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Research Article

Seizure Precipitating Factors in Patients With Epilepsy

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Summary

Objective: Aim of the study was (a) to estimate the frequency of seizure precipitating factors; (b) to determine the most frequently reported seizure precipitating factors (c) to identify the differences in distribution of these precipitating factors among epilepsy syndromes and (d) to evaluate differences in the frequency of seizure precipitating factors with regard to demographic features, seizure types, epilepsy syndromes, neuroimaging and electroencephalographic findings.
Methods: We retrospectively analyzed patients who were followed up in our epilepsy outpatient clinic between 2011 and 2014. Information about precipitating factors was obtained during the interview or from the medical reports and telephone inquiries.
Results: Of 365 patients, 61% reported at least one seizure precipitating factor. The most frequently reported precipitating factors were stress (30.4%), sleep deprivation (23.6%) and fatigue (16.2%). Patients were divided into 3 groups regarding the classification of epilepsy syndromes; genetic (18.6%), structural-metabolic (39.2%) and unknown (42.2%). Patients with genetic epilepsy seemed to be less sensitive to stress than those with structural-metabolic and unknown epilepsies. Patients who had myoclonic and generalized tonic clonic seizures had greater tendency to report precipitating factors than patients having other types of seizures. Precipitating factors were less reported by patients whose EEG showed nonspecific paroxysmal activity and who had periventricular ischemic-gliotic lesions in neuroimaging modalities.
Conclusion: Awareness of seizure precipitating factors in the clinical management of the patients with epilepsy may significantly reduce seizure frequency and future studies may contribute to the clarification of the relationship between precipitating factors and seizure occurrence.

Key words: Seizure, epilepsy, seizure precipitating factors

Epilepsisi Olan Hastalarda Nöbet Tetikleyici Faktörler

Özet

Amaç: Çalışmanın amacı a) nöbet tetikleyici faktörlerin sıklığını hesaplamak, b) en sık bildirilen nöbet tetikleyici faktörleri tanımlamak, c) tetikleyici faktörlerin epilepsi sendromları içinde dağılımındaki farkları bulmak, d) nöbet tetikleyici faktörlerin varlığının, demografik özelliklere, nöbet tiplerine, epilepsi sendromlarına, görüntüleme bulgularına ve elektroensefalografik özelliklere göre farklarını değerlendirmek idi.
Metod: Epilepsi polikliniğimizde, 2011-2014 yılları arasında takip edilmiş olan hastalarımızı, retrospektif olarak inceledik. Tetikleyici faktörler ile ilgili bilgi, görüşmeler sırasında ya da hasta dosyalarından ve telefon görüşmelerinden edinildi.

Sonuçlar: Toplam 365 hastanın %61'i en az bir tetikleyici faktör bildirdi. En sık bildirilen tetikleyici faktörler, stres (%30,4), uykusuzluk (%23,6) ve yorgunluk (%16,2) idi. Hastalar, epilepsi sendromlarının sınıflamasına göre 3 gruba ayrıldı; genetik (%18,6), yapısal-metabolik (%39,2) ve bilinmeyen (%42,2). Genetik epilepsisi olan hastalar, yapısal-metabolik ve bilinmeyen epilepsisi olan hastalara göre strese daha az duyarlı idi. Miyoklonik ve jeneralize tonik klonik nöbetleri olan hastalar, diğer nöbet tipleri olan hastalara göre tetikleyici faktör bildirmeye daha fazla eğilimli idi. Tetikleyici faktörler, EEG'sinde spesifik olmayan paroksismal aktivite ve görüntülemelerinde periventriküler iskemik-gliotik odaklar olan hastalar tarafından daha az oranda bildirildi.
Tartışma: Epilepsisi olan hastaların klinik değerlendirmelerinde nöbet tetikleyici faktörler konusunda farkındalık, nöbet sıklığını anlamlı şekilde azaltabilir ve gelecek çalışmalar, tetikleyici faktörler ve nöbet oluşumu arasındaki kompleks ilişkinin aydınlatılmasına katkıda bulunabilir.

