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Which seizure-precipitating factors do patients with epilepsy most frequently report?

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Abstract

When treating patients with epilepsy, dealing with seizure-precipitating factors is a partly neglected and underestimated supplement to more traditional therapies. The aim of this study was to investigate the incidence of seizure precipitants in a large epilepsy population and to determine which precipitants patients most often reported. Study participants included twins and their family members ascertained from the Norwegian Twin Panel (NTP), the Danish Twin Registry (DTR), and the Mid-Atlantic Twin Registry (MATR). One thousand six hundred seventy-seven patients with epilepsy were identified and were asked about seizure precipitants using a closed-ended questionnaire. Fifty-three percent reported at least one seizure-precipitating factor, while 30% claimed to have experienced two or more such factors. Emotional stress, sleep deprivation, and tiredness were the three most frequently reported precipitants. Patients with generalized seizures seemed to be more sensitive to sleep deprivation and flickering light than those with partial seizures, while women with partial seizures appeared to be more prone to seizures during menstruation than women with generalized seizures. Knowledge of seizure precipitants has practical implications, not only in patient treatment and counseling, but also for diagnosis, in that it may be helpful in facilitating the appearance of interictal epileptiform discharges in EEG and ictal EEG recordings.

Keywords: Epilepsy; Seizure-precipitating factors

1. Introduction

Seizure susceptibility varies over time in most people with epilepsy. Although epilepsy is characterized by recurrent, unprovoked seizures, it is generally accepted that even though most seizures appear to occur spontaneously, they may be precipitated by a variety of endogenous or exogenous factors. Such seizure-precipitating factors have been defined as "those circumstances that precede the onset of an epileptic attack and are considered by both patient and neurologist to be a possible explanation for why the seizure happened when it did, and not earlier or later" [1]. According to Aird [2], seizure precipitants include both seizure-inducing and seizure-triggering factors. Inducing factors are of environmental or endogenous origin and cause a transient lowering of the seizure threshold, while triggering factors involve chemical or physiological stimulation capable of precipitating a seizure.

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Seizure precipitants have received surprisingly little attention in the literature. Less than 1% of 30,000 epilepsy-related articles have dealt with seizure precipitants [2], despite the fact that the identification and avoidance of such factors and the development of specific countermeasures constitute an important and underestimated supplement to more traditional epilepsy therapies [2,3]. The present study was designed to examine seizure-precipitating factors in a large epilepsy population and estimate the frequency of the precipitants most often reported by study subjects.

2. Material and methods

As part of an ongoing study of seizures in twins ascertained from population-based twin registries in the United States, Denmark, and Norway, we identified 1677 twins and their relatives in whom it was possible to verify a history of epilepsy. For the purpose of this study, those with febrile seizures without subsequent epilepsy or whose seizures were classified as acute symptomatic or situation-related were excluded. The demographic and clinical characteristics of the study population are listed in Table 1. Epilepsy syndromes were broadly classified according to the ILAE classification [4] as localization related, generalized, unclassified, and epilepsy with and without known etiology (symptomatic and cryptogenic/idiopathic epilepsy, respectively). Classification was carried out by experienced epileptologists based on a detailed personal interview carried out by a study nurse and medical record information. In many cases the available data did not permit the classification of cases into more specific epilepsy syndromes. The mean age of the population was 42.3 ± 19.1 years (range, 3–103 years), with a slight preponderance of females (53%). The twins constituted 47% of the study population, the rest being affected relatives.

As part of the overall study protocol, all participants underwent a personal interview in which detailed information on their seizure history was collected. Information on the precipitants that were perceived to be associated with the occurrence of seizures was obtained using a closed-ended questionnaire in which a list of 37 precipitants was provided (Table 2). This information serves as the basis for the results reported herein.

The distribution of reported precipitants was determined both within and across populations and partitioned by seizure and epilepsy type. The significance of observed differences between groups was determined using χ^2. These values were calculated using Epi Info (Version 5.01a) [5]. A P value < 0.05 was considered statistically significant.

