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ORIGINAL ARTICLE

Predictors of Seizure Recurrence after Antiepileptic Drugs Withdrawal: A Prospective Study in Zagazig University Hospitals

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ABSTRACT

Background: Relapsing seizures following discontinuation of anti-seizure drugs (ASDs) has been the focus of several researches in recent years.This research aimed to identify the predictive factors of seizure recurrence after anti-seizure drugs withdrawal among epileptic patients who had achieved two years seizures remission.**Methods**: A total of 60 epileptic patients who had achieved two years seizures remission and began ASDs withdrawal were followed prospectively for one year. The patients were divided into two groups; patients with and without relapsed seizures. Clinical and demographic details were recorded. National Hospital Seizure Severity Scale (NHS3) was used to assess theseverity of epilepsy. Regular Electroencephalogram (EEG) monitoring was done. Anxiety and depressive symptoms were assessed by usinggeneralized anxiety disorder 7 (GAD7) and Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) scales respectively. **Results:** Risk of post-withdrawal relapsed seizures increased with; history of status epilepticus (p=0.002), focal seizures (p=0.005), late remission of initial epileptic seizures (p=0.002), delay of ASD therapy (p<0.001), Poly-therapy (p<0.001), post-withdrawal epileptiform EEG (p<0.001), high NHS3, GAD7, NDDI-E scores (p<0.001) **Conclusions**: Risk of relapsing seizures after ASDs withdrawal during the first year was 60%. The decision to withdraw ASDs necessitates individual evaluation of each case with accurate assessment of risk factors associating with relapsed seizures.

Keywords: Relapsed seizures; Predictors; Drug withdrawal

INTRODUCTION

Epilepsy is one of the most neurological diseases. According to world health organization, about 50 million patients are suffering from epilepsy worldwide with high incidence in developing countries [1]. Epileptic seizures pose mental and physical harm to the patients and create considerable medical burden to the patients 'families and community [2].

Approximately 70% of epileptic patients could achieve seizure remission by regular anti- seizure drugs (ASDs) treatment. However long-term use of ASDs exerts serious effect on central nervous system including; dizziness, sedation, ataxia,and behavioral and cognitive dysfunction, beside many other adverse effects such as weight gain, fertility issues, liver and kidney dysfunction, pancytopenia, and economic burden[3]. In addition, long term use of this medication is not a guarantee against seizures relapse [4].

The ideal goal of treating epileptic patients is achieving complete seizures remission then withdrawing ASDs without seizures relapse. Risk of post withdrawal relapsed seizures in seizure free patients ranged from 10 % to 70 % in different studies. However, these studies don't reach a unified opinion and there is still

lack of guidance for patients and clinicians [1]. Hazards might accompany seizure relapse after ASDs withdrawal such as drug resistant epilepsy, anxiety, depression, and loss of perceived self-control. Therefore, the decision to discontinue ASDs in seizure free patients is difficult challenge for clinicians [5].

The decision to withdraw ASDs should base on the possibility of continuous seizures remission after ASDs withdrawal, the presence of potent predictors of post withdrawal relapsed seizures and the medical and economic burden of the withdrawal compared to continuation of ASDs [6].

METHODS

This prospective study included 60 epileptic patients. Diagnosis of epilepsy was based on guidelines proposed by international league against epilepsy (ILAE- 2017). The patients were recruited from neurology department and epilepsy clinic, Zagazig university hospitals during the period from November 2020 to November 2022.

Patients with the following criteria were included in the study; epileptic patients who had been receiving regular ASDs and were reported to be seizures free for 2 years prior to ASDs withdrawal; Age between 16 to 80 years old. Exclusion criteria included; patients with symptomatic or provoked seizures, patients who underwent epilepsy surgery, lesions on brain imaging such as tumor, brain injury, cerebral infarction or cerebral hemorrhage and history of irregular ASDs treatment.