Anahtar Kelimeler: Nöbet, epilepsi, nöbet tetikleyici faktörler

INTRODUCTION

Epilepsy is a chronic neurological condition which is characterized by recurrent, unprovoked seizures. Although seizures occur spontaneously, they may also be precipitated by various exogenous and endogeneus factors. The term ‘seizure precipitants' may include both seizure-inducing and seizure-triggering factors[2]. Inducing factors are mainly environmental or endogenous in origin, whereas triggering factors consist of chemical or physiological stimulation capable of precipitating a seizure[23].

The prevalence of seizure precipitating factors (SPF) ranged between 49% and 91% in previous studies[3,9,11,28,29,30]. It has been shown that majority of the patients with epilepsy can identify at least one SPF[3,9,23,28,30]. These seizure precipitants are mostly nonspecific like stress, fatigue and fever, but they may also be specific like a certain type of music. The most common SPF reported previously were missing medication, emotional stress, sleep deprivation, fatigue, missing meals, fever and smoking. Knowledge of SPF has importance not only in treatment of patients but also in diagnosis. Also this may help to unravel the pathophysiology of epilepsy. However, reports on seizure precipitants are scant in the literature. The purpose of the study was (a) to estimate the frequency of seizure precipitating factors; (b) to determine the most frequently reported seizure precipitating factors (c) to identify the differences in distribution of these precipitating factors among different types of epilepsy syndromes and (d) to evaluate differences in the frequency of seizure precipitating factors with regard to demographic features, seizure types, types of epilepsy syndromes, neuroimaging and electroencephalographic (EEG) findings.

MATERIAL AND METHODS

We retrospectively analyzed patients who were followed up in our epilepsy outpatient clinic between 2011 and 2014. Patients with a confirmed diagnosis of epilepsy were included and well-documented data was evaluated. Patients who were evaluated as having pseudo-seizures were ruled out of the study. Information about SPF was obtained during the interview or from the medical reports and telephone inquiries. Especially patients who attended to the out-patient clinic before the last 6 months were interviewed once more by telephone inquiries. Primary caregivers were asked about SPF when the patient was unable to participate to the interview. Besides demographic and clinical findings of the patients, seizure types, types of epilepsy syndromes, neuroimaging and

electroencephalographic findings, all precipitating factors were recorded. Epilepsy syndromes were classified according to the ILAE's 2010 revised classification of the epilepsies as genetic, structural-metabolic and unknown[7]. According to the report, these modified concepts were suggested to replace idiopathic, symptomatic and cryptogenic epilepsies. In our series, the group of 'genetic' epilepsies consisted of patients who had childhood absence epilepsy, juvenile myoclonic epilepsy or juvenile absence epilepsy. Patients in the group of 'structural-metabolic' epilepsies had acquired structural or metabolic diseases which were demonstrated to be associated with their seizures. In the 'unknown' group, the underlying cause of the seizures could not be defined yet.

A list of SPF was personally presented to the patients by one of the authors. The list was composed of the following precipitating factors; sleep deprivation, emotional stress, fatigue, auditory stimuli, tactile stimuli, alcohol, hyperventilation, menstrual cycle, fever, flickering lights, television/computer, missing meals and missing medication. After completing the close-ended questions (yes/no), patients were asked open questions to identify other precipitating factors that were not included in the list.

Statistical analysis was performed by NCSS (Number Cruncher Statistical System) 2007 program (NCSS, LLC Kaysville, Utah, USA). Besides descriptive statistical methods (mean, standard deviation, median, frequency and ratio), data was analyzed by using Student's t test, Mann-Whitney U test for quantitative variables and Pearson's chi-square test (χ^2), Fisher's exact test for qualitative variables. Differences in the frequency of SPF with regard to age, gender, seizure type, type of epilepsy syndromes, neuroimaging and electroencephalographic findings were determined. Data was evaluated within a 95% confidence interval and a p value <0.05 was considered statistically significant.

