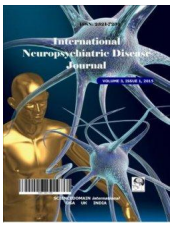

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Triggering Factors for Breakthrough Seizures among Epileptic Patients. Cross Sectional Study in Epileptic Patients Attending Epilepsy Clinic Mansoura University Hospital, Egypt

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Authors' contributions

This study was completed in cooperation among all authors. Author AE structured the work, performed the statistical analysis, composed the protocol and the principal draft of the original copy. Authors MG and MS dealt with the analyses of the study and approved the final research.

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ABSTRACT

Background: The prevalence of breakthrough seizures in persons with epilepsy is very high in developing countries. Consequently, patients and physicians should be aware of the possible factors that may cause breakthrough seizures.
Objective: The aim of our study is to determine the possible factors that may be a precipitating cause for breakthrough seizures in patients with epilepsy.
Methods: This cross-sectional study included 100 persons with epilepsy with idiopathic epilepsy receiving antiepileptic drugs (AEDs). They were divided into two groups. Group 1 included 50 persons with epilepsy with a history of recent breakthrough seizures. Group 2 included 50 persons with epilepsy who had not experienced any recent breakthrough seizures. Patients were subjected to a thorough questionnaire addressing precipitating factors. All participants were subjected to an electroencephalogram (EEG) and medication adherence assessment.
Results: There was no significant differences between group 1 and group 2 regarding age, sex, age

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of onset of epilepsy, occupation and marital status (P value range 0.5 – 0.2). The patients in group 1 were found to have longer durations of epilepsy, lower adherence to AEDs (P = 0.001), more missed doses of AEDs (P = 0.0001), more side effects of AEDs (P = 0.0005), more sleep deprivation, lower level of AEDs (P = 0.0006), more frequently on AED polytherapy (P = 0.0002), and more flickering lights (P = 0.04) than the participants in group 2. In terms of the EEG, group 1 showed a higher percentage of abnormal EEGs and more frequent focal epileptiform discharges (P = 0.003). Also, pathological findings in MRI brain were associated with higher breakthrough seizures (P = 0.005). No significant difference was found in both group1 and group 2 regarding emotional stress (P = 0.55), substitution of brand AEDs by generic one (P = 0.83), concurrent illness (P = 1), or the use of non AEDs (P = 0.79).

Conclusion: The precipitating factors of breakthrough seizures are multifactorial and it is very important to educate patients about these precipitating factors to achieve better control of epilepsy.

Keywords: Epilepsy; breakthrough seizures; triggering factors.

1. INTRODUCTION

The World Health Organization 2019 determined that epilepsy as one of the most common neurological disorders around the world, affecting more than 50 million individuals [1]. Epilepsy is the fourth commonest neurological disorder after migraine, stroke, and Alzheimer's disease [2]. The etiology of seizures is multi factorial in affected individuals [3]. The overall prevalence of Epilepsy varies between 5 and 10 per 1000 [4]. While the prevalence in Egypt, was about 6.98 / 1000 [5].

Approximately 50% of all patients with epilepsy were reported to have seizures of varying frequency and severity despite antiepileptic drug (AED) treatment. Although, the recent introduction of recent AEDs, about 33% of patients with epilepsy have seizures unmanageable to treatment [6].

Breakthrough seizures are seizures that happen in an individual who had already great reliable control of epilepsy and considered as proof of lacking control and so failure of treatment [7]. And consequently, causing unfavorable outcome in persons with epilepsy [8].

Breakthrough seizures may be due forgotten medications, AED below therapeutic level, and use of generic drugs. Other factors that may be the precipitating factor include watching TV, playing computer games, lack of sleep, effort and stressful life [9]. In the research of Yirga Legesse Niriayo, et al. 2019 a large number of persons with epilepsy were non follower to their drugs, and neglect was the commonest etiology of non adherence [10]. A single breakthrough seizure for a controlled patient has a marked mental and social outcomes, including loss of work and loss of driving benefits wellbeing, self-esteem, social interactions, and employment [11].

