Research Article

Predictor factors for relapse after remission of seizure in adults with remote symptomatic epilepsy

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Abstract

Background: Several studies have examined remission in individuals with epilepsy and relied on factors that may affect seizure outcome. However, the information on those patients with remote symptomatic epilepsy who are prone to present remission is quite less.

Objective: To evaluate the remission rate and relapse in adult population with remote symptomatic epilepsy.

Materials and Methods: Between 2012 and 2013, we performed a retrospective study of epilepsy patients seen in 2007 at the King Abdulaziz Hospital, Jeddah, Saudi Arabia, and followed up subsequently. To be eligible for our study, potential subjects had to meet all the following criteria of symptomatic epilepsy: adult patients 12 years and above with seizures that were the result of one or more identifiable neurological insults of the brain, people with seizure-free period of 2 years and more and followed up by stopping antiepileptic drugs (AEDs), and people with follow-up of at least 2 years after the discontinuation of AED at the first visit in 2001 in which they met the inclusion criteria.

Result: The study included 145 patients with remote symptomatic epilepsy. Among most of the patients (80.6%), the type of the seizures was generalized symptomatic epilepsy, while both the focal and generalized types were reported among 16.6% of them. Patients with number of seizures ranged between three and five were significantly less likely to present remission when compared with those with one or two seizures [crude odds ratio (OR) = 0.39; 95% confidence interval (CI) = 0.18–0.83]. Patients who reported history of status epilepticus were significantly less likely to show remission when compared with those with no history of status epilepticus (crude OR = 0.33; 95%CI = 0.13–0.83). Patients who showed abnormal magnetic resonance imaging (MRI) were 57% less likely to exhibit remission when compared with those who showed normal MRI (crude OR = 0.43; 95%CI = 0.23–0.99).

Conclusion: Among the acquired causes of symptomatic etiology, the traumatic brain injury is found to be associated with a high rate of remission and good seizure outcome when compared with mesial temporal sclerosis, central nervous system infection, and vascular causes, while the malignant tumor was associated with a high rate of relapse and drug refractory epilepsy.

KEY WORDS: Epilepsy, seizure, predictor factors, relapse, remission

Introduction

Epilepsy is a common neurological disorder among all the types of population worldwide[1] and, based on causative factors, is classified as idiopathic, symptomatic, or cryptogenic.[2] This classification is important in determining the prognosis of epilepsy, how people may experience the period of seizure remission and achieve seizure freedom, and those who will develop intractable epilepsy.[3]

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Around 70%–80% of seizure patients eventually become seizure free; on the other hand, one-third of all the patients present intractable epilepsy[4–7]; however, for each subtype individually, this figure is not well known.

Symptomatic epilepsy is defined as epilepsy of predominantly in which the epileptic seizures are the result of one or more acquired or genetic cause that are related to the malfunctions in the gross anatomic or pathologic anomalies:

for instance, the epilepsy owing to tuberous sclerosis, neurofibromatosis, posttraumatic, and infections.[8,9]

The remission in people with epilepsy has been analyzed through various studies, which relied on factors that may affect seizure outcome: causative factors, age of onset, family history, electroencephalogram (EEG) finding, and seizure type. The remote symptomatic epilepsy serves as an important predictor for seizure outcome, as an epilepsy cause is largely determined by seizure relapse or remission.[10,11]

The information on those patients with remote symptomatic epilepsy who are prone to present remission is quite less.

We conducted this study to evaluate the remission rate and relapse in adult population with remote symptomatic epilepsy.

Materials and Methods

Between 2012 and 2013, we performed a retrospective study of epilepsy patients seen in 2007 at the King Abdulaziz Hospital, Jeddah, Saudi Arabia, and followed up subsequently. Our study population included all the adult patients seen in 2007 at our center, who met the criteria for symptomatic epilepsy. We identified the subjects by searching our electronic practice and, then, screened their outpatient medical charts to determine the eligibility. To be eligible for our study, potential subjects had to meet all the following criteria of symptomatic epilepsy: adult patients 12 years and above with seizures that were the result of one or more identifiable neurological insults of the brain, people with seizure-free period of 2 years and more and followed up by stopping antiepileptic drugs (AEDs), and people with follow-up of at least 2 years after the discontinuation of AED at the first visit in 2001 in which they met the inclusion criteria. We excluded those with a diagnosis of nonepileptic psychogenic seizures, people with idiopathic and cryptogenic types, and all cases of pediatric age group.