Table 2
Seizure precipitants asked about

1. Startle, fright
2. School situation
3. Diet
4. Low blood sugar
5. Menstruation
6. Alcohol
7. Constipation
8. Sleep deprivation
9. Physical exercise
10. Breath holding
11. Hyperventilation
12. Auditory stimuli
13. Touch
14. Sexual intercourse
15. Alcohol withdrawal
16. Tiredness, fatigue
17. Pregnancy
18. Cocaine
19. Other illegal drugs
20. Sunshine, flickering light
21. Emotional stress
22. Pain
23. Fasting
24. Known electrolyte disturbance
25. Ovulation
26. Noncompliance
27. Taking other drugs
28. Fever
29. Head trauma
30. Known hypoxia
31. Reading
32. Self-induced, photic
33. Self-induced, other
34. Television
35. Strobe lights
36. Allergy
37. Heath

Table 1
Demographic and clinical characteristics of the study population ($n = 1677$)

	n	Females	Mean age ± SD (range)	Twins	Generalized epilepsy	Localization-related epilepsy	Unclassified epilepsy	Symptomatic epilepsy	Active epilepsy[a]
United States	582	319 (55%)	38.6 ± 19.4 (3–95)	288 (50%)	86 (15%)	114 (20%)	382 (66%)	77 (13%)	178 (31%)
Denmark	301	157 (52%)	34.9 ± 9.1 (5–77)	288 (96%)	75 (25%)	135 (45%)	91 (30%)	73 (24%)	114 (38%)
Norway	794	413 (52%)	46.9 ± 20.7 (4–103)	211 (27%)	237 (30%)	411 (52%)	146 (18%)	151 (19%)	355 (45%)
Total	1677	889 (53%)	42.3 ± 19.1 (3–103)	787 (47%)	398 (24%)	660 (39%)	619 (37%)	301 (18%)	647 (39%)

[a] Active epilepsy = seizures the last year and/or still on AEDs.

Table 3
Occurrence of perceived seizure-precipitating factors ($n = 1677$)

	n	At least one factor	Two or more factors
United States	582	273 (47%)	173 (30%)
Denmark	301	180 (60%)	103 (34%)
Norway	794	436 (55%)	222 (28%)
Total	1677	889 (53%)	498 (30%)

3. Results

Among the 1677 subjects included in this study, 53% reported at least one seizure-precipitating factor, while 30% claimed that two or more such factors may have brought on a seizure (Table 3). The 10 most frequently reported precipitants are listed in Table 4. Emotional stress, sleep deprivation, and tiredness were the most frequently cited (20.9, 11.6, and 9.5%, respectively). Significant differences in the distribution of precipitating factors between the three populations were found for sleep deprivation ($\chi^2(2) = 13.65$, $P = 0.0011$), fever ($\chi^2(2) = 14.46$, $P = 0.00007$), flickering light ($\chi^2(2) = 12.42$, $P = 0.002$), noncompliance ($\chi^2(2) = 18.59$, $P = 0.0001$), and physical exercise ($\chi^2(2) = 37.37$, $P < 0.0001$). The frequency with which seizure precipitants were reported varied across populations, with flickering light and alcohol being more prevalent in Denmark, physical exercise being more prevalent and noncompliance being less prevalent in Norway, and flickering light and sleep deprivation being less prevalent in the United States.

Analyses of precipitating factors in generalized versus localization related epilepsy cases suggest that differences exist in the distribution of these factors between epilepsy syndromes. The distribution of the five most frequent factors partitioned by major epilepsy syndromes is shown in Fig. 1. Patients with generalized seizures and those with partial seizures seemed to be equally sensitive to emotional stress and tiredness. However, those with generalized seizures appeared to be more sensitive to sleep deprivation and flickering light, as compared with those with partial seizures (19.5% vs 12%, $\chi^2(1) = 11.23$, $P < 0.001$; 12.1% vs 3.6%, $\chi^2(1) = 29.24$, $P < 0.0001$), respectively. This difference in sensitivity to sleep deprivation, although not found in the US sample, was observed in both the Danish ($\chi^2(1) = 6.32$, $P = 0.003$) and Norwegian ($\chi^2(1) = 5.73$, $P = 0.009$) populations. Subjects suffering from generalized epilepsy were more sensitive to flickering light than those with localization-related epilepsy in all three populations (United States: $\chi^2(1) = 8.08$, $P = 0.004$; Denmark; $\chi^2(1) = 6.32$ (Yates correction), $P = 0.007$; Norway: $\chi^2(1) = 14.02$, $P = 0.0002$). In the US sample there were an excess of individuals with localization-related epilepsy who reported emotional stress as a precipitant ($\chi^2(1) = 9.45$, $P = 0.0021$). This was not seen among either Danish or Norwegian patients. No significant differences were found with respect to existence or type of precipitant in those with known versus unknown epilepsy etiology.