RESULTS

A total of 365 patients were included in our study. The clinical characteristics of patients and the overall frequencies of SPF are given in Table 1 and 2, respectively. At least one SPF was reported by 221 (61%) patients. Only one SPF was reported by 33% of the patients whereas 28% reported two or more. Among the patients who reported at least one SPF, the distribution of the most frequent SPF were as follows: stress (50.2%), sleep deprivation (38.9%) and fatigue (26.7%).

There was no significant difference in the frequency of SPF with regard to sex, age, age at onset of epilepsy and the type of epilepsy syndrome (p=0.059, p=0.489, p=0.334 and p= 0.163, respectively) (Table 3).

Neurological examination of the patients were unremarkable in 77.5% of the patients (n=283). Abnormal findings in neurological examination included mental retardation, motor-mental retardation, hemiparesis, ataxia, tremor, vision loss, nystagmus, dysarthria. Mental status were normal in 86.3% of the patients, 7 patients (1.9%) had severe cognitive impairment and 43 patients (11.8%) had mild cognitive impairment. History of perinatal problems were reported in 55 (15.1%) patients. There were no significant differences between the frequency of SPF and mental status and perinatal problems (p=0.354 and 0.697).

Types of seizures were classified as absence, myclonic, focal, generalized tonic-clonic seizures and status epilepticus. The frequencies of these seizure types were as follows: absence (16.4%), myclonic (17.0%), focal (47.1%), generalized tonic clonic seizures (73.4%) and status epilepticus (3.8%). Analysis revealed significant differences in the frequency of SPF with regard to myoclonic seizures and generalized tonic clonic

seizures (odds ratio 2.323, 95% Cl 1.244-4.337, p=0.007 and odds ratio 1.969, 95% Cl 1.230-3.153, p=0.004) (Table 4). Patients who had myoclonic and generalized tonic clonic seizures had greater tendency to report SPF than patients having other types of seizures.

Pathological findings in neuroimaging modalities were found in 158 patients (43.3%). The most frequently detected pathological findings were encephalomalacia (29.7%), periventricular ischemic-gliotic lesions (19.0%), global or regional (fronto-temporal) atrophies (12.7%) and mesial temporal sclerosis (10.1%).

Electroencephalographic findings were grouped in five which were focal epileptogenic focus (39.6%), generalized epileptiform activity (30.9%), focal slowing in fronto-temporal region (30.0%), nonspecific paroxysmal activity (22.7%) and generalized slowing (20.8%).

There were no significant differences between the frequency of SPF with respect to pathological neuroimaging and electroencephalographic findings globally (p=0.773 and p=0.150, respectively). However, there existed significant differences in subgroups. SPF were less reported by patients whose EEG showed nonspecific paroxysmal activity (odds ratio 0.502, 95% Cl 0.259-0.973, p=0.039). Patients who had periventricular ischemic-gliotic lesions are less likely to report at least one SPF (odds ratio 0.401, 95% Cl 0.178-0.900, p=0.024).

The analysis of the relationship between the SPF and the types of epilepsy syndromes showed significance only in stress factor (p=0.05). Patients with genetic epilepsy seemed to be less sensitive to stress than those with structural-metabolic and unknown epilepsies.

Tablo 1. Clinical characteristics of patients

Clinical characteristics	**Years (Range/Mean)**
Age	10-83 (30.88±13.90)
Age at onset of epilepsy	0-80 (17.59±12.83)
	Number of patients(%)
Sex (male/female)	183(50.1%) / 182(49.9%)
Types of epilepsy syndromes	
i. Genetic	68 (18.6)
ii. Structural-metabolic	143 (39.2)
iii. Unknown	154 (42.2)

Tablo 2. Overall distibution of SPF in the study population

Precipitating factor	**Number of patients (%)**
Stress	111 (30.4%)
Sleep deprivation	86 (23.6%)
Fatigue	59 (16.2%)
Television/Computer	29 (7.9%)
Missing meals	23 (6.3%)
Missing medication	20 (5.5%)
Menstruation	15 (4.1%)
Fever	11 (3.0 %)
Emotions	10 (2.7%)
Flickering lights	8 (2.2%)