So it is essential to recognize the diverse precipitating factors that may influence seizure control. The aim of this study is to identify such a precipitating factors hence a better control of seizures.

2. STUDY PARTICIPANTS AND METHODS

2.1 Study Participants

This research was carried out on 100 persons with epilepsy. All patients were recruited from the Epilepsy Clinic at Mansoura University Hospital, Mansoura University. All patients were diagnosed as epileptic according to recent classification of epilepsy based on the criteria of ILEA [12].

Patients were divided into two groups: Group 1 included 50 epileptic persons who had recent breakthrough seizures characterized by an epileptic attack that happened in spite of the utilization of AEDs in a patient who had achieved seizure control for at least the past 6 months. While, group 2 consisted of 50 persons with epilepsy in whom seizure control had been achieved, and who had not experienced a seizure for at least six months. Group 1 and group 2 participants were age and sex-matched.

Patients were excluded if there was unclear history reporting or had a history indicate a psychogenic non epileptic seizures. This study was approved by the local ethics committee Institutional Research Board (IRB) and all patients provided a written consents.

2.2 Methods

All patients were subjected to:

a) Thorough history to determined triggering factors of breakthrough seizures
b) General medical examination,
c) Neurological examination.
d) Medication adherence assessment.
e) Electroencephalography (EEG):
f) CT brain and MRI brain in selected cases.

Triggering factors were conditions that happen before the onset of an epileptic seizure and provide a possible explanation of the occurrence of the seizure [13].

The following were the expected triggering factors:

1- Non compliance to AED. 2- Substitution of AED to a generic names of AEDs. 3-Side effects of AED. 4-Concurrent use of epileptogenic drugs. 5-Missed doses of AEDs. 6-Sleep deprivation, which was impaired either the quantity or the quality of sleep. 7-Emotional stress exceeded adaptive psychological capacity. 8-Flickering lights as that occur during watching TV or playing video games. 9-Physical and mental stress because of intense physical activity and a prolonged cognitive activity respectively. 10-Concurrent illness like fever during breakthrough seizures.

Adherence to AEDs in all patients was assessed by using Medication Adherence Assessment by self-reported, medication-taking behavior scale used by Pande Ayu et al. 2019 in his study of Medication adherence and quality of life among epilepsy patients.

The adherence is classified into the following:

i. Low adherence (a score < 6)
ii. Medium adherence (a score of 6–7)
iii. High adherence (a score 8 or more) [14].

Electroencephalography (EEG): Electroencephalogram was done for all patients to document the presence or absence of any epileptiform activity. Electroencephalogram (EEG) was carried out using the 10 – 20 international system for about 20 min under a standard conditions and by using provocative techniques like hyperventilation and photic stimulation. Recordings were performed using EB Neuro Basis BE Hardware (Firenze, Italy) and Galileo Software (Firenze, Italy) for EEG data acquisition and review.

2.3 Statistical Methods

All statistical calculations were performed using statistical package for the social science (SPSS, version 21; SPSS Inc., Chicago, Illinois, USA). Data were statistically described as mean, SD, frequencies (number of cases), and relative frequencies (percentages) for all patients. The comparison of categorical data was done using $\chi 2$ and Mann – Whitney U tests. The Fischer exact test is used for frequencies less than 5. P value of less than 0.05 was considered statistically significant.

Univariable logistic regression analysis was performed to assess the association of triggering factors with breakthrough seizures, which allows adjustment for triggering factors. Results were expressed as adjusted odds ratio (OR) with the corresponding 95% confidence interval (CI).

3. RESULTS

There was no significant differences between group 1 and group 2 regarding age, sex, age of onset of epilepsy, occupation and marital status (P value range 0.5 – 0.2). A significantly greater proportion of group 1 participants were educated compared to group 2." (P = 0.04).

Group 1 was associated with significant prolonged duration of epilepsy and significant lower medication adherence in comparison with controlled group 2 indicating lower adherence to medication in breakthrough seizures patients (P<0.05).

