Seizure (2005) 14, 464–469

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

Frequency of provocative factors in epileptic patients admitted for seizures: A prospective study in Singapore

Joo-Hui Tan [a], Einar Wilder-Smith [a,*], Erle C.H. Lim [a,b], Benjamin K.C. Ong [a]

[a] *Division of Neurology, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore*
[b] *Department of Medicine (Neurology), Alexandra Hospital, Singapore*

Received 10 September 2004

KEYWORDS
Seizure precipitants;
Hospital admissions;
Epilepsy;
Singapore;
Seizure;
Provocative factors;
Education;
Sleep deprivation

Summary Intractable epilepsy is commonly believed to be the main cause of uncontrolled seizures and hospitalization in epileptic patients. We study frequency and types of potential provocative factors in epileptic patients admitted with seizures, and suggest methods to decrease seizure occurrence and hospitalization. Over 6 months we prospectively studied all epileptic patients hospitalized for seizures. A structured interview and laboratory investigations were used to determine type and number of potential seizure precipitants. Precipitants thought to be avoidable through actions taken by the patient or physicians were termed potentially preventable provocative factors (PPPF). Patients' awareness and knowledge of seizure precipitants were also assessed. Three quarters of all seizures leading to admission were associated with PPPF, the commonest being non-compliance (71%), sub-therapeutic doses of antiepileptic drugs (26%) and sleep deprivation (9%). Only one patient had intractable epilepsy. Patients' knowledge of seizure precipitants was poor. The majority of hospital admissions for seizures in epileptic patients are associated with potentially preventable causes amenable to education programmes. Patient education involving epilepsy nurse educators may play an important role in decreasing seizure occurrence and possibly unnecessary hospital admissions.

Introduction

Epilepsy is a common and potentially serious chronic neurological condition, with a reported prevalence of 4–7 per 1000 population in developed countries.[1–5] Based on these figures, Singapore is estimated to have about 200,000 patients with epilepsy. Patients with uncontrolled seizures exert a considerable economic strain on themselves, the health care resources and the community at large.[6] Recurrent seizures may require repeated hospitalization

* Corresponding author. Tel.: +65 67795555.
E-mail address: mdcwse@nus.edu.sg (E. Wilder-Smith).

1059-1311/$ – see front matter © 2005 BEA Trading Ltd. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2005.07.010

and this has led to a local misconception within the health care community that most admissions are due to intractable epilepsy.

Contrary to common belief, recent health care studies showed that about a third of seizure occurrences are due to non-compliance to medication.[7,8] In this study, we explore the frequency and nature of potentially preventable provocative factors (PPPF) in epileptic patients hospitalized for seizures. We are particularly interested in potentially preventable provocative factors amenable to education programmes designed for the patient or their primary care doctors. This study also explores the patients' awareness and knowledge of preventable factors. In-patients are sampled instead of conducting a questionnaire survey of out-patients to maximise the clinical identification of potentially preventable provocative factors and to increase the yield of patients' memory recall.

Methods

In a prospective 6-month study, we examined all admissions due to seizures in patients with epilepsy. The seizure that led to a patient's admission during the study period was termed the target seizure. The two participating hospitals, the National University and the Alexandra Hospitals are tertiary public referral hospitals serving the south-western region of Singapore and provide 24-h admitting facilities. Patients with seizures were usually brought in to the Emergency Medicine services by relatives or a passerby. The patients were seen by doctors at the Emergency Medicine service, medically stabilized and assessed for the necessity of admission. They were transferred to the medical wards and attended by the ward doctor before being seen by a neurologist within 24 h of admission. In this study, we included all epileptic patients aged 18 and above who were admitted through the Emergency Medicine services with seizures. Further inclusion criteria were a clear history of at least two seizures with concomitant antiepileptic drug (AED) treatment. Patients with an ambiguous cause for admission or suspected to have had a non-epileptic attack were excluded. Data collection consisted of a face-to-face interview, blood tests and when necessary, neuroimaging, chest X-ray and an electroencephalogram. The interview, based on a structured questionnaire, was conducted in the ward by the attending physician or neurologist after the patient had recovered from the post-ictal period. The main care-giver was interviewed instead if the patient was physically unable to participate in the questionnaire.