Tablo 3. Precipitating factors according to demographic findings and the type of epilepsy syndrome

		Precipitating factor		
		No (n=144)	**Yes (n=221)**	***p***
Sex; *n(%)*	**Male**	81 (56.3)	102 (46.2)	***0.059***
	Female	63 (43.8)	119 (53.8)	
Age (year)	**Mean±SD**	30.94±15.65	30.84±12.67	[c]***0.344***
	Min-Max (Median)	10-83 (26)	15-73 (28)	
Epilepsy syndrome	**Genetic**	22 (15.3)	46 (20.8)	[a]***0.163***
	Structural-metabolic	53 (36.8)	90 (40.7)	
	Unknown	69 (47.9)	85 (38.5)	

[a]*Pearson Chi-square Test* [c]*Student t Test* *SD: standard deviation*

Tablo 4. Precipitating factors according to seizure types

	Precipitating factor		***p***
	No (n=144)	**Yes(n=221)**	
Absence	19 (13.2)	41 (18.6)	***0.177***
Myoclonic	15 (10.4)	47 (21.3)	***0.007****
Focal	69 (47.9)	103 (46.6)	***0.806***
Generalized tonic-clonic	94 (65.3)	74 (78.7)	***0.004****
Status epilepticus	4 (2.8)	10 (4.5)	***0.396***

Pearson Chi-square Test **p<0.01*

DISCUSSION

The prevalence of SPF in patients with epilepsy were found up to 91% in previous studies[3,11,23,28,29]. More than 40 precipitating factors were reported previously[1]. In our study, 61% of the patients reported SPF and 28% of the patients reported more than one. Among the patients who reported at least one SPF, most frequent precipitating factors were stress (50.2%), sleep deprivation (38.9%) and fatigue (26.7%). These most frequently reported SPF were consistent with previous studies[8,16,23,29,30]. The overall frequency of SPF (61%) in our study may be equal or slightly lower than what was stated in previous reports in which the frequency of precitating factors were given as 62-91%[11,27,28]. This may be related with the awareness of our study population as it was suggested by Nakken et al in their previous study[22].

Stress was the most frequently reported SPF as in line with many of the previous studies[6,8,11,18,24,30]. In these studies, a strong correlation between seizures and stress was reported. Moreover, Temkin and

Davis observed that pleasent life experiences were inversely proportional to seizure occurence and reduction in stress results in decreased seizure frequency[31].

Sleep deprivation was the second most frequently reported precipitating factor. The relationship between sleep and epilepsy was the subject of many studies[10,20,21,26]. These studies mostly concluded that sleep deprivation could provoke seizures and epileptiform activity in EEG[10,12,21,26]. But Malow et al found no association between sleep deprivation and seizure frequency[20].

Fatigue was the third most common precipitating factor reported. We found no significant difference between the frequency of fatigue and type of epilepsy syndrome. Balamurugan et al reported that patients with generalized seizures cited fatigue more than patients with focal seizures[6]. In contrast, Tan et al documented that patients with focal seizures were more likely to report fatigue than patients with generalized seizures[30]. Patients with generalized and focal seizures were found equally sensitive to fatigue in another study[2].

Missing medication was the most frequently reported precipitating factor in some of the series but it was the sixth most common precipitating factor in our study[6,29].

Knowledge about the distribution of SPF among epilepsy syndromes is limited[11,23]. In a previous study, it was stated that patients with generalized seizures appeared to be more sensitive to sleep deprivation and flickering lights, as compared to those with partial seizures[23]. The authors studied the distribution of precipitating factors in patients with generalized and localization-related epilepsy whereas Frucht et al classified epileptic syndromes in more detail as idiopathic partial/generalized, symptomatic partial/generalized and cryptogenic partial/generalized[11,23]. Although epilepsy syndromes were classified as genetic, structural-metabolic and unknown in our study, we found association between precipitating factors and epileptic syndromes only in terms of stress. Patients with genetic epilepsy seemed to be less sensitive to stress than those with structural-metabolic and unknown epilepsies.