The ASDs were discontinued gradually over a period a period of 6 months for the patients on monotherapy and 12 months for the patients on polytherapy, ASDs withdrawal started by reducing one of the ASDs then the withdrawal of the next ASD begins when the previous drug had been completely discounted [5]. The decision to discontinue ASDs was made after clarifying the relative benefits and risks to the patients.

These patients were followed up for one year after complete ASDs withdrawal or until unprovoked seizures relapse occurred. The patients were divided into two groups; patients with relapsed seizures and another group of patients without relapsed seizures.

The study was authorized by the research ethical of Zagazig University, faculty of medicine, and all participants provided written informed permission. The research followed the guidelines laid out in the Declaration of Helsinki, which is part of the World Medical Association's Code of Ethics for Research Involving Humans. This study was performed after the approval of the Institutional Review Board (IRB # 6477, in October 2020).

All the patients were subjected to the followings;

A) Clinical assessment

Complete general and neurological examination.

The following demographic and clinical information were documented; age at onset of seizures, age at initiation of ASDs, age at ASDs withdrawal, course of epilepsy and seizure frequency prior to initiation of ASD (>1 seizure/month or ≤1 seizure/month), time between onset of seizure and the onset of ASDs initiation(more or less than 6 months),efficacy of ASDs therapy in the first 6 month (early remission was defined as an achievement of a one-year seizure free period within 6 months of ASDs . late remission was defined as an achievement of a one-year seizure free period within more than 6 months of ASDs, change in ASDs therapy, the number of ASDs prior to withdrawal, failure of previous ASD withdrawal and history of febrile convulsions previous status epilepticus or infectious diseases after ASDs withdrawal.

Assessment of severity of epileptic seizures was based on The National Hospital Seizure Severity Scale(NHS3) [7]. The scale has eight seizure-related factors and generate a score from 1-27, high score is reflecting worse seizure severity.

Detection of depression in these patients was done by using The Neurological Disorders Depression Inventory for Epilepsy (NDDI.E). It has the potential to quickly diagnose depression, as well as distinguish depressive symptoms from those symptoms caused by

pharmaceutical adverse effect and cognitive effects of epilepsy. Score above 15 is considered positive for depression [8].

Generalized Anxiety Disorder Scale (GAD-7) was used to measure the symptoms of anxiety. Five, ten and fifteen points respectively indicated mild, moderate, severe anxiety [9].

B) Electroencephalogram Monitoring (EEG)

The patients received a follow up EEG assessment at the beginning of ASDs withdrawal then every 6 months following withdrawal. The EEG was performed on 20 channel machines using 10-20 electrode system. All patients were submitted to EEG using XM3-19 W LCD monitor, XEROX. Recording time was at least 30 minutes. The following EEG findings were considered abnormal; spikes, sharp waves, poly spike, diffuse or focal slowing.

C) Magnetic resonance imaging (MRI)

All the patients were examined by the MRI of the brain at MR units of Radiology Department of faculty of medicine, Zagazig University Hospitals using 1.5 Tesla Philips Achiva with a standard head coil**.**

Statistical analysis:

For this study, we consulted SPSS (SPSS Inc., PASW statistics for Windows, version 22), a statistical program, that is Published by SPSS, Inc. in Chicago, Illinois. To characterize the qualitative data, percentages and numbers were utilized. When quantitative data that are normally distributed, was being described; mean± Standard deviation were employed, after testing normality by Kolmogrov-Smirnov test. In order to assess the outcomes, a significance level of (0.05) was utilized. Our statistical tools of choice included chi-square, Fischer exact, and Monte Carlo tests for comparing qualitative data across categories as needed. Kruskal Wallis and Mann Whitney U tests were used when the data is not normally distributed. The student t test was used to compare the two sets of data when the data did not follow a normal distribution. The Kaplan-Meier test is used to find the overall and disease-free survival rates. Using binary logistic regression, we were able to assess the effect of three or more independent variables on an Enter-based binary outcome.