The patients' demographic details were recorded and blood tests performed on admission. The questionnaire and blood tests were designed to identify the potentially preventable provocative factors (PPPF) for each target seizure. The following are commonly encountered factors in our local setting were studied (definitions and methods of identification in parenthesis):

Non-compliance to AEDs (seizures occurring within 1 week of self-reported failure to take the correct AED doses); sleep deprivation (seizures occurring at least 24 h after the last uninterrupted sleep period of at least 4 h)[9]; alcohol withdrawal (seizures occurring within 6–30 h of acute alcohol withdrawal)[10]; sub-therapeutic serum AED levels despite correct dosing (serum phenytoin $<$10 mg/L, carbamazepine $<$5 mg/L, or sodium valproate $<$50 mg/L taken during admission); emotional stress (seizures occurring within 24 h of subjective increase in stress levels above daily average)[11]; electronic screen displays (seizures occurring while viewing an electronic screen display, e.g. video games, television, computer graphics display)[12]; concurrent infections (infections are identified clinically and by relevant changes on the chest X-ray, cultures of relevant body fluids, raised erythrocyte sedimentation rate, raised total white cell blood count or microscopic pyuria); electrolyte imbalance (serum sodium $<$135 mmol/L or $>$145 mmol/L, serum calcium $<$2.15 mmol/L or $>$2.55 mmol/L, serum magnesium $<$0.70 mmol/L or $>$0.91 mmol/L); acute encephalopathy (clinical uraemic, hepatic encephalopathy or encephalopathy from any other identifiable cause); hypoglycaemia (capillary blood glucose and/or random venous blood glucose of $<$2.5 mmol/L) and hyperglycaemic crises (hyperosmolar hyperglycaemic non-ketosis or diabetic ketoacidosis) and any other identifiable triggers.

To assess the patients' knowledge of PPPF, they were asked to describe in a free text manner and without the provision of cues, what they thought had triggered their target seizures. The patients were also asked to name as many as they could, factors that are known to precipitate seizures in general.

Factors implicated in each patient were analysed and categorized into the two groups of those with were potentially preventable provocative factors could be identified and those were none could be identified. A PPPF is further characterized as a trigger that could potentially be avoided either through actions taken by the patient himself or by his primary-care physician. Examples include non-compliance, sleep deprivation, alcohol abuse and withdrawal, sub-therapeutic doses of AEDs and intercurrent infections.

The type and etiology of epilepsy were classified as partial or generalized, and idiopathic or symptomatic based on the patient's epilepsy work-up from the medical records. To aid in the classification of the epilepsy, a CT or MRI brain and an EEG were performed in patients not investigated before.

Although definition of intractable epilepsy vary, we defined this as repeated seizures frequent enough to result in a significant impact on the quality of life, despite a proper diagnosis and maximal therapy with antiepileptic drugs.

Results

There were 41 admissions involving 40 patients during the 6-month recruitment period. One patient was admitted twice. He was counted only once. Verbal consent was obtained in all the cases and none declined to participate in the study. Caregivers were interviewed in three cases with post-stroke dysphasia and five who were admitted with status epilepticus. The following percentage calculations were based on total number of patients and not the number of admissions. Twenty-four (60%) were males with a mean age of 41.4 years, and 48.3 years for females. The age range for the entire cohort was 19—78 years. The mean number of AEDs the patients were on during the occurrence of the target seizure was 1.2 (range 1—3). Drug levels were performed for phenytoin, carbamazepine and sodium valproate. Five patients were on combination of AEDs with unavailable levels for one of the drugs, namely lamotrigine, topiramate, levetiracetam and clonazepam. In two of them, the second AED was sub-therapeutic, one was totally non-compliant and two others had no obvious triggers.