The types of seizures in both groups showed no significant differences (i.e. focal vs. generalized; P = 0.84), however, there was significant difference in the EEG findings between both groups as the finding of epileptogenic activity (especially the focal activity 28%) was significantly more prevalent in the patients in group 1 in 40% of patients and in group 2 only 12% of patients (P = 0.003).

Missed dosages of anti epileptic drugs, flickering lights, watching TV, Sleep deprivation and lower compliance in the previous weeks of breakthrough seizures was found significantly in group1 of patients (P value were 0.0001, 0.04, 0.0004 and 0.001 respectively).

The side effects and poly therapy of AEDs were associated with significant breakthrough seizures (P = 0.0005 and 0.0002 respectively). Also, there was significant relationship between breakthrough seizures and below the therapeutic level of AEDs and pathological finding in MRI brain in group 1 patients (P = 0.0006 and 0.005 respectively).

While, emotional stress prior to breakthrough seizures, concurrent illness or fever, and the replacement of AED by generic form or concurrent intake of other non AEDs were not associated with significant difference between both groups of patients (P = 0.55, 1, 0.83 and 0.79 respectively).

Logistic regression analysis of triggering factors showing that breakthrough seizures were strongly associated with missed doses of AED, number of used AED , sleep deprivation , side effects of AEDs , and serum level of AEDs.

4. DISCUSSION

In this study, there is slightly non significant higher prevalence of breakthrough seizures in males compared to females which may be explained by the fact that female patients are more adherent to medications and ask for health care better when contrasted with men [15].

Four patients (8%) of group 1 revealed tramadol misuse. Similarly,Manal et al., 2015 in an Egyptian study on 55 persons with epilepsy with breakthrough seizures, reported 6 patients (11%) of tramadol intake before the breakthrough seizure [16]. This may alert the expansion in tramadol misuse in the Egyptian people group, particularly among the adolescent [17].

The results showed that the duration of epilepsy in patients subjected to this study was more in patients having breakthrough seizures in group 1 compared with controlled group 2 (15.23 ± 9.98 and 7.1 ± 8.76 respectively). This match with a study conducted in Uganda, that detected a significant relationship between the occurrence of breakthrough seizures and duration of epilepsy [18].

Regarding to the kind of seizures, there was no critical distinction between the two groups (60% in group 1 and 56% in group 2). This result was in agreement with the view of Joseph I, 2015 who mentioned that the kind and distribution of seizure precipitating factors are more or less similar in patients with different epilepsy subtypes [19].

Our results showed that 56% of the patients in group 1 were on polytherapy AEDs while, only 18% of the patients in group 2 were on polytherapy AED. Also 40% of the patients in group 1 were non compliant on medications while, only 10% of the patients in group 2 were non compliant on medications. This implies in these patients, the breakthrough seizures may be because of thediminished consistence with different medications. Rajagopalan K et al. 2018 concluded, reducing treatment burden via selection of AED therapy with reduced pill

Table 1. The demographic data of patients

	Group 1	Group 2	Test of significance
Age	34.15 ± 13.32	32.91 ± 14.28	P= 0.51
Sex			
Male	28 (56%)	24 (48%)	P= 0.55
Female	22 (44%)	26 (52%)	
Age at onset			
≤18	33 (66%)	39 (78%)	P= 0.27
>18	17 (34%)	11 (22%)	
Occupation			
Not working	40 (80%)	35 (70%)	P= 0.36
Working	10 (20%)	15 (30%)	
Marital status			
Single	35 (70%)	31 (62%)	P= 0.51
Married	13 (26%)	17 (34%)	
Divorced	2 (4%)	2 (4%)	
Education			
Educated	21 (42%)	31(62%)	P= 0.04
Non-educated	29 (58%)	19 (38%)	

Table 2. Clinical history and EEG findings

	Group 1	Group 2	Test of significance
Duration of epilepsy	15.23 ± 9.98	7.1 ± 8.76	P < 0.05*
Type of seizures			
Focal	20 (40%)	22 (44%)	P= 0.84
Generalized	30 (60%)	28 (56%)	
Medication adherence	5.27 ± 0.95	6.3 ± 1.12	P < 0.05*
EEG findings			
Generalized	6 (12%)	4 (8%)	P= 0.003
Focal	14 (28%)	2 (4%)	
Normal	30 (60%)	44 (88%)	

** t tests*

numbers and dosing frequency should be considered to improve health and economic outcomes [20]. On the contrary, Asmamaw Getnet et al., 2016 found that the average number of the utilized AEDs was marginally higher in compliant patients as it was associated with better control and socioeconomic status was the main indicator of non-adherence. But Close to our study, they found that more than one-third of people with epilepsy were not compliant with their AEDs [21].

