormalities on brain MRI significantly associated with epilepsy, such as cortical dysplasia, temporal sclerosis, and hematomas; (9) 24 h VEEG findings: wave types, spatial distribution (focal, unilateral/hemispheric, diffuse symmetrical, generalized and multifocal), and time distribution (sporadic/solitary, paroxysmal, and frequent); (10) family history of epilepsy: first-generation relatives including parents, siblings and children; (11) previous history: febrile seizures, central nervous system infection, brain trauma, intracranial tumor, brain surgery, and other related neurologic conditions; (12) seizure frequency before remission (monthly seizure): average frequency of seizure per month during the first to last seizure; (13) number of episodes before remission: classified into ≤ 10 or > 10 episodes; (14) epilepsy duration before remission (years): period from seizure onset to last seizure; (15) treatment response time (months): period from the start of ASM treatment to the last seizure before withdrawal; (16) seizure-free interval before deciding whether to taper off medication; (17) number of ASMs administered for long-term seizure control: monotherapy or multitherapy; (18) failure history of ASM withdrawal; (19) duration of follow-up; and (20) classification of seizure outcomes in accordance with the duration of the terminal remission: good outcome, at least one year seizure-free at the end of follow-up with/without medication; poor outcome, less than one year seizure-free at the end of follow-up.

2.5. Statistical analysis

Quantitative variables with a normal distribution were expressed as mean values with standard deviations ($\bar{x}\pm s$). Medians with interquartile ranges (*IQRs*) were used to present data without normal distribution. The Mann–Whitney U test was used to compare continuous variables,

and the chi-squared test was used to compare categorical variables. Fisher's exact test was used to compare two independent groups for qualitative parameters. The cumulative time-dependent probability of recurrence was determined using the Kaplan–Meier method, whereas the log-rank test was used to compare overall survival rates between patients in the continuous treatment and ASM withdrawal groups. Independent predictors associated with seizure recurrence and outcomes of five-year-remission patients were identified using stepwise Cox regression analysis. Variables with P values < 0.1 in the univariate analysis were included in the multivariate Cox proportional hazards model. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA), and the survival curve was plotted by GraphPad Prism 7 (GraphPad software Inc., La Jolla, CA, USA). $P < 0.05$ (two-tailed) was considered significant.

3. Results

3.1. Demographics and baseline clinical characteristics

A total of 106 patients with epilepsy in five-year remission and persistent IEDs were recruited during the study period. Of these, 83 were eligible, while 23 (21.7%) were eliminated through exclusion criteria, including BECTs and GEFS+ (3 cases), accidental pregnancy (3 cases), and incomplete information (7 cases). In addition, four patients discontinued drugs without medical advice, and six were lost to follow-up, resulting in an actual loss rate of 9.4% (Fig. 1). The majority of patients underwent 24 h VEEG examinations once a year, and only ten (12.0%, 10/83) had examinations twice a year before enrollment. Among the remaining 83 eligible patients, 41 (49.4%) and 42 (50.6%) were classified into the continuous treatment and ASM withdrawal groups, respectively, with a median follow-up time of 36.8 months (range from 18.7 to 104.6 months). A total of 50 male and 33 female patients with ages ranging from 8 years to 72 years (median 23 years) were included. In the continuous treatment group, the epilepsy etiology in 14 patients was structural-metabolic or an unknown cause. For epilepsy syndromes in this group, six patients had generalized tonic-clonic seizures only (EGTCS), one patient had juvenile myoclonic epilepsy (JME), one patient had childhood absence epilepsy (CAE), and one patient had occipital epilepsy. Moreover, there were 16 patients with structural-metabolic or unknown etiology in the ASM withdrawal group, five patients had EGTCS, two patients had JME, and one patient had CAE (Table 1).