RESULTS

The mean age of the studied cases was 19.6±5.67. Thirty-four (56.7%) males and 26(43.3%) females were included in our study. Twenty (33.3%) patient had focal seizures, 33 (55%) patients had generalized seizures and 7 (11.7%) patients had focal seizures with secondary generalization. Twenty-four (40%) patients obtained one year seizures remission and 36 (60%) had subsequent relapsed seizures after ASDs withdrawal. (Table 1).

There were no significant differences between patients with and without relapsed seizures as regard; age at onset of first seizures (p= 0.07), age at ASDs initiation (p=0.07), age at ASDs withdrawal (p= 0.087), marital state (p= 0.012), consanguinity (p=0.140), body mass index (p= 0.428). Fifteen (41.7%) patients that presented with relapsed seizures have family history of epilepsy versus only 1(4.2%) patient in group of none relapsed seizures and this difference was of significant value (p= 0.001) (Table 2).

Compared with patients in the non-relapsed group, patients with history of previous status epilepticus were significantly more likely to have relapsed seizures (p= 0.002). Thirteen (36.1%) patients who have relapsed seizures gave a history of previous infectious diseases that occurred in the follow up period after ASDs withdrawal versus 2(8.3%) patients in the none- relapsed group (p= 0.015). regarding initial seizures frequency, there was a significant difference between two groups as 97.2% of patients with relapsed seizures had frequent seizures attacks during early course of disease versus 75% of patients with none relapsed seizures (p= 0.009). Focal seizures were associated with high risk of seizures recurrence, 47.2% of relapsed group had focal seizures, however only 12.5% of none relapsed group had focal seizures (p= 0.005). No significant difference was detected between two groups regarding history of febrile convulsion (p= 0.645) (Table 3).

The results of this study showed that patientswho delayed use of ASD, were more likely to relapse than those who received ASD early, as 88.9% of the relapsed patients delayed use of ASD more than 6 months after epilepsy's onset, conversely 91.7% of patients with none relapsed seizures use ASDs early, within less than 6 months (p< 0.001). Thirty-three (91.7%) patients of relapsed seizures treated with poly-therapy versus 10 (41.7%) patients in none relapsed group treated with poly- therapy (p< 0.001). Thirty-four (94.4%) patients in the relapsed group achieved late seizures remission, more than 6 months after initiating ASDs treatment, in contrast 18 (75%) patients of none relapsed seizures achieved early seizures remission within less than 6 months and the difference between two groups was of significant value (p= 0.002). According to our findings, changes of ASDs, duration of ASDs withdrawal and failure of previous ASDs withdrawal were not related significantly to increase risk of relapsed seizures. There were no significant differences between two groups as regard; changes of ASDs (p= 0.06), duration of ASDs withdrawal (p= 0.762), failure of previous ASDs withdrawal (p= 0.139) (Table 4).

Table (5) shows that mean NIHS3 scores among patients with relapsed seizure was 4.28±1.26 versus 2.95±1.16 for patients without relapsed seizure**,** with a significant difference between two groups(p<0.001). While there was no statistically significant difference between two groups as regard Anti-epileptic drug withdrawal risk calculator within 2 years (p=0.136). The mean scores of NDDI-E were 14.4±4.85 in the relapsed group versus 8.83±3.8 in the non-relapsed group. Inaddition, patients with relapsed seizures had worse scores on GAD-7 scale than patients with none- relapsed seizures **(**10.56±3.92 Vs 6.67±3.19**),** bycomparing two groups, differences of significant value were detected (p<0.001)**,** (p<0.001).The Statisticalanalysis of EEG related data revealed that 91.7% of relapsed group versus 87.5% of non-relapsed group have epileptiformEEG at diagnosis, with no significant differences between them, (P=0.675). All cases have normal EEG at beginning of ASDs withdrawal. Thirty-five (97.2 %) patients in the relapsed group had epileptiform EEG versus 1(4.2%) patient in the non-relapsed group during withdrawal or during follow up period, with a significant difference between two groups (p<0.001).