Twenty-six cases (65.0%) were classified as idiopathic epilepsy and thirteen (32.5%) had symptomatic epilepsy. Of the latter group, one had mesial temporal sclerosis and the rest were secondary to previous strokes. Thirty-nine patients (97.5%) had active epilepsy on treatment and one was in remission without medication for at least 3 years. The target seizure consisted of 33 generalized convulsive seizures, 5 convulsive status epilepticus, 1 complex partial seizure and 1 simple partial seizure.

Subjects with an identifiable potentially preventable provocating factors

The distribution and type of PPPFs are shown in Table 1. Of the 31 patients with PPPFs, 27 patients had only one factor, three patients had a combination of two PPPFs. In one subject with three PPPF, non-compliance was noted over 1 year with the target seizure occurring after sleep deprivation and emotional stress during bereavement.

Table 1 Distribution of potentially preventable and non-preventable provocating factors.

Potentially preventable provocating factors (PPPF)	Number of patients (%)
Subjects with PPPFs	31 (85)
Non-compliance alone	18 (45)
Non-compliance + sleep deprivation	3 (7.5)
Non-compliance + sleep deprivation + stress	1 (2.5)
Sub-therapeutic AED levels despite correct dosing	9 (22.5)
Concurrent infections	3 (7.5)
Hyponatremia	1 (2.5)
No identifiable PPPFs	6 (15)
Total no patients	40

Non-compliance was the commonest PPPF. Seventeen patients were non-compliant on their own accord, one defaulted as a direct result of personal neglect from alcohol abuse and four patients took the wrong doses. Of the latter, two were mentally impaired patients taking AEDs without supervision. Twenty of the non-compliant patients (90.9%) were unaware that poor compliance was the cause of their seizures. Only two patients were able to identify non-compliance as a PPPF, but despite this knowledge both had poor compliance. In Table 2, the demographics and clinical characteristics of non-compliant patients were compared to those who were compliant. All five cases of status epilepticus occurred in compliant patients.

Patients with sub-therapeutic AED levels despite good compliance represented the second most common PPPF. Patients were on low maintenance doses

Table 2 Comparison between non-compliant with compliant patients.

Patient and clinical characteristics	Non-compliant	Compliant
Number of patients (%)	22 (71)	18 (29)
Mean age (years)	42.8	45.7
Males (%)	63.6	55.5
Mean age for males (years)	41.9	40.7
Mean age for females (years)	44.5	52.0
Secondary epilepsy (%)	13.6	55.5
Mean number of AEDs	1.13	1.22
Status epilepticus as target seizure	0	5

of either one or two AEDs prescribed by their primary care physicians, with one patient on a combination of three AEDs, all at low doses. One patient with a subtherapeutic AED level was also on risperidone, which may decrease seizure thresholds.

Of the three patients with sleep deprivation in combination with non-compliance, two were sleep-deprived from a social night-out and the other was the previously described patient with considerable concurrent emotional stress.

In one patient with a concurrent infection, there was additional hyponatraemia secondary to a thiazide antihypertensive.

Subjects with no identifiable potentially preventable provocating factors

Six patients (15%) had no apparent triggers; of special interest was a patient with mesial temporal sclerosis with intractable epilepsy on three AEDs at therapeutic doses. One patient had a relapse after being seizure-free without medication for 3 years. Another patient with infrequent post-stroke epilepsy was admitted with status epilepticus as the target seizure.

Knowledge of seizure precipitant

Table 3 summarises the distribution of PPPFs that were volunteered by the patients in response to questions on their awareness of PPPFs. Knowledge of factors among the entire cohort was poor. Twenty-seven patients (67.5%) were unable to name a single factor. The rest could only identify one each. Stress, non-compliance and sleep deprivation were the commonest answers.