3.2. Rate and time of seizure relapse

The Kaplan–Meier analysis results showed that the recurrence rate of five-year-remission patients with persistent IEDs increased over time. The cumulative time-dependent probability of seizure relapse was 7.2%

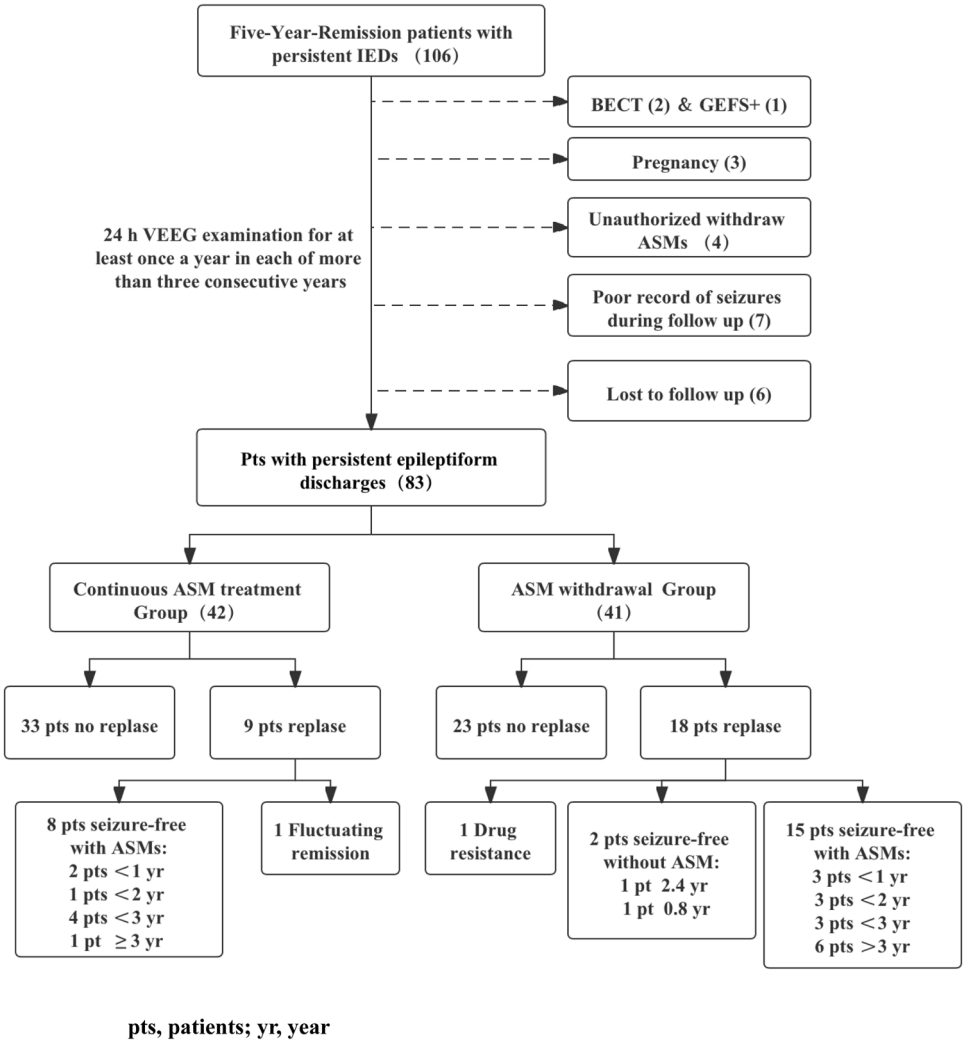

Fig. 1. Patient enrollment flow chat. The patients were divided into ASM withdrawal group and continuous ASM treatment group according to personal preference. pts, patients; yr, year.

Table 1
The clinical characteristics of enrolled patients.