On the other hand there was a significant higher AEDs side effects in patients with breakthrough seizures (42% of group 1 and 10% of group 2). This could be explained as an expected reason of non-compliance as reported by Trevor Resnick, and R. Edward Faught, 2019 who concluded that patients don't want to take the medication because the medication has side effects. And because they don't take their medication on a consistent basis, they're more liable to have seizures. Also, large percentage of patients reported that generic AEDs were responsible for breakthrough seizures and increased side effects [22].

Also, a significant higher rates of missed doses of AEDs were found in group 1 compared to group 2 (P = 0.0001). Similarly, Azra Zafar et al., 2109 found that 48.7% of 152 patients, were non-adherent to their AED therapy and the most usually recognized factor was forgetfulness and consequently non-adherence was significantly associated with poor seizure control [23].

In our study, the replacement of an original (brand) AED with a generic one was not associated with a significant incidence of breakthrough seizures. This results are in agreement with study of Bosak M, Słowik A 2017 who conclude that patients with increased frequency of seizures did not differ from other patients after replacement of their medication by drug formulation with FDA-approved generic products [24]. In the contrary to Trevor Resnick, and R. Edward Faught, 2019 reported that generic AEDs products were associated with more frequent breakthrough seizures [22].

We found no significant difference between patients in group 1 who were taking other concurrent medication at the onset of the breakthrough seizure (mostly analgesics & antibiotics) and, patients in group 2 were taking other non-AED (P = 0.79). Also, there was no difference between both group 1 and group 2 regarding concurrent illnesses (mainly upper respiratory tract infections) and breakthrough seizures (P = 1). But, Hsien Yi Chen et al., 2016 mentioned that certain medications as antidepressants, diphenhydramine, stimulants (as cocaine and methamphetamine), tramadol and isoniazid are drug inducing seizures, and can precipitate breakthrough seizures [25]. Also, Ettinger & Adigha 2008 mentioned that infections can predispose to the incidence of breakthrough seizures [26].

In the current study, 36% of group 1 and only 6% of group 2 reported to have sleep deprivation (P = 0.0004) which is highly significant for precipitation of breakthrough seizures. Samsonsen et al., 2016 concluded that Epileptic seizures are often precipitated by sleep deprivation [27]. Ferlisi M and Shorvon S 2014 reported that sleep deprivation, was one of the most frequently reported precipitants breakthrough seizures [28].

Emotional stress before the onset breakthrough seizures were found in 58% of the patients in group 1 and also 50% of patients in group 2 were complaining of stress and depression. This non significant difference between the two groups (P = 0.54) may be explained by higher

incidence of stress and depression in both group. However, Heather et al., 2017 have identified that anxiety, depression, and childhood trauma as the most common precipitating factor reported by patients to trigger seizures [29].

In our study, flickering lights or sounds were reported in 24% of group 1 and 8% of group 2 and considered a statistically significant for precipitating breakthrough seizure (P = 0.04). This is in opposition to what was found by Martin et al., 2013 who found that flashing lights was not related breakthrough seizures. On the other hand, the study done by Zeynep Vildan and Çiğdem Özkara 2018 revealed that flashing lights was considered as a main seizure precipitant [30].