Table 3 Potential provocating factors of seizures as identified by patients.

Precipitant	Number of responses (percent of total 40 patients)
No idea	27 (67.5)
Stress	4 (10)
Non-compliance	2 (5)
Sleep deprivation	2 (5)
Menses	1 (2.5)
Fever	1 (2.5)
Sudden loud sound	1 (2.5)
Drug interactions with traditional medications	1 (2.5)
Cold weather	1 (2.5)
Total number of responses	40 (100)

Discussion

We found that potentially preventable provocating factors were implicated in nearly 80% of seizure admissions among epileptic patients. This seems to contradict the common belief that the main cause for hospitalization is intractable epilepsy. Self-reported non-compliance was by far the commonest potentially preventable factor, followed by sub-therapeutic doses of AEDs despite good compliance, and sleep deprivation. Our data is in keeping with previous literature that failure of compliance is common in epileptic patients, with reported rates of about 30—40%.[7,13] All of the PPPF looked for in our study are potentially amenable to epilepsy education programmes directed at the patient, the caregiver or health-care workers. One needs to remain aware of the fact that although PPPF were identified in association with a seizure resulting in hospitalization, this does not necessarily prove the causal relationship between the two. However, the considerable body of evidence supporting an association between the identified PPPF and seizure provocation would seem to argue for addressing these in education programs. Conclusive evidence on both the causality of the identified PPPF and improved seizure control following their removal would need to be gathered from carefully designed epilepsy education trials employing clearly specified and comparative prevention strategies.

Despite the frequent occurrence of non-compliance amongst our patients, only 5% were aware that neglecting their medication was the precipitant for their target seizures. More than half of our patients were unable to name a single potential provocating factor. This is an alarming proportion compared to studies in Europe and Australia that reported 70—86% of patients with no learning disabilities were able to identify at least one.[14—17] Ignorance amongst our patients seems to reflect that a poor level of epilepsy education is rife, despite a national literacy rate of more than 95%. However, there is a possibility that patients may choose to appear ignorant in a face-to-face interview and be absolved of responsibilities for certain actions which they perceive to be undesirable. This seems to be supported by some of the types of potential seizure precipitants identified, namely factors perceived to be beyond one's control such as stress, menses, sudden loud sounds and cold.

The reasons for non-compliance, however, cannot be only blamed on education and can be complex and multifactorial.[7,13,18,19] Exact analysis of local causes requires further study. A simple comparison of patient demographics and clinical characteristics between the non-compliant and

compliant groups in our study shows a higher proportion of stroke patients with secondary epilepsy in the latter group. This suggests that patients with a significant medical history may receive better epilepsy education, or tend to be more attentive to their medication.

The frequent occurrence of sub-therapeutic doses despite active epilepsy may appear to lie with the primary-care physician's understanding of epilepsy management. Combination regimes of 2—3 AEDs at low doses support this. However, the underlying factors for sub-therapeutic levels require deeper exploration including assessment of the frequency and severity of the seizures, rate of incremental AED titration and patient's side effect profile to AED. This study was not designed to address these issues. The discovery of two patients with mental incapacity taking AEDs unsupervised reflects the often-neglected need for socio-environmental assessment and identification of a responsible care-giver.

There is new and controversial evidence on the uncertain relationship between sleep deprivation and the yield of interictal epileptiform discharges on EEG monitoring.[20—23] We decided to include sleep deprivation as a potential provocative factor despite these data as there are yet no conclusive studies to dispute its co-relation with clinical seizures. Sleep deprivation has long been viewed as a seizure precipitant[9,24] and is an easily preventable factor in most cases. We found differing definitions for sleep deprivation in the literature, and decided against using a fixed number of sleep-deprived hours, as sleep patterns are highly variable in each patient.