	Total *N* = 83 *N (%)/M (IQR)*	Continuous treatment group *n* = 42 (50.6%) *n (%)/m (IQR)*	ASM withdrawal group *n* = 41 (49.4%) *n (%)/m (IQR)*	*Statistics Values* [a]	*P values*
Female	33 (39.8%)	12 (28.6%)	21 (51.2%)	4.443	*0.035*
Age of onset of epilepsy (years)					
Childhood (0~11y)	32 (38.6%)	14 (33.3%)	18 (43.9%)	0.978	*0.323*
Adolescent (12~17y)	31 (37.3%)	15 (35.7%)	16 (39.0%)	0.097	*0.755*
Adult age (≥18y)	20 (24.1%)	13 (31.0%)	7 (17.1%)	2.185	*0.139*
Age at enrollment (years)	23.0 (17.0~29.0)	25.0 (18.8~29.0)	21.0 (15.0~29.0)	705.0	*0.155*
Epilepsy duration before remission (years)	2.9 (1.0~5.0)	3.3 (1.3~5.0)	2.8 (0.7~5.3)	757.5	*0.198*
Treatment response (months)	12.5 (1.3~48.2)	21.0 (2.4~50.6)	9.3 (0.4~37.2)	757.0	*0.341*
Structural-metabolic epilepsy & Unknown cause	30 (36.1%)	14 (33.3%)	16 (39.0%)	0.291	*0.589*
Epilepsy with generalized tonic-clonic seizures alone	11 (13.3%)	6 (14.3%)	5 (12.2%)	0.079	*0.779*
Juvenile myoclonic epilepsy	3 (3.6%)	1 (2.4%)	2 (4.9%)	0.371	*0.983*
Childhood absence epilepsy	2 (2.4%)	1 (2.4%)	1 (2.4%)	0	*1.000*
Occipital epilepsy	1 (1.2%)	1 (2.4%)	0	0.988	*1.000*
Focal seizures	66 (79.5%)	33 (78.6%)	33 (80.5%)	0.047	*0.829*
Multiple seizure types	37 (44.6%)	17 (40.5%)	20 (48.8%)	0.579	*0.447*
Febrile seizures	14 (17.2%)	8 (19.0%)	6 (14.6%)	0.288	*0.591*
Family history of epilepsy	3 (3.6%)	1 (2.4%)	2 (4.9%)	0.371	*0.983*[#]
Abnormal neuroimaging	25 (30.1%)	13 (31.0%)	12 (29.3%)	0.028	*0.867*
Failure of previous ASM withdrawal	9 (10.8%)	5 (11.9%)	4 (9.8%)	0.099	*1.000*
Seizure frequency before remission (episodes monthly)					
≤ 1	57 (68.7%)	34 (81.0%)	23 (56.1%)	0.958	*0.015*
2~ 3	10 (12.0%)	3 (7.1%)	7 (17.1%)	1.931	*0.293*
≥ 4	16 (19.3%)	5 (11.9%)	11 (26.8%)	2.970	*0.085*
At least ten eiures before remission	39 (47.0%)	17 (40.5%)	22 (53.7%)	1.447	*0.229*
Multiple ASMs	14 (16.9%)	8 (19.0%)	6 (14.6%)	0.288	*0.591*
Seizure-free time(years)	5.3 (5.0~6.4)	5.3 (5.0~6.2)	5.4 (5.1~6.8)	798.5	*0.568*
Seizure recurrence	27/83 (32.5%)	9/42 (21.4%)	18/41 (43.9%)	4.774	*0.029*

[#] = *Chi-squared test (Fisher's exact test)*.

at three months after treatment, and 12.1%, 24.1%, and 30.1% at 6, 12, and 24 months, respectively. Finally, out of 83 patients, 27 relapsed (32.5%), including 18 (43.9%) in the ASM withdrawal group and nine (21.4%) in the continuous treatment group. The difference between the two groups was statistically significant (*log-rank test* $\chi^2 = 4.666$, $P = 0.031$; Fig. 2). The recurrence rate of structural-metabolic epilepsy or epilepsy of unknown cause was 53.3% (16/30), and that of EGTCS was 18.18% (2/11). Two of three patients with JME experienced recurrence, whereas two CAE patients and one patient with occipital epilepsy remained seizure-free (Table 2).

3.3. Risk factors for seizure recurrence

In the univariate analysis, structural-metabolic epilepsy or epilepsy of unknown cause, multiple seizure types, ≥ 4 episodes per month before remission, abnormal neuroimaging, and ASM withdrawal were associated with seizure recurrence in five-year-remission patients with persistent IEDs (Table 2). However, different IEDs characteristics were not associated with seizure recurrence (Table 3). Multivariate Cox regression analysis further revealed that structural-metabolic epilepsy or an unknown cause (*HR* = 6.185, 95% *CI* 1.166–32.805) and multiple seizure types (*HR* = 2.807, 95% *CI* 1.051–7.502) were independent predictors. Nevertheless, ASM withdrawal was not identified as an independent risk factor for seizure recurrence.