To detect the significant predictors of post withdrawal relapsed seizures among studied cases, the Binary logistic regression analysis (Table 6) shows that previous history of status epilepticus, receiving polytherapy, focal seizures, late remission of seizures after ASDs using, history of infectious diseases after ASDs withdrawal, elapsed time between onset of seizures and onset of ASD treatment more than 6 months, sever epileptic seizures based on NHS3 scale, high GAD7 and NDDI-E score , were statistically significant predictors of post withdrawal relapsed seizures among studied cases with adjusted odds ratio (95% CI) was as following ; 6.11(1,25-29.3, p=0.22), 14.45(3.37-61.99, p <0.001), 6.11(1,25-29.3, p=0.031), 51.0(9.32-278.95, p <0.001), 6.21(1.26-30.77, p=0.025), 16.9(7.69-36.98, p=0.004), 2.30(1.43-3.72, p=0.001), 39 (15.6-58.9, p=0.006) and 13(3.55-47.59, p<0.001) respectively.

Figure (1) Kaplan-Meier curve shows that 3 months disease free survival rate was 93.3%, 4 months disease free survival was 83.3%, 6 months disease free survival rate is 55%, 8 months and 12 months disease free survival rates were 43.3% & 40%, respectively.

Table (1): Basic characteristics of included patients.

	Number (60)	%
Gender		
Male **Female**	**34** **26**	**56.7** **43.3**
Age /years (Mean ± SD)	**19.6±5.67**	
Range	**16.0 – 39.0**	
Type of seizures		
Focal **Generalized** **Focal with secondary generalized**	**20** **33** **7**	**33.3** **55.0** **11.7**
Patients with seizure relapse	**36**	**60.0**
Patients without seizure relapse	**24**	**40.0**

SD; standard deviation

Table (2): Demographic data among the patients.

	Relapsed group	Non-relapsed group	Test of significance
	Number=36	Number=24	
Age at onset of first seizure (years) Mean ± SD	16.03±5.83	13.33±5.10	t=1.84 p=0.07
Age at ASD initiation (years) Mean ± SD	12.03±4.02	9.92±5.05	t=1.79 p=0.07
Age at ASD withdrawal (years) Mean ± SD	21.11±6.31	18.54±4.27	t=1.74 p=0.087
Marital state • Married • Single	9(25.0%) 27(75%)	2(8.3%) 22(91.7%)	X^2=2.67 p=0.102
Family history of epilepsy • -ve • +ve	21(58.3%) 15(41.7%)	23(95.8%) 1(4.2%)	X^2**=10.36** **p=0.001***
Consanguinity • -ve • +ve	30(83.3%) 6(16.7%)	23(95.8%) 1(4.2%)	X^2=2.18 p=0.140
Body mass index Mean ± SD	29.05±1.25	28.65±2.6	t=0.797 p=0.428

X^2: Chi-Squaretest **, t:**Student t test**, MC:** Monte Carlo test **, ASD:** anti-seizure drug **,p:**p value for comparing between the two groups ***: Statistically significant at p ≤ 0.05**

Table (3): Clinical characteristics of the patients with and without relapsed seizure.

	Relapsed group	Non-relapsed group	test of significance
	Number=36	Number=24	
History of status epilepticus			
-ve +ve	24(66.7%) 12(33.3%)	24(100%) 0	X^2=10.0 **p=0.002***
History of febrile seizures			
-ve +ve	26(72.2%) 10(27.8%)	16(66.7%) 8(33.3%)	X^2=0.212 P=0.645
History of previous infectious diseases after ASD withdrawal period			
-ve +ve	23(63.9%) 13(36.1%)	22(91.7%) 2(8.3%)	X^2=5.93 **p=0.015***
Initial seizures frequency			
>1 attack/month ≤1 attack/ month	35(97.2%) 1(2.8%)	18(75%) 6(25%)	X^2=6.9 **p=0.009***
Seizure type			
Focal GTC Focal with secondary generalized	17(47.2%) 15(41.6%) 4(11.1%)	3(12.5%) 18(75%) 3(12.5%)	**p=0.005*** p=0.11 p=0.139