The serum level of the utilized AEDs was lower than the therapeutic range in 50% of Group 1 while, the serum level of the utilized AEDs estimated in Group 2 was only 16% below the therapeutic level (P = 0.0006). This indicate that sub-therapeutic AEDs levels was highly significant in breakthrough seizure. In the study done by Madhuradhar Chegondi et al., 2019, it

Table 3. Precipitating factors for breakthrough seizures

	Group 1	Group 2	Test of significance
Special habits			
Smoking	10 (20%)	5 (10%)	P= 0.16
Tramadol abuse	4 (8%)	0 (0%)	P= 0.03
Number of used AED			
Single	22 (44%)	41 (82%)	P= 0.0002
Multiple	28 (56%)	9 (18%)	
Substitution of AED by generic form			
Yes	16 (32%)	14 (28%)	P= 0.83
No	34 (86%)	36 (72%)	
Side effects of the used AEDs			
Yes	21 (42%)	5 (10%)	P= 0.0005
No	29 (58%)	45 (90%)	
Compliance			
Compliant	30 (60%)	45 (90%)	P= 0.001
Non-compliant	20 (40%)	5 (10%)	
Missed doses of AED			
Yes	33 (66%)	4 (8%)	P = 0.0001
No	17 (34%)	46 (92%)	
Other drug intake			
Yes	10 (20%)	8 (16%)	P= 0.79
No	40 (80%)	42 (84%)	
Concurrent illness and fever			
Yes	5 (10%)	6 (12%)	P= 1
No	45 (90%)	44 (88%)	
Sleep deprivation			
Yes	18 (36%)	3 (6%)	P= 0.0004
No	32 (64%)	47 (94%)	
Emotional stress			
Yes	29 (58%)	25 (50%)	P= 0.55
No	21 (42%)	25 (50%)	
Flickers of light or sound			
Yes	12 (24%)	4 (8%)	P= 0.04
No	38 (76%)	46 (92%)	
Serum level of AEDs			
Therapeutic level	25 (50%)	42 (84%)	P= 0.0006
Below the therapeutic level	25 (50%)	8 (16%)	
MRI findings			
Pathological finding	8 (16%)	0 (0%)	P= 0.005
Normal	42 (84%)	50 (100%)	