3.4. Prognosis of seizure-relapsed patients

Relapse occurred in 27 of 83 patients (32.5%) who were seizure-free for at least five years with persisting IEDs, including 18 (43.9%) in the ASM withdrawal group and nine (21.4%) in the continuous treatment group. The follow-up continued after recurrence for 3.47 ± 2.05 years. Of the 18 patients who relapsed after ASM withdrawal, 16 patients were given reinstitution medication therapy, and two patients chose to suspend medication and continue observation. At the end of follow-up, 70.4% (19/27) of recurrence patients were completely free from seizures for at least one year again, while 78.9% (15/19) were seizure-free for over two years. However, one patient showed fluctuating remission, and only one patient developed refractory epilepsy. Two patients with

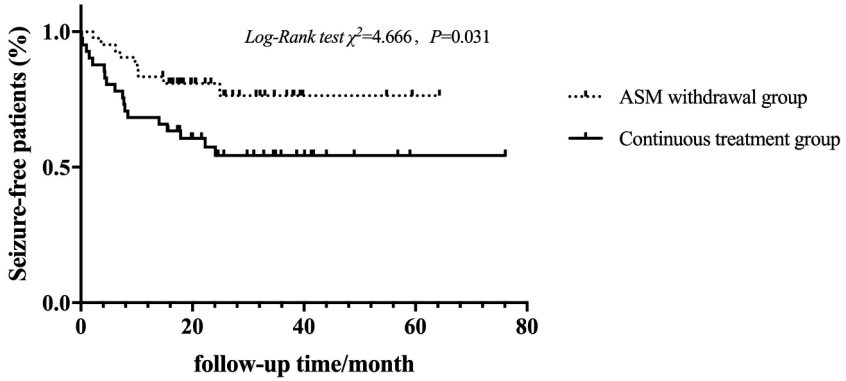

Fig. 2. The cumulative probability of remaining seizure-free in the 5-year-remission patients with IEDs.

Table 2
The univariable predictors of seizure recurrence.

	No relapse	Relapse	Univariate analysis	
	n = 56 (67.5%)	*n* = 27 (32.5%)	*HR (95% CI)*	*P values*
	n (%) / m (IQR)	*n (%) / m (IQR)*		
Female	20 (35.7%)	13 (48.1%)	1.625 (0.762~3.467)	*0.209*
Age of onset of epilepsy (years)				
Childhood (0~11y)	25 (44.6%)	7 (25.9%)	*Ref*	
Adolescent (12~17y)	20 (35.7%)	11 (40.8%)	1.721 (0.666~4.451)	*0.263*
Adult age (≥18y)	11 (19.6%)	9 (33.3%)	2.345 (0.868~6.330)	*0.093*
Age at enrolled (years)	23.1 (16.3~26.8)	25.0 (20.0~31.0)	1.011 (0.982~1.041)	*0.454*
Epilepsy duration before remission (years)	3.0 (1.33~5.0)	2.6 (0.8~5.3)	1.063 (0.969~1.166)	*0.198*
Treatment response (months)	15.1 (0.1~48.6)	10.8 (6.0~37.5)	1.003 (0.993~1.013)	*0.516*
Structural-metabolic epilepsy & Unknown cause	14 (25.0%)	16 (59.3%)	3.467 (1.602~7.503)	*0.002**
Epilepsy with generalized tonic- clonic seizures alone	9 (16.1%)	2 (7.4%)	0.468 (0.111~1.976)	*0.301*
Juvenile myoclonic epilepsy	1 (1.8%)	2 (7.4%)	2.641 (0.618~11.285)	*0.190*
Childhood absence epilepsy	2 (3.6%)	0	–	*1.000*[#]
Occipital epilepsy	1 (1.8%)	0	–	*1.000*[#]
Focal seizures	43 (76.8%)	23 (85.2%)	1.592 (0.550~4.606)	*0.391*
Multiple seizure types	20 (35.7%)	17 (63.0%)	2.519 (1.152~5.508)	*0.021**
Febrile seizures	11 (19.6%)	3 (11.1%)	0.578 (0.174~1.920)	*0.371*
Family history of epilepsy	3 (5.4%)	0	–	*0.547*[#]
Abnormal neuroimaging	13 (23.2%)	12 (44.4%)	2.213 (1.034~4.736)	*0.041*
Failure of previous ASM withdrawal	7 (12.5%)	2 (7.4%)	0.601 (0.142~2.541)	*0.489*
Seizure frequency before remission (episodes monthly)				
≤ 1	42 (75.0%)	15 (55.6%)	*Ref*	
2~ 3	6 (10.7%)	4 (14.8%)	1.584 (0.525~4.778)	*0.414*
≥ 4	8 (14.3%)	8 (29.6%)	2.369 (1.002~5.598)	*0.049*
At least ten seizures before remission	22 (39.3%)	17 (63.0%)	2.155 (0.986~4.711)	*0.054*
Multiple ASMs	9 (16.1%)	5 (18.5%)	1.185 (0.449~3.130)	*0.732*
Seizure-free time (years)	5.4 (5.0~6.6)	5.2 (5.0~6.1)	0.858 (0.643~1.145)	*0.289*
ASM withdrawal	23 (41.1%)	18 (66.7%)	2.354 (1.057~5.243)	*0.036*