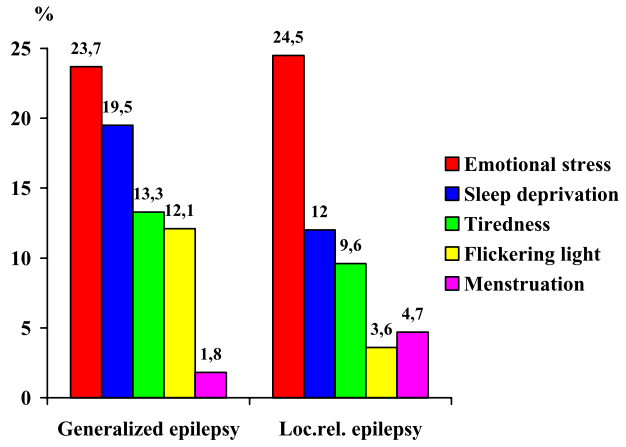

Fig. 1. Distribution of five seizure-precipitating factors in those with generalized and localization-related epilepsy combined over populations, respectively.

4. Discussion

We believe that this large population-based sample is representative of epilepsy cases in general. The severity

Table 4
Most frequently reported seizure-precipitating factors ($n = 1677$)

	United States	Denmark	Norway	Total
1. Emotional stress	106 (18.2%)	73 (24.3%)	171 (21.5%)	350 (20.9%)
2. Sleep deprivation	32 (5.5%)	54 (17.9%)	108 (13.6%)	194 (11.6%)
3. Tiredness	51 (8.8%)	35 (11.6%)	74 (9.3%)	160 (9.5%)
4. Alcohol	21 (3.6%)	28 (9.3%)	46 (5.8%)	95 (5.7%)
5. Fever	37 (6.4%)	22 (7.3%)	27 (3.4%)	86 (5.1%)
6. Flickering light	10 (1.7%)	28 (9.3%)	35 (4.4%)	73 (4.4%)
7. Noncompliance	27 (4.6%)	21 (7.0%)	14 (1.8%)	62 (3.7%)
8. Menstruation	4 (1.3%)	5 (3.2%)	20 (4.8%)	29 (3.3%)
9. Physical exercise	4 (0.7%)	1 (0,3%)	47 (5.9%)	52 (3.1%)
10. Heath	10 (1.7%)	7 (2.3%)	10 (1.3%)	27 (1.6%)
11. Other	26 (4.5%)	10 (3.3%)	38 (4.8%)	74 (4.4%)

of disease among the participants varied considerably, i.e., from those with frequent, difficult-to-control seizures to those who have been seizure-free for many years and have been taken off medication. Thirty-nine percent of the population had active epilepsy, here defined as having experienced seizures the last 5 years and/or were still on AEDs.

There are several potential causes for an epileptic seizure. These include a genetic predisposition, an underlying central nervous lesion, one or more precipitants, or a combination of these. More than 40 precipitating factors have been described in the literature [2]. It is difficult, and maybe impossible, for a patient to determine which precipitant(s) may have facilitated an actual seizure. Sometimes several factors can converge such that a complex relationship exists between precipitating factors and seizure occurrence; e.g., emotional stress may lead to sleep deprivation, noncompliance, and excessive alcohol drinking. In such cases it may be difficult to discern the relative importance of the individual factors. In other cases, however, patients may oversimplify the explanations for their seizures. Therefore, self-reported information on seizure precipitants should be interpreted with caution.

As closed-ended questionnaires tend to be associated with an increased number of false positives, it was somewhat surprising to find that only 53% of the sample reported seizure precipitants. This figure is lower than what has been reported in previous studies, in which seizure precipitants were identified by 62–91% of those included in the study populations [6–12]. This discrepancy could be due to the fact that most of the previous studies were based on clinical series with subjects very aware of precipitants, while many of the patients in our sample had seizures many years ago, they were not followed in clinics for more refractory patients, and many had probably forgotten about factors that might have precipitated their seizures. This assumption corresponds well with the fact that while 73% of those with active epilepsy stated having experienced precipitants, only 42% of those who no longer had active epilepsy quoted the same ($\chi^2 = 107.70$, $P < 0.0001$).