One attending neurologist reviewed the medical charts and collected information on the association of previously defined predictor variables between the clinical characteristics and achieving 2 years of seizure remission after stopping AED.

Predictor Variables

History of head trauma, status epilepticus, age of onset, magnetic resonance imaging (MRI) lesion, EEG finding, and number of failed AED > 1.

Measures

Remission criteria

The primary outcome of the study was achieving a ≥2-year seizure remission after the discontinuation of AED. Remission was defined as being free of any seizures by self-report for 2-year on medications and 2-year off medications in all the subjects during medical treatment. When the beginning date of seizure freedom was not noted in the chart, the first clinic visit in which no seizure was reported was considered the start date of remission.

Relapse criteria

The secondary outcome of the study was the occurrence of seizure relapse after experiencing a ≥2-year on medications and 12-month off medications seizure remission. Relapse was defined as the occurrence of a seizure after having at least 1 year of seizure freedom. When the exact date of seizure relapse was not noted in the chart, the first clinic visit in which seizure was reported was considered the date of relapse.

Independent Variables

Variables tested for association with study end point included the following: history of status epilepticus; age of onset; epilepsy classification; causes; mesial temporal lobe sclerosis; history of significant brain trauma, central nervous system (CNS) infection, ischemic stroke or other vascular insult and brain tumor; and number of AEDs. The age of onset was categorized as >12 years of age. The epilepsy types were categorized as idiopathic generalized epilepsy (IGE) and symptomatic generalized epilepsy (SGE).

Result

The study included 145 cases with remote symptomatic epilepsy. Table 1 presents their demographic and baseline characteristics. Sixty-three (43.4%) patients were in the age group 23–34 years and 27 (18.6%) cases were older than 45 years. Male subjects constituted 41.4%, while the female subjects constituted 58.6% of the study sample. Among most of the patients (80.6%), the type of the seizures prevalent was SGE, while both focal and generalized types were reported among 16.6% of them. Among more than half the number of patients (53%), the seizure began at the age group 12–22 years. Temporal lobe epilepsy was reported among 55.2% of the studied patients. The number of seizures ranged between one and two among 48.3% of patients and ranged between three and four among 47.6% of them. Fifty-nine (40.7%) patients reported a history of treatment by one AED, whereas 68 (46.9%) patients were treated by two AEDs. The EEG finding was abnormal among the majority (97.9%) of them. Almost one-third (31.7%) of the patients revealed a history of status epilepticus. MRI was abnormal in almost two-thirds (61.4%) of patients. All the patients were treated medically.

Regarding the risk factors (remote symptomatic causes), traumatic brain injury (TBI) was reported among 22.8% of cases, whereas CNS infection, ischemic stroke, other vascular causes [intracerebral hemorrhage, subarachnoid hemorrhage, arteriovenous malformations (AVM), and cerebral venous sinus thrombosis (CVST)], and mesial temporal sclerosis (MTS) were reported among 16.6%, 13.8%, 12.4%, and 16.6% of patients, respectively.

As obvious from Figure 1, remission for 2 years was reported among almost one-third (334.5%) of the patients.

Table 1: Demographic and baseline characteristics of the participants (n = 145)

Demographic and baseline characteristics	Frequency	Percentage
Age in years		
12–22	12	8.3
23–34	63	43.4
35–45	43	29.7
>45	27	18.6
Gender		
Males	60	41.4
Females	85	58.6
Type of seizure		
Generalized	117	80.6
Partial	4	2.8
Both	24	16.6
Age at first seizure in years		
12–22	77	53
23–32	21	14.5
33–42	24	16.6
43–52	10	6.9
>52	13	9
Epilepsy classification		
Temporal lobe	80	55.2
Others	65	44.8
Number of seizures		
1–2	70	48.3
3–5	69	47.6
>5	6	4.1
AED		
One	59	40.7
Two	68	46.9
Three	16	11
More than three	2	1.4
Medical problems		
No	103	71
Yes	42	29
EEG		
Normal	3	2.1
Abnormal	142	97.9
Status epilepticus		
No	99	68.3
Yes	46	31.7
MRI		
Normal	56	38.6
Abnormal	89	61.4