It is of no surprise that there is interplay between sleep deprivation, compliance and emotional stress in our patients with combinations of PPPFs, as was previously noted by Aird.[25] Though stress did not play a large role in our cohort, it remained the commonest factor identified by patients. In Temkin's paper, seizures have been shown to occur more frequently on days when the stress level was higher than the individual patient's average.[11] These were ''minor'' daily hassles easily remedied by educating the patient on coping skills and stress management. On the rare occasion of a major life event or an emergency situation, both stress and sleep deprivation may well be rendered an unpreventable potential seizure precipitant. It seems likely that the majority of patients would benefit if these issues were explored and addressed during epilepsy education sessions.

Most of our patients were poorly informed on epilepsy and seizure prevention. This shortcoming requires rectification because patients who are aware of the issues involving seizure prevention utilize this knowledge to change their life-style and improve control their epilepsy.[14] Surveys of patients with epilepsy in the United Kingdom found that patients perceived provision of epilepsy information from their health-care providers to be very poor.[17,26] Similar problems occur in Singapore, whereby a patient with newly diagnosed epilepsy may be seen by different hospital-based doctors at each visit. The patient is subsequently discharged to the out-patient services once his seizures are deemed reasonably controlled. The bulk of counseling and epilepsy education is left to the initial doctor who made the diagnosis; however, time constraints (an average of 6 min allocated for follow-up consultation in a busy clinic) only allow the most urgent matters to be addressed. This emphasizes the need to engage specialist nurse educators who can dedicate time to provide comprehensive epilepsy education, improve compliance and the patient's quality of life in a primary care setting.[27—31]

In this study, the vast majority of PPPFs implicated with the target seizures seem to represent the direct cause and burden of hospitalization. This infers that measures to decrease or prevent PPPFs should lead to fewer hospital admissions for seizures. This direct causality remains to be proven as this study only concerned patients hospitalized because of a seizure. A weakness of this study is a selection bias of not identifying patients with seizures who were not brought to hospital for reasons of being well educated and socially well supported.

As a next step in the management of non-compliance, we suggest an epidemiological analysis of patients with epilepsy to explore the interplay of psychosocial and medical factors that lead to compliance failure and sub-therapeutic AED levels. Data from such a study could be used to design or modify existing structured epilepsy care packages[27,32] to suit the needs of the local population.

References

1. Brown S, Betts T, Chadwick D, Halls B, Shorvon D, Wallace S. An epilepsy needs document. *Seizure* 1993;**2**:91—103.
2. Goodridg DMG, Shorvon SD. Epilepsy in a population of 6000. *Br Med J* 1983;**287**:641—7.
3. Haerer AF, Anderson DW, Schoenberg BS. Prevalence and clinical features of epilepsy in a biracial United States population. *Epilepsia* 1986;**27**:66—75.
4. de Graaf AS. Epidemiological aspects of epilepsy in northern Norway. *Epilepsia* 1974;**15**:291—9.
5. Granieri E, Rosati G, Bonucelli U, Murri L. Descriptive epidemiological study of epileptic syndromes in a district of North-West Tuscany, Italy. *Epilepsia* 1991;**32**:294—8.