Emotional stress was the precipitant most often reported in this sample. This is not an unexpected finding, given clinical experience and the results of studies that have suggested a strong association between stressful life events and/or tension states and seizures [13–18]. Temkin and Davis claim that daily difficulties increase the risk of seizure occurrence, while pleasant experiences seldom do [14]. The notion that emotional stress lowers seizure threshold is also consistent with the results of psychopharmacologic and behavioral intervention studies, in which a reduction in stress and anxiety levels resulted in decreased seizure frequency [8,19–21].

Among those who reported a seizure precipitant, 4.4% indicated that they were sensitive to flickering light. This figure is consistent with previous findings that ~5% of those with epilepsy are photosensitive [22]. Alcohol consumption was the fourth most frequent precipitant (5.7%) cited by study participants. Given the usual reluctance to admit alcohol use, this is probably an underestimation. Similar concerns exist with respect to reports of noncompliance (3.7%). Therefore, it is quite likely that the frequencies with which alcohol use and noncompliance as precipitants of seizures were reported may not reflect their true importance. The relatively small number of women (3.3%) who reported that their seizures were precipitated by menstruation was surprising, particularly because many women report an increase in seizure frequency around menses. Seizure diaries, however, often show that seizures do seem to occur throughout the cycle [15].

As was shown in Table 1, there were large differences in the percentage of cases where it was possible to classify epilepsy and seizure types between the US and Scandinavian study sites. The large percentage of unclassified cases in the US sample is likely due to the poor quality of medical record information that was available for patients whose seizures occurred more than 10 years ago. Epilepsy classifications were made only when adequate medical record/clinical interview information was available. Those cases for which such information was not available, but for which there was convincing evidence for a history of seizures, were not classified.

We found that there were differences between study sites with respect to the frequency of several of the seizure-precipitating factors reported. Physical activity was given as a precipitating factor by 6% of the Norwegian sample, but accounted for only 0.3 and 0.7% of the precipitants reported by Danish and American subjects, respectively. The explanation for these differences is not clear. However, in Norway, the Norwegian Epilepsy Association has promoted increased physical activity among their members. Therefore, it is possible that Norwegian epilepsy patients are physically more active than those in Denmark or the United States. For sleep deprivation, the percentage of those reporting it precipitated their seizures is decreased in the United States compared with Norway and Denmark. It would seem unlikely that Americans are less sleep deprived than Scandinavians. Therefore it is possible that the dissimilarities observed could represent differences in the prevalence of the specific epilepsy syndromes occurring between these geographical regions.

We found those with generalized epilepsy to be more sensitive to flickering light, compared with those with localization-related epilepsy. This finding corresponds to what we generally assume about the precipitants of generalized epilepsies, e.g., in juvenile myoclonic epilepsy [23].

To our knowledge, little is known about the distribution of seizure precipitants among epilepsy syndromes.

Among 400 patients in a tertiary care epilepsy center, Frucht et al. found that 62% cited at least one precipitant. In this study, stress (30%), and sleep deprivation (18%) were most frequently reported precipitants. Those with temporal lobe epilepsy cited sleep deprivation less frequently and menstruation more frequently compared with those with other epilepsy syndromes [6]. We found women with localization-related epilepsy to report menstruation as a precipitant more frequently than those with generalized epilepsy; however, only a small number of cases were observed.

The mechanisms by which seizure precipitants may reduce seizure threshold or modulate its occurrence are not fully understood. The high levels of inter- and intraindividual variability that have been observed in precipitants of seizures provide a further indication of the complexity of the relationship between seizure precipitants and seizure occurrence. Etiological heterogeneity is one possible explanation for these observations. Among our twin pairs, the concordance rates for precipitating factors were 0.80 for monozygotic pairs and 0.33 for dizygotic pairs, which strongly indicates a genetic contribution [24]. As is well recognized, the epilepsies are a group of heterogeneous disorders whose pathophysiologies differ. Therefore interindividual variability in seizure precipitants is not unexpected [13].

Further studies within this largely neglected, but clinically important field of epileptology are clearly needed. Among 500 difficult-to-treat patients with epilepsy, Aird [2] achieved surprisingly good results simply by promoting moderate lifestyle changes (17% became seizure-free and 25% experienced significantly reduced seizure frequency). These results are in fact better than those achieved by most new AEDs. Seizure-precipitating factors should, therefore, be taken into account in patient management, including them both in discussions with patients and in tailoring of their treatment regimens.

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