AED, antiepileptic drug

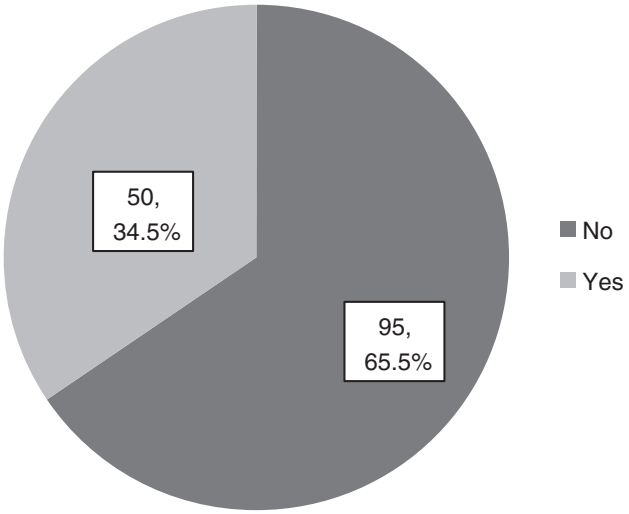

Figure 1: Prevalence of remission for 2 years among the symptomatic epileptic patients, KAAUH, Jeddah, KSA.

Predictors of Remission for 2 Years: Univariate Analysis

Demographic Predictors

Although male patients and those in the age group 35–45 years were more likely to report remission for 2 years, the patients' gender and age were not significant predictors for remission, as seen in Table 2.

Clinical Predictors

As shown in Table 2, patients with the number of seizures that ranged between three and five were significantly less likely to show remission when compared with those with one or two seizures [crude odds ratio (OR) = 0.34; 95% confidence interval (CI) = 0.16–0.70]. Patients with history of CNS infection, ischemic stroke, and other comorbid diseases (hemorrhagic shock, AVM, CVST, vasculitis, anoxic, etc) were significantly less likely to develop remission when compared with those who reported TBI (OR = 0.28, 95%CI = 0.09–0.88; OR = 0.28, 95%CI = 0.08–0.94; and OR = 0.33, 95%CI = 0.12–0.91, respectively). Patients who reported history of status epilepticus were significantly less likely to show remission when compared with those with no history of status epilepticus (crude OR = 0.23; 95%CI = 0.10–0.57). Age at first seizure, epilepsy classification, type of seizure, and presenting medical problems were not proved to be significant predictors for remission.

Investigation-Related Predictors

As illustrated in Table 3, patients who showed abnormal EEG findings were 66.7% less likely to present remission opposed to those who showed normal EEG signals. However, crude OR and 95%CI were not computed owing to nonexistence of cases with normal EEG and showing no history of remission. Patients who revealed abnormal MRI findings were 63% less likely to show remission when compared with those who showed normal MRI findings (crude OR = 0.37; 95%CI = 0.19–0.76).

Therapeutic Predictors

From Table 3, it is evident that the patients who were treated by two or three AEDs were significantly less likely to develop remission when compared with those treated with

Table 2: Demographic and clinical predictors for remission among epileptic patients