$X^{2:\ Chi}$-Squaretest **, GTC:** generalized tonic clonic**, p:** p value for comparing between the two groups ***: Statistically significant at p ≤ 0.05**

Table (4): Comparison of Anti-seizure drugs related parameter among the groups.

	Relapsed group	Non-relapsed group	test of significance
	Number=36	Number=24	
Time between onset of 1st seizure and onset of ASD treatment (months)			
<6 months ≥6 months	4(11.1%) 32(88.9%)	22(91.7%) 2(8.3%)	FET=38.05 **P<0.001***
Change in ASD			
-ve +ve	12(33.3%) 24(66.7%)	14(58.3%) 10(41.7%)	X^2=3.66 p=0.06
Number of ASD therapy prior to withdrawal			
Mono therapy Poly therapy	3(8.3%) 33(91.7%)	14(58.3%) 10(41.7%)	X^2=17.73 **p<0.001***
Efficacy of ASD			
Early remission (within 6 months) Late remission (more than 6 months)	2(5.6%) 34(94.4%)	18(75%) 6(25%)	X^2=31.25 **p=0.002***
Duration of ASD withdrawal			
<6 months >6months	10(27.8%) 26(72.2%)	5(20.8%) 19(79.2%)	X^2=0.370 p=0.762
Failure Of previous ASD withdrawal			
-ve +ve	22(61.1%) 14(38.9%)	10(41.7%) 14(58.3%)	X^2=2.19 p=0.139

FET; Fischer exact test**, X^2 ;**Chi-Square test**, ASD;** anti-seizure drug **,p:** p value for comparing between the two groups ***: Statistically significant at p ≤ 0.05**

Table (5): Clinical scales and electroencephalographic related data among patients' groups.

	Relapsed group Number=36	Non relapsed group Number=24	Test of significance
NHS3 (Mean ± SD)	4.28±1.26	2.95±1.16	t=4.11 **p<0.001***
Anti-epileptic drug withdrawal risk calculator within 2 years (Mean ± SD)	61.28±18.02	55.0±11.44	t=1.51 p=0.136
NDDIE Mean ± SD -ve +ve	14.4±4.85 10(27.8%) 26(72.2%)	8.83±3.8 20(83.3%) 4(16.7%)	X^2=17.78 **p<0.001***
GAD-7	10.56±3.92	6.67±3.19	t=4.04 **p<0.001***
EEG at diagnosis			
Normal Epileptiform	3(8.3%) 33(91.7%)	3(12.5%) 21(87.5%)	FET=0.278 P=0.675
EEG at beginning of ASD withdrawal			
Normal Epileptiform	36(100%) 0	24(100%) 0	**...**
EEG during ASD withdrawal and follow up			
Normal Epileptiform	1(2.8%) 35(97.2%)	23(95.8%) 1(4.2%)	FET=51.96 **P<0.001***

NHS3= national hospital seizure severity scale**, SD;** standard deviation**, p:** p value for comparing between the two groups ***: Statistically significant at p ≤ 0.05,t: Student t test**

Table (6): Binary logistic regression for prediction of relapsed seizure among studied cases.