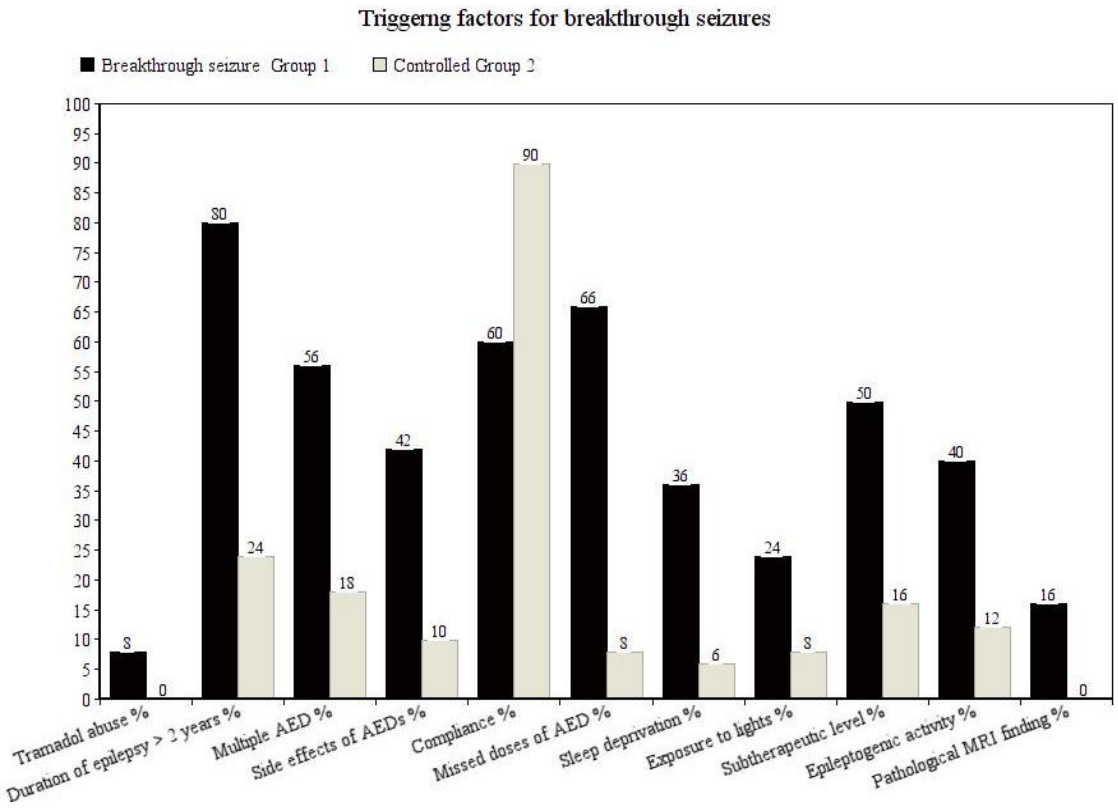

Fig. 1. Triggering factors for breakthrough seizures

Table 4. Univariable logistic regression analysis for triggering factors associated with breakthrough seizures

Variable	Odds ratio	95% confidence interval	P value
Age	0.85	(0.39 - 1.43)	P= 0.51
Sex	1.03	(0.46 - 2.93)	P= 0.55
Education	5.95	(3.69 - 10.38)	P= 0.04
Duration of epilepsy	3.24	(2.59 - 7.35)	P < 0.05
Medication adherence	4.92	(3.69 - 11.28)	P < 0.05
EEG findings	8.59	(6.62 - 20.92)	P= 0.003
Smoking	0.95	(0.64 - 2.17)	P= 0.16
Tramadol abuse	6.58	(4.31 - 12.48)	P= 0.03
Number of used AED	16.67	(5.79 - 45.71)	P= 0.0002*
generic form of AED	1.27	(0.59 - 6.8)	P= 0.83
Side effects of AEDs	11.74	(8.91 - 30.29)	P= 0.0005*
Compliance	9.27	(6.98 - 22.64)	P= 0.001
Missed doses of AED	17.91	(8.85 - 36.32)	P = 0.0001*
Concurrent illness	1	(0.99 - 1.03)	P= 1
Sleep deprivation	12.88	(9.72 - 34.81)	P= 0.0004*
Emotional stress	1.05	(0.39 - 1.99)	P= 0.55
Other drug intake	1.19	(0.53 - 4.34)	P= 0.79
Flickers of light	6.1	(3.79 - 11.46)	P= 0.04
Serum level of AEDs	10.09	(7.23 - 27.85)	P= 0.0006*
Pathological MRI finding	8.07	(6.32 - 15.47)	P= 0.005*

AED (antiepileptic drug)

was found that AED levels were lower than therapeutic level in children with a seizure disorder in most of children with breakthrough seizures [31].

As regard the EEG findings, 40% of group 1 and 12% of group 2 had epileptogenic activities (P = 0.003). This is very similar to the study of Manal Al-Kattan et al., 2015 who, found epileptogenic activities in about 40% of the studied 55 patients with breakthrough seizures [16].

Eight patients (16%) of group 1 had pathological findings in MRI brain study while, all patients in group 2 had normal MRI brain. Most of these were either congenital or acquired pathological findings causing breakthrough seizures. On the contrary, Sudhir, 2005 in a study done in India on 30 children diagnosed to have breakthrough seizures, it was discovered that the MRI brain was normal [32]. According to Zhibin Chenet al., 2018 patients with newly diagnosed epilepsy an epileptogenic abnormality in the brain that portended recurrent seizures and cause a fluctuation in seizure control [33].

Finally, Logistic regression analysis of triggering factors showing that breakthrough seizures were strongly associated with missed doses of AED, number of used AED, sleep deprivation, side effects of AEDs, and serum level of AEDs.

5. CONCLUSION

It is essential to recognize and properly address known triggering factors of breakthrough seizures especially missed doses of AED, number of used AED, sleep deprivation, side effects of AEDs, and below therapeutic serum level of AEDs. These together with regular doctor patient discussions will help for better control of breakthrough seizures in persons with epilepsy.

CONSENT AND ETHICAL APPROVAL

This study was approved by the local ethics committee Institutional Research Board (IRB) and all patients provided a written consents.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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