Variables	Remission		Crude OR	95%CI
	No, *N* = 95, N (%)	Yes, *N* = 50, *N* (%)		
Gender				
Males[a] (*n* = 60)	35 (58.3)	25 (41.7)	1	—
Females (*n* = 85)	60 (70.6)	25 (29.4)	0.58	0.29–1.17
Age (years)				
12–22[a] (*n* = 12)	9 (75.0)	3 (25.0)	1	—
23–34 (*n* = 63)	41 (65.1)	22 (34.9)	1.61	0.39–6.56
35–45 (*n* = 43)	25 (58.1)	18 (41.9)	2.16	0.51–9.12
>45 (*n* = 27)	20 (74.1)	7 (25.9)	1.05	0.22–5.02
Age at first seizures (years)				
12–22[a] (*n* = 77)	47 (61.0)	30 (39.0)	1	—
23–32 (*n* = 21)	14 (66.7)	7 (33.3)	0.78	0.28–2016
33–42 (*n* = 24)	16 (66.7)	8 (33.3)	0.78	0.30–2.05
43–52 (*n* = 10)	7 (70.0)	3 (30.0)	0.67	0.16–2.80
>52 (*n* = 13)	11 (84.6)	2 (15.4)	0.28	0.06–1.38
Epilepsy classification				
Temporal lobe[a] (*n* = 80)	49 (61.3)	31 (38.8)	1	—
Others (*n* = 65)	46 (70.8)	19 (29.2)	0.65	0.33–1.31
Type of seizures				
Generalized[a] (*n* = 117)	77 (65.8)	40 (34.2)	1	—
Partial (*n* = 4)	2 (50.0)	2 (50.0)	1.93	0.26–14.18
Both (*n* = 24)	16 (66.7)	8 (33.3)	0.96	0.38–2.44
Number of seizures				
1–2[a] (*n* = 70)	37 (52.9)	33 (47.1)	1	—
3–5 (*n* = 69)	53 (76.8)	16 (23.2)	0.34	0.16–0.70*
>5 (*n* = 6)	5 (83.3)	1 (16.7)	0.22	0.02–2.02
Medical problems				
No[a] (*n* = 103)	64 (62.1)	39 (37.9)	1	—
Yes (*n*=42)	31 (73.8)	11 (26.2)	0.58	0.26–1.29
Symptomatic causes				
TBI[a] (*n*=33)	15 (45.5)	18 (54.5)	1	—
CNS infection (*n* = 24)	18 (75.0)	6 (25.0)	0.28	0.09–0.88*
Benign tumors (*n* = 9)	7 (77.8)	2 (22.2)	0.24	0.04–1.32
Malignant tumors (*n* = 6)	6 (100)	0 (0.0)	—	—
Ischemic stroke (*n*=20)	15 (75.0)	5 (25.0)	0.28	0.08–0.94*
Other vascular (*n* = 18)	9 (50.0)	9 (50.0)	0.83	0.26–2.63
MTS (*n* = 20)	25 (71.4)	10 (28.6)	0.33	0.12–0.91*
Status epilepticus				
No[a] (*n* = 99)	56 (56.6)	43 (43.4)	1	—
Yes (n = 46)	39 (84.8)	7 (15.2)	0.23	0.10–0.57*

CI, confidence interval; OR, Odds ratio; NA, not applicable.

[a]Reference category.

*$p < 0.05$.

only one AED (crude OR = 0.37, 95%CI = 0.10–0.78, and OR = 0.24, 95%CI = 0.06–0.93, respectively).

Results of Multivariate Logistic Regression Analysis

Table 4 shows that patients with the number of seizures that ranged between three and five were significantly less likely to show remission when compared with those with one or two seizures (crude OR = 0.39; 95%CI = 0.18–0.83). Patients who reported history of status epilepticus were significantly less likely to show remission when compared with those with no history of status epilepticus (crude OR = 0.33; 95%CI = 0.13–0.83). Patients who showed abnormal MRI findings were 57% less likely to show remission when compared with those who presented normal MRI results (crude OR = 0.43; 95%CI = 0.23–0.99). The risk factors were not significant predictors for remission after controlling for confounders.

Table 3: Therapeutic- and investigation-related predictors for remission among epileptic patients

Variables	Remission		Crude OR	95%CI
	No, *N* = 95, *N* (%)	Yes, *N* = 50, *N* (%)		
AED				
One[a] (*n* = 59)	30 (50.8)	29 (49.2)	1	—
Two (*n* = 68)	50 (73.5)	18 (26.5)	0.37	0.10–0.78*
Three (*n* = 16)	13 (81.3)	3 (18.8)	0.24	0.06–0.93*
More than three (*n* = 2)	2 (100)	0 (0.0)	NA	—
EEG				
Normal[a] (*n* = 3)	0 (0.0)	3 (100)	1	—
Abnormal (*n* = 142)	95 (66.9)	47 (33.1)	NA	—
MRI				
Normal[a] (*n* = 56)	29 (51.8)	27 (48.2)	1	—
Abnormal (*n* = 89)	66 (74.2)	23 (25.8)	0.37	0.19–0.76*

CI, confidence interval; OR, Odds ratio; NA, not applicable.

[a]Reference category.