6. Currie CJ, Morgan CL, Peters JR, Kerr M. The demand for hospital services for patients with epilepsy. *Epilepsia* 1998;**39**:537—44.
7. Stanaway L, Lambie DJ, Johnson RH. Non-compliance with anticonvulsant therapy as a cause of seizures. *N Z Med J* 1985;**98**:150—2.
8. Irving P, Al Dahma A, Srinivasan A, Greenwood R. An audit of admission of patients with epilepsy to a district general hospital. *Seizure* 1999;**8**:166—9.
9. Gunderson CH, Dunne PB, Feyer TL. Sleep deprived seizures. *Neurology* 1973;**23**:678—86.
10. Porter RJ, Mattson RH. Alcohol and drug abuse. In: Engel Jr J, Pedley TA, editors. *Epilepsy: A comprehensive textbook*. Philadelphia: Lippincott-Raven; 1997. p. 2629—34.
11. Temkin NR, Davis GR. Stress as a risk factor for seizures among adults with epilepsy. *Epilepsia* 1984;**25**:450—6.
12. Quirk JA, Fish DR, Smith SJM, Sander JWAS, Shorvon SD, Allen PL. Incidence of photosensitive epilepsy: a prospective national study. *Electroencephalogr Clin Neurophysiol* 1995;**95**:260—7.
13. Buck D, Jacoby A, Baker GA, Chadwick DW. Factors influencing compliance with antiepileptic drug regimes. *Seizure* 1997;**6**:87—93.
14. Spector S, Cull C, Goldstien LH. Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. *Epilepsy Res* 2000;**38**:207—16.
15. Spatt J, Langbauer G, Mamoli B. Subjective perception of seizure precipitants: results of a questionnaire study. *Seizure* 1998;**7**:391—5.
16. Hayden M, Penna C, Buchanan N. Epilepsy: patient perceptions of their condition. *Seizure* 1992;**1**:191—7.
17. Hart YM, Shorvon SD. The nature of epilepsy in the general population. II. Medical care. *Epilepsy Res* 1995;**21**:51—8.
18. Feuerstein M, Lieb-Juckstock V, Schaus H, Springmann E, Weber B, Wunderlich M. Compliance—a joint effort of the patient and his doctor. *Epilepsy Res* 1988;**1**(Suppl.):51—6.
19. Loiseau P, Marchal C. Determinants of compliance in epileptic patients. *Epilepsy Res* 1988;**1**(Suppl.):135—40.
20. Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants among epilepsy syndromes. *Epilepsia* 2000;**41**:1534—9.
21. Mendez M, Radtke RA. Interactions between sleep and epilepsy. *J Clin Neurophysiol* 2001;**18**:106—27.
22. Malow BA, Passaro E, Milling C, Minecan DN, Levy K. Sleep deprivation does not affect seizure frequency during inpatient video-EEG monitoring. *Neurology* 2002;**59**:1371—4.
23. Bazil CW. Sleep-related epilepsy. *Curr Neurol Neurosci Rep* 2003;**3**:167—72.
24. Rajna P, Veres J. Correlations between night sleep duration and seizure frequency in temporal lobe epilepsy. *Epilepsia* 1993;**34**:574—9.
25. Aird RB. The importance of seizure-inducing factors in the control of refractory forms of epilepsy. *Epilepsia* 1983;**24**: 567—83.
26. Poole K, Moran N, Bell G, Solomon J, Kendall S, McCarthy M, et al. Patients' perspective on services for epilepsy; a survey of patient satisfaction, preferences and information provision in 2394 people with epilepsy. *Seizure* 2000;**9**: 551—8.
27. Kwan I, Ridsdale L, Robins D. An epilepsy care package: the nurse specialist's role. *J Neurosci Nurs* 2000;**32**: 145—52.
28. Ridsdale L. The effect of specially trained epilepsy nurses in primary care: a review. *Seizure* 2000;**9**:43—6.
29. Ridsdale L, Robins D, Baker GA, Chadwick DW. Factors influencing compliance with antiepileptic regimes. *Seizure* 1997; **6**:87—93.
30. Scrambler A, Scrambler G, Ridsdale L, Robins D. Towards an evaluation of the effectiveness of an epilepsy nurse in primary care. *Seizure* 1996;**5**:225—8.
31. Hausman SV, Luckstein RR, Zwygart AM, Cicora KM, Schroeder VM, Weinhold OM. Epilepsy education: a nursing perspective. *Mayo Clin Proc* 1996;**71**:1114—7.
32. Reid S, Specht U, Thorbecke R, Goecke K, Wohlfarth R. MOSES: an educational program for patients with epilepsy and their relatives. *Epilepsia* 2001;**42**(Suppl. 3):76—80.