	B	p value	AOR (95%CI)
Status epilepticus	1.72	0.22*	6.1(1.23-29.62)
Number of ASDs monotherapy (r) polytherapy	2.67	<0.001*	1 14.45(3.37-61.99)
Family history of epilepsy (+ve)	2.65	0.19	5.8(0.692-10.58)
initial seizures frequency >1 attack/month ≤1 attack/ month(r)	21.89	0.08	1.69(0.898-4.56)
Seizure type GTC Focal	4.25 1.73	0.25 0.031*	1 1.36(0.455-6.69) 6.11(7.25-29.3)
Efficacy of ASD Early remission(r) Late remission	3.93	<0.001*	51.0(9.32-278.95)
History of previous infectious diseases after ASD withdrawal period	1.83	0.025*	6.21(1.26-30.77)
time between onset of seizure and onset of ASD treatment <6 months (r) ≥6 months	4.56	0.004*	1 16.9(7.69-36.98)
Severity of epilepsy	0.833	0.001*	2.30(1.43-3.72)
GAD7	3.66	0.006*	39(15.6-58.9)
NDDI-E -ve (r) +ve	2.56	<0.001*	13(3.55-47.59)

AOR: Adjusted odds ratio**,r:** referencegroup, ***statistically significant, ASDs:**anti-seizure drugs, **NDDIE=** The Neurological Disorders Depression Inventory for Epilepsy**, GAD-7=** Generalized Anxiety Disorder Scale 7 item

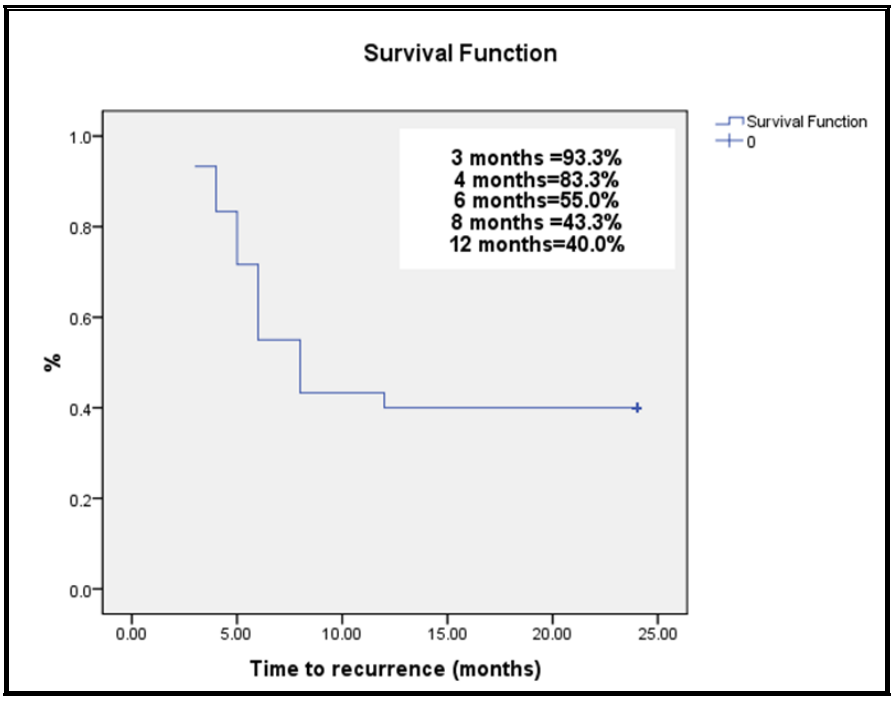

Figure (1): Kaplan-Meier curve showing time to recurrence

DISCUSSION

Concerns over the safety of ASD withdrawal and the potential for further improvement in quality of life following medical therapy for people who are no longer experiencing seizures are shared by both clinicians and patients[10].

Given the difficulty in accurately predicting the risk of relapsed seizures after ASD withdrawal in patients who have been seizure-free after treatment, our study aimed to identify the predictive factors of seizure recurrence after anti-seizure drugs withdrawal among epileptic patients who had achieved two years seizures remission.