[#] =*Chi-squared* test (*Fisher's* exact test), *= Independent risk factors for seizure recurrence significantly at $P < 0.05$ after multivariate analysis.

only one episode chose not to reinstitute therapy based on their personal wishes and physicians' recommendations, and no further seizures occurred during the follow-up period, resulting in clinical remission of 0.8 years and 2.4 years (Fig. 1, Fig. 3). No risk predictor affecting outcome was identified on either univariate or multivariate analyses to further estimate the prognosis of recurrence patients.

Table 3
The relationship between IEDs characteristics and seizure recurrence.

	No relapse	Relapse	Univariate analysis	
	n = 56 (67.5%)	*n* = 27 (32.5%)	*HR (95% CI)*	*P values*
	n (%) / m (IQR)	*n (%) / m (IQR)*		
Wave type				
Sharp	17 (30.4%)	4 (14.8%)	2.087 (0.721~6.036)	*0.175*
spike	1 (1.8%)	1 (3.7%)	2.485 (0.335~18.451)	*0.374*
Sharp slow/spike slow complex waves	44 (78.6%)	21 (77.8%)	0.895 (0.361~2.218)	*0.811*
Polyspike and slow wave complex	3 (5.3%)	2 (7.4%)	1.417 (0.336~5.986)	*0.635*
Multiple types	9 (16.1%)	1 (3.7%)	0.250 (0.034~1.844)	*0.174*
Spatial Distribution				
Focal	15 (26.8%)	7 (26.0%)	1.143 (0.483~2.705)	*0.761*
Frontal	7 (12.5%)	2 (7.4%)	0.254 (0.129~2.294)	*0.406*
Temporal	7 (12.5%)	5 (18.5%)	1.372 (0.519~3.625)	*0.523*
Occipital	1 (1.8%)	0	–	*1.000*[#]
Unilateral/ hemispheric	14 (25.0%)	9 (33.3%)	1.481 (0.664~3.300)	*0.337*
Diffuse symmetrical	12 (21.4%)	6 (22.2%)	1.104 (0.445~2.736)	*0.831*
Generalized	10 (17.9%)	5 (18.5%)	0.999 (0.378~2.642)	*0.999*
Multifocal	5 (8.9%)	0	–	*1.000*[#]
Time Distribution				
Sporadic/solitary	35 (62.5%)	16 (59.3%)	0.904 (0.419~1.948)	*0.796*
Paroxysmal	17 (30.4%)	8 (29.6%)	0.954 (0.417~2.181)	*0.911*
Frequent	4 (7.1%)	3 (11.1%)	1.498 (0.451~4.978)	*0.509*

[#] = *Chi-squared test (Fisher's exact test).*

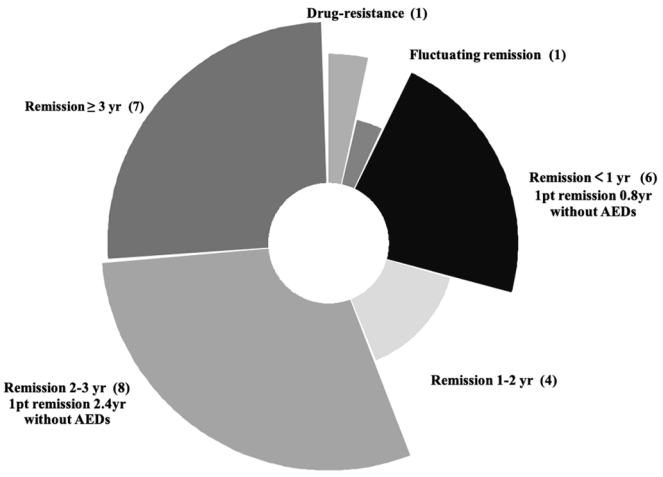

Fig. 3. Epilepsy outcomes in 27 patients with seizure recurrence. pts, patients; yr, year.