*$p < 0.05$

Table 4: Predictors for remission among epileptic patients, KAAUH, Jeddah: results of logistic regression analysis

Variables	B	SE	Adjusted OR	*p*	95%CI
Number of seizures					
1–2[a] (*n* = 70)	—	—	1	—	—
3–5 (*n* = 69)	- 0.951	0.39	0.39	0.015	0.18–0.83
>5 (*n* = 6)	- 1.145	1.167	0.32	0.326	0.03–3.13
Status epilepticus					
No[a] (*n* = 99)	—	—	1	—	—
Yes (*n* = 46)	- 1.123	0.48	0.33	0.019	0.13–0.83
MRI					
Normal[a] (*n* = 56)	—	—	1	—	—
Abnormal (*n* = 89)	- 0.721	0.389	0.46	0.043	0.23–0.99

Terms of antiepileptic drugs and comorbid diseases were removed from the final logistic regression model.

B Slope.

CI, confidence interval; SE, standard error; OR, odds ratio.

[a]Reference category.

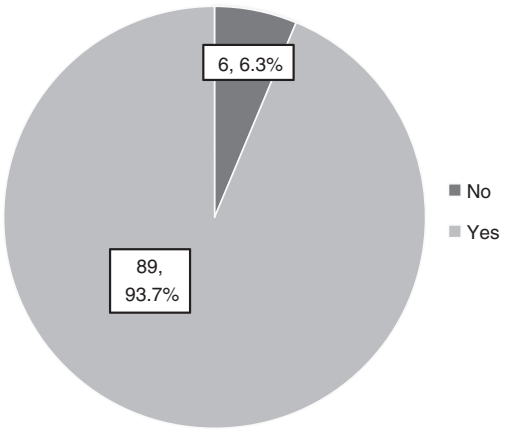

Figure 2: Improvement of the epileptic cases who did not develop remission after resuming therapy.

As obvious from Figure2, the majority of epileptic cases (93.7%) who did not develop remission for 2 years improved by resuming AED therapy, whereas only 6.3% did not show improvement and developed intractability.

Discussion

Epilepsy with remote symptomatic causative factors is usually considered as a predictor for relapse after remission and drug-resistance epilepsy.[12–14] Unexpectedly, 34% (one-third) of our population developed 2 years of seizure remission, which can be expected to develop a prolonged seizure remission over a longer period and percentage that is likely to grow over time, given the interest to note that continued medication does not guarantee permanent remission and, in the same, does not protect from relapse after discontinuing medication.

The short-term prognosis for patients with remote symptomatic epilepsy is perhaps not as bleak as previously believed[15]; however, a large number of our population (93.7%) who developed relapse improved after resuming medication indicate good seizure outcome, although 6.3% of them developed intractability and drug refractory epilepsy (DRE) after stopping medication. DRE is defined as failure of the AEDs owing to lack of efficacy and no remission greater than 1 year by the time of the second AED failure.[16]

Factors that can influence the relapse in symptomatic group of adult population in our study are patients with seizure frequency of more than 3attacks per month, history of status epilepticus, abnormal MRI finding, and number of antiepileptic medication used to control seizure to be more than one AEDs.

Among the risk factors and symptomatic causes, which were included in our study, people with history of CNS infection, vascular insult, tumor, and MTS less likely to develop remission when compared with those who reported history of TBI.

People with MTS and tumor are more likely to develop drug-resistance epilepsy and intractability after resuming AED. Age at onset among adult patients, seizure type (generalized versus focal), and presenting medical problems were not proved to be significant predictors for relapse or remission; however, results from other studies reported symptomatic causes to be associated with a higher rate of intractability,[17] and in our population, the significant factor among the acquired symptomatic causes, TBI, was found to be highly a predictor for remission when compared with other causes. Another study assessed the relative contribution of several factors to the prognosis after withdrawal of drugs and found that a normal EEG before discontinuing AED and history of only a few tonic–clonic seizures were of the greatest importance.[18]

Unfortunately, there are not much data available about symptomatic epilepsy and its prognosis, and such information is in need in our practice as epileptologist, and the most important question is perhaps not the absolute risk when treatment stops but which patient will end in DRE after resuming medication.

Conclusion

We can conclude that, among the acquired causes of symptomatic epilepsy, the TBI was found to be associated with a high rate of remission and good seizure outcome when compared with MTS, CNS infection, and vascular causes, while the malignant tumor was associated with a high rate of relapse and DRE. Seizure frequency, history of status epilepticus, abnormal MRI findings, and the number of antiepileptic medications to achieve seizure control are considered as clinical predictors for early relapse and DRE.

Finally, we believe that additional predictors should be identified and additional well-designed studies are warranted. We emphasized that stopping AED among the TBI group should be taken into consideration.

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