Our result showed that the risk of relapsed seizure was 60% during first year after ASDs withdrawal. The survival factor analysis in the current study revealed that 3 months disease free survival rate was 93.3%, 4 months disease free survival was 83.3%, 6 months disease free survival rate was 55%, 8 months and 12 months disease free survival rates were 43.3% & 40%, respectively. This result was approximated to the study of **Kitchener et al.** who showed that risk of relapsed seizure after ASD withdrawal in their patients was 57.5%[11]. Also, our result was near to the study of **Zhang et al.** who reported that incidence of seizure recurrence after ASDs withdrawal was 55.3% in 1 year and 61.9% in 2 years [1].

Our findings revealed that family history of epilepsy was considered a significant risk factor for relapsed epileptic seizure. Our result agreed with [6,12]. In addition, **Schupf and Ottman**revealed thatchildren with a positive family history have a greater recurrence rate of relapsed seizure following drug withdrawal than epileptic patients without family history of epilepsy[13].In this context**, Maria et al.** showed that a family history of epilepsy was associated with an earlier age at seizure onset and focal cortical dysplasia with subsequent uncontrolled and recurrent epileptic fits [14]. On the contrary some studies found that the family history of epilepsy wasn't considered a risk factor of seizure recurrence[15].

The result of this study revealed that about 33% of relapsed group gave a history of pervious status epilepticus, while no patient in non-relapsed group had previous status epilepticus. previous studies proposed that epileptic patients who experienced previous status epilepticus have high risk for recurrent uncontrolled epileptic fits in the future [16]. The risk of recurrent epileptic seizures in those patients with history of status epilepticus ranged from 31% to 46.7% [17].

The analysis of patients' data revealed

that occurrence of infection episodes after AED withdrawal could increase the risk of seizures relapse. Systemic infection is one of the critical factors that provoke epileptic seizures and could predispose to seizures in variable ways [18]. Inflammation that accompanied systemic infection could elevate cytokines level. Cytokines can cross the blood brain, damage brain cells, and finally trigger epileptic seizures. Changes in the permeability of the blood-brain barrier that is associating with infection could enable drugs and toxins to pass across the blood-brain barrier. These substances could increase neuronal excitability and contribute to trigger seizures [19].

Certainly, certain types of antibiotics have the ability to trigger seizures. In antibiotic-induced seizures, the most widely recognized mechanisms involve blocking the production of gamma-aminobutyric acid (GABA), inhibiting its direct and indirect antagonism, and activating glutaminergic N-methyl-D-Aspartate (NMDA) receptors. Neuronal excitability is raised and the seizure threshold is decreased when this inhibitory pathway is inhibited [20].

The results of current study showed that the epileptic patients presented with focal epilepsy were more vulnerable to relapsed epileptic seizures when compared with patients presented by generalized seizures.In agreement with our results, several studies showed that patients with focal seizures are susceptible to epileptic seizures recurrence after ASD withdrawal [2, 21, 22]. In addition, **Schmidt and Löscher**conducted a meta-analysis of 14 studies in children and adult patients with epilepsy and found that focal epilepsy was a risk factor for post withdrawal epileptic seizures [23].

Sofroniewin his study,reported that focal epileptic zones are characterized by prominent gliotic scar that has the potential ability to increase neuronal excitability and induce epileptic seizures. Tumour necrosis factor (TNF) released from reactivated glia can increase the level of excitatory neurotransmitters [24].

The results of this study pointed out that frequent Initial seizures frequency of more than one attack per month was detected among 97.2% of relapsed group, that make it a significant predicator for relapsing seizures after ASD withdrawal. These finding was in line with results of **[**25,26]. Indeed, Binary logistic regression analysis of our data showed that the severity of epileptic seizures was independent significant factor for predication of post withdrawal relapsed seizures.In consistent with our finding,**Specchio et al**.reported that severity of epilepsy was a significant factor for predicting epilepsy recurrence after ASD withdrawal[27]. **Callaghan et al**. reported that long duration of frequent and intractable epileptic seizures was associated with decreased cumulative probability for 12 month or greater seizures remission[28].