4. Discussion

In this prospective study, we investigated adult and pediatric patients in five-year-remission with persistent IEDs over a median follow-

up period of 36.8 months for continuous treatment and ASM withdrawal groups. Our results showed an overall cumulative risk of relapse of 32.5% and a recurrence rate of 43.9% after ASM discontinuation. The present rate of seizure relapse was consistent with a meta-analysis [12] of 13 studies, with 12%–66% upon discontinuation of ASMs, and 34% (95% *CI* 27%–43%) of a mean relapse rate. The total recurrence rates reported in the literature after tapering off ASMs ranged from 22% to 35% [13,14]. Most relapses occurred in the first 12 months (especially in the first six months) and tended to decrease thereafter. Aktekin et al. [15]. reported that the rate of relapse was 52% after 36 months of follow-up in 79 adult patients with a seizure-free period of four years before withdrawal. Therefore, the overall relapse risk of five-year-remission patients with persistent IEDs after tapering off ASMs was not significantly higher than that in previous studies among patients following two seizure-free years. Thus, ASM withdrawal might be considered in those patients after an individualized discussion of risks and benefits.

To date, the largest RCT study of the Medical Research Council ASM withdrawal study was published in 1991[3]. The criterion for inclusion was a seizure-free period of two years on ASMs, and 1013 patients were randomized into either continued drug treatment or slow withdrawal. The seizure recurrence rate continued to demonstrate a high risk in the withdrawal group in the first one to two years (41% in the withdrawal group *vs.* 22% in the continued treatment group). After two years, the hazard ratio inverted, and the withdrawal group no longer exhibited a higher rate of recurrence. Lossius et al. [6]. conducted a double-blind RCT on ASM withdrawal in 149 adult patients with more than two years of remission, and showed no significant difference in seizure recurrence between the treatment withdrawal (15%) and the treatment maintained (7%) groups at 12 months. In addition, the delayed relapse rate was only 6% after a five-year remission period in patients, regardless of whether medication was tapered off after a median of 47 months.

In the present study, we emphatically evaluated the effect of ASM withdrawal on patients with persistent IEDs after having a five-year seizure-free condition. Our results showed that seizure relapse occurred in 43.9% (18/41) of off-medication patients and in 21.4% (9/42) of on-medication patients, with a significantly difference. However, multivariate analysis showed that ASM withdrawal was not an independent risk factor for recurrence (*HR* = 2.374, 95% *CI* 0.937–6.013, *P* = 0.068). In conclusion, ASM withdrawal might increase the risk of early recurrence but has little effect on the overall recurrence risk. Thus far, there is little evidence that continuous treatment could ensure a prolonged seizure-free survival.

Another meta-analysis [14] reported that the overall recurrence risk of patients with symptomatic etiology is higher than that of patients with idiopathic epilepsy, suggesting that the former (including abnormal neuroimaging, neurological deficits, etc.) may increase the relapse risk after ASM withdrawal. Consistent with this result, our results showed that structural-metabolic epilepsy or with unknown cause was an independent risk factor for subsequent seizure recurrence among five-year-remission patients with persistent IEDs (*HR* = 6.185, 95% *CI* 1.166–32.805). Several other studies [4,13,16] also supported this hypothesis of an increasing recurrence risk in definite symptomatic etiology. ASM withdrawal was not advocated in patients with persistent IEDs combined with definite symptomatic etiology. Instead, a prolonged seizure-free period is recommended. Thus, the predictive value of epilepsy etiology for recurrence and prognosis should be emphasized.

Limited neuroimaging studies have focused on seizure recurrence [17]. Our results showed that abnormal neuroimaging findings were associated with seizure relapse, but were not independent risk factors. This finding might be attributed to the small sample size and limited imaging technology of subtle focal structural damage. For example, conventional MRI techniques are insufficiently equipped to visualize small gray matter lesions, and subtle abnormalities, such as early gray matter heterotopia, often remain invisible. The same is true in microvascular malformations. Recent advances in neuroimaging have made accessible new ways of evaluating the complex interaction between genetic and environmental factors that influence structural brain development.

A higher rate of relapse after drug withdrawal has recently been found in patients [18] with more than two seizure types. Consistent with previous studies, we found that multiple seizure types were independent risk factor for seizure recurrence, emphasizing that a comprehensive assessment of epilepsy severity should not ignore seizure types.

Moreover, epilepsy syndrome and epilepsy etiology should always be assessed as predictors of recurrence. Long-term remission was observed in some epilepsy syndromes. Our results showed an 18.18% recurrence rate in patients with EGTCS and a higher relapse risk (66.7%) in patients with JME. However, we found no significant association between epilepsy syndromes and seizure recurrence. These negative results might be associated with the small sample size, suggesting that future studies should include a large number of patients.