To our knowledge, association of precipitating factors with seizure types, neuroimaging and electroencephalographic findings were not analyzed previously. Our analysis with neuroimaging and electroencephalographic findings might imply indirect support to generalized versus partial involvement. Although there were no significant differences between the frequencies of precipitating factors with regard to neuroimaging and electroencephalographic findings globally, there existed significant differences in subgroups. Precipitating factors were less reported by patients whose EEG showed nonspecific paroxysmal activity and who had periventricular ischemic-gliotic lesions in neuroimaging modalities. As both of these pathological findings were diffuse and nonspesific and they were mostly detected in diseases other than epilepsy, this was not surprising. Analysis on the association between seizure precipitating factors and seizure types revealed that patients who had myoclonic and generalized tonic clonic seizures had greater tendency to report precipitating factors than patients having other types of seizures. Association between SPF and myoclonic seizures might be in concordence with some previous studies on seizure precipitants influencing juvenile myoclonic epilepsy (JME). Several SPF were defined in patients with JME[4,5,8,14,22,25]. Also it has been known that patients with generalized-onset seizures were more likely to report sleep deprivation compared with patients with focal-onset seizures[18,23]. These findings might be investigated in further studies which would be performed with detailed

observations and investigations like video EEG monitorization.

Limitations of our study were that closed-ended questionnaires used in routine follow up of the patients included limited number of seizure precipitating factors (13 items) and the data used in the analysis was derived retrospectively. However, questioning about SPF was not limited to only one visit of the patient and patients who attended to the out-patient clinic before the last 6 months were interviewed once more by telephone inquiries. We observed that questioning about these factors did sensitize patients to what could be a precipitating factor for seizure occurrence, thus recognition of a precipitating factor might be possible in the following visits. Detailed seizure diaries and prospective long term monitoring might strengthen our findings as suggested in other studies[13,28].

It was suggested by Ferlisi and Shorvon that seizure precipitation was a spectrum and seizures occurred as a result of complex mixture of endogenous and exogenous factors.[9]. Besides, one seizure precipitant might sometimes lead to another and seizures might be provoked as a result of this complex interaction. It might not be so easy to assess the relative precedence of the individual factors[6]. The mechanisms by which seizure precipitating factors modulate seizure occurrence are not clear. This may be related with the complexity of the relationship between precipitating factors and seizure occurence. Efforts to provide a greater recognition of the multifactorial nature of the'cause' might help to enlighten the pathophysiological mechanisms of seizures. Two recent studies focused on reflex seizures for the assessment of dynamics of seizure initiation and termination[15,17]. Koepp et al. stated that stimulatory input and areas of hyperexcitability might vary for different seizure types and might depend on the stage of brain maturation. Nevertheless, once specific triggers activated the a critical neuronal mass and a tipping point or threshold were reached, ictogenesis was initiated. Advances in electrophysiology and imaging data acquisition and analysis techniques might help to explain this tipping point from physiological to pathological activity in the future[17]. Irmen et al. emphasized that triggers were also found in non-reflex seizures. The authors suggested the possibility of a conceptual continuum between reflex and spontaneous seizures rather than a dichotomy and further investigations were needed to clarify the triggering mechanisms across all seizure types[15].

As emphasized in a previous report, seizure precipitant should be taken into account as a cause of epilepsy as well as underlying pathologies and genetic predisposition[9]. Identification of a precipitating factor and avoidence from that factor (if possible) might make a great difference in the clinical management of a patient. Aird achieved very good results simply by promoting moderate lifestyle changes among 500 difficult-to-treat patients with epilepsy[1].

CONCLUSION

We conclude that seizure precipitating factors should be considered in the clinical management of the patients with epilepsy. Emotional stress, sleep deprivation and fatigue are the most frequently reported seizure precipitating factors in our study. Some of the seizures may be precipitated by one or more factors, thus they may be predictable. Awareness of patients about seizure precipitants and modification of life styles may significantly reduce the seizure frequency. Further studies to clarify the relationship between seizure precipitating factors and seizure occurrence are needed.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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