In terms of pathogenesis, it is well known that the frequent active seizures induce neuronal loss and mossy fiber sprouting in the hippocampus which could reinforce the production of excitatory recurrent circuits and therefor worse and aggravate epilepsy [21].

In our study, late remission of initial epileptic fits was detected among 94.4% of relapsed group versus 25% of non-relapsed group with statistically significant difference between the two groups.In agreement with this finding**, Tang et al**. and**Park and Lee** reported that the late remission of initial epileptic fits was considered as a strong predictor of relapsed seizures after ASDs withdrawal [6,29]. Actually, late remission of initial epileptic fits made epileptic patients more vulnerable to poly therapy, drug interactions, chronic toxicity, complicated clinical course and other unsatisfactory aspects of treatment[30].

According to our results, we found that early treatment of epileptic seizures within the first six months after first seizure reduced the risk of recurrence significantly, compared to delay treatment. In the line with our findings, previous studies had assessed the impact of early treatment on the risk of seizure recurrence and they found that immediate treatment reduced the risk of early relapse but does not affect the long-term prognosis [6, 21,31].

Our result revealed that epileptic patients treated withpolytherapy have higher risk of seizures relapse after ASDs withdrawal than patients treated with monotherapy.In line with

our results, **Wang et al.** found in their study that the risk of seizures relapse in patients treated with poly therapy after ASD withdrawal was about twice the relapse risk of patients with monotherapy[21]. **Tang et al.** reported that most of epileptic patients treated with polytherapyhad history of sever uncontrolled epileptic fits that made them more exposed to post withdrawal epileptic seizures[6].

In the current study, we found that epileptiform EEG after ASD withdrawal was related significantly to occurrence of relapsed epileptic seizures.This finding was consistentwith results of **Su et al.** whofound that epileptiform EEG within first year after withdrawal was independent predictor of seizure relapse[25]. In this context**, Zhang et al.** in their study classified epileptiform discharges of EEG traces into mild, moderate and sever degree, based on sensitive and accurate EEG data, and found that the lager the abnormalities on EEG results after ASD withdrawal the greater the possibility of seizures relapse [1].

We detected an obvious relation between the occurrence of post withdrawal relapsed seizures and the depressive symptoms in our studied cases. In addition, Binary logistic regression analysis of our data showed that the anxiety and depression wereimportant significant risk factors for post withdrawal relapsed seizures. It is well known thatepileptic patients show high prevalence of comorbid depressive and anxiety disorders [32].**Carson et al.** reported that there were positive associations between high seizure frequency and depression [33].

To highlight the relation between depression and post withdrawal epileptic seizures, previous studies reported that epileptogensis could be triggered by excess hormones that released during the chronic state of stress that accompanied depression in epileptic patients. The presence of large quantities of corticosteroid receptors in hippocampus make it more vulnerable to these hormones. The corticosteroid increases excitability of neurons in hippocampus and facilitate the state of seizures [34**,** 35].**Wiglusz et al.** in their study found that 43% of epileptic patients with recurrent uncontrolled epileptic fits were clinically anxious and added that limbic structures including amygdala, insula and hippocampus were among the most commonly involved regions in focal epilepsy and anxiety[36]. In the state of anxiety, the process of neurogenesis and granule cells production are reduced in the hippocampus, therefore dentate gyrus become more vulnerable to excitatory neurotransmitters that enhance neuronal hyper-excitability [37].

CONCLUSIONS

Based on our results, focal seizures, previous status epilepticus, history of previous infectious disease during withdrawal period, polytherapyof ASDs, late remission of seizures after ASDs initiation, delay treatment of initial epileptic seizures, depression, anxiety, sever form of epileptic seizures, epileptiform EEG during or after withdrawal period were independent predictors of poor remission of epileptic seizures after 2 years of seizures remission. Therefore, the decision to discontinue ASDs should always be made individually after accurate assessment of all risk factors related to relapsed seizures.

Declaration of interest
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