Current drug withdrawal studies on the characteristics of IEDs also provide some practical advice to clinicians. Tang L et al. [19]. found that patients with epilepsy and paroxysmal IEDs before withdrawal had a higher relapse rate than those with normal EEG (95% *CI* 1.68–2.95, *P* = 0.00001), whereas no significant difference was observed between the non-paroxysmal and normal groups. The same conclusion was reached in other studies [20,21], suggesting that paroxysmal IEDs may be a risk factor for seizure recurrence. Most studies have demonstrated that epileptiform abnormalities are more predictive of recurrence after withdrawal, but do not compare different wave subtypes of IEDs. Additionally, few studies [22] have reported on the spatial distribution of IEDs, mainly because the IEDs distribution is influenced by the definite etiology, seizure type and epilepsy syndrome, which limits the prediction ability for recurrence after drugs withdrawal. In this study, we found no association between the risk of recurrence and IEDs characteristics.

Previous epilepsy medication withdrawal studies mainly focused on seizure recurrence and its predictive factors. To date, no data have been presented on assessing the long-term outcomes of patients with ASM withdrawal due to a tendency to have very small sample sizes, a high rate of loss, and short duration of follow-up. Despite 32.5% of our patients had a five-year seizure-free status with IEDs relapse, most patients achieved seizure remission again after ASM retreatment with a median follow-up time of 36.8 months. Camfield et al. [23]. reported that 356 of 367 (97%) relapsed children with epilepsy achieved remission again after ASM reconstitution, and less than 1% of those developed refractory epilepsy after continued follow-up for 20 years. A relevant meta-analysis by Schmidt et al. [12]. found that reinstitution of ASMs after recurrent seizures resulted in seizure remission in 64%–91% of patients, and 19% of those were unable to achieve seizure freedom again.

In addition, neurological deficits and poor responsiveness to ASMs in early treatment were common predictors of poor outcome in past studies [24,25]. To investigate the risk factors for poor outcomes after seizure relapse, univariate and multivariate Cox regression analyses were performed in the current study. The results did not show any independent risk factors related to the prognosis of patients with recurrence. Once again, this finding might be due to the small sample size and short follow-up period. Taken together, the majority of patients who relapsed after ASM withdrawal could achieve seizure remission after medication reinstitution or adjustment. Moreover, patients with definite epilepsy etiology were at risk of developing refractory epilepsy although the risk seemed to be very low. For those who had only one episode during or after ASM withdrawal, especially if directly precipitated by withdrawal or the presence of triggers, resuming medication immediately was not needed. In this regard, studies are still needed to further explore the optimal timing and modality of ASM reinstitution in the future.

5. Limitations

To the best of our knowledge, the present study is the only

prospective trial that has investigated seizure relapse and its risk factors in seizure-free patients with persistent IEDs. However, this study has several limitations. First, observational prospective studies can be biased; however, randomized double-blind controlled trials are not possible due to ethical considerations. Second, the number of patients with persistent IEDs was small, which was attributed to its low percentage in seizure-free populations. Therefore, some potential risk factors, such as epilepsy syndrome, could not be assessed precisely. Third, the length of follow-up was short in some patients, and 5.6% patients were lost to follow-up, which might have influenced the result. Moreover, only 27 relapsed patients were followed up in this study, causing difficulties in providing information regarding patients' long-term outcomes and the corresponding predictors. Thus, further investigations, including large, prospective, multicenter studies are warranted to provide complete information regarding the recurrence rate and long-term outcomes in patients with persistent IEDs.

6. Conclusion

The overall relapse risk of five-year-remission patients with persistent IEDs was 32.5%. No evidence showed that continuous ASM therapy guaranteed a prolonged seizure-free for those patients. Thus, drug withdrawal might be reasonable for those patients with epilepsy after undergoing individualized assessment of benefits and risks. Patients with structural-metabolic or with unknown etiology, and with multiple seizure types were at a higher risk of recurrence and required careful tapering off of medication after comprehensive consideration of seizure severity. Thus, ASM withdrawal was not found to be an independent risk factor for recurrence in our study. In fact, most patients with epilepsy who relapsed after ASM withdrawal could achieve seizure remission after medication reinstitution or adjustment.

Declaration of Competing Interest

We declare that we have no financial or personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.11.009.

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