The effect of depression and side effects of antiepileptic drugs on injuries in patients with epilepsy

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AUTHORS' CONTRIBUTIONS

SGO performed statistical analyses, participated in the sequence alignment and drafted the manuscript. MM participated in the study design, coordination, reviewed statistical analyses and the manuscript for intellectual content. NA collected the data, participated in the study design and coordination. HRC collected the data and reviewed the manuscript. DL collected the data and reviewed the manuscript. TVO conceived the study, participated in its design and coordination, participated in the sequence alignment and drafted the manuscript.

Abstract

Background: People with epilepsy are at increased risk of accidents and injuries but despite several studies on this subject, data regarding preventable causes are still contradictory. The aim of this study is to investigate the relationship between injuries, side effects of antiepileptic drugs (AED) and depression.

Methods: Data from a consecutive sample of adult patients with epilepsy attending the Outpatient Clinics at St George's University Hospital in London were included. All patients were asked if they had any injury since last clinic appointment and completed the Liverpool Adverse Event Profile (LAEP) and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).

Results: Among 407 patients, 243 females, mean age 43.1 years, 71 (17.4%) reported injuries since last appointment. A two-step cluster analysis revealed two clusters with the major one (53.5% of the injured group) showing a total score for LAEP ≥45, a positive NDDI-E screening and presence of AED polytherapy. A total score for LAEP ≥45 was the most important predictor.

Conclusion: AED treatment should be reviewed in patients reporting injuries in order to evaluate the potential contribution and burden of AED side effects.

BACKGROUND

People with epilepsy are at increased risk of injury when compared to the general population [1]. This is obviously associated with increased costs and poor quality of life. Previous studies attempted to identify implicated variables to develop prevention strategies. In adult patients, multivariate analyses show that seizure severity, type and frequency are the best predictors of all types of injuries [2,3] but seizure frequency and number of drug-related side effects have been associated with injuries as well [4,5]. In children with epilepsy, attention-deficit/hyperactivity disorder [6,7] and intellectual disabilities [8] were found to be implicated while epilepsy duration, gender and age were never found to be associated [9].

Although, ideally, a better seizure control represents the best way to reduce the likelihood for accidents and injuries, this cannot be always achieved as one third of patients present with drug-refractory epilepsy. It is, therefore, important to explore other possible modifiable factors increasing the risk of injuries in patients with epilepsy. Mood disorders represent the most frequently encountered psychiatric comorbidities in patients with epilepsy. These are associated with poor quality of life (QoL), seizure severity, side effects of anti-epileptic drugs, drug-resistance and a poor outcome after epilepsy surgery [10-12]. However, it is unknown whether psychiatric comorbidities represent an additional risk factor for injuries.

The aim of the present paper is to look at the relationship between injuries, side effects of AEDs and depression.

MATERIALS AND METHODS

Data from a consecutive sample of patients with an established diagnosis of epilepsy attending the epilepsy outpatient clinics at the Atkinson Morley Regional Neurosciences Centre, St George's University Hospitals NHS Foundation Trust in London, were analysed. As part of our routine clinical activity, all patients filled a self-administered questionnaire. This comprised of a question whether they suffered any injuries since their last appointment (usually six months), the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and the Liverpool Adverse Event Profile (LAEP).

The NDDI-E is a well-known clinical instrument, developed for the rapid and objective detection of a major depressive episode in patients with epilepsy using a cut off score >15. It is accepted as a practical and user-friendly screening instrument in an outpatient setting. The LAEP is a 19-item, self-report instrument specifically developed to investigate side effects of AEDs. It is possible to analyse the scores of individual symptoms as well as calculate overall symptom score. Each symptom is quantified on a four-point Likert scale, with 1 indicating that there was "never" a problem; 2 "rarely" a problem; 3 "sometimes" a problem; 4 "always" problem.

As per Research Ethic Committee (REC) advice, research limited to secondary use of anonymized information previously collected in the course of normal care is excluded from formal REC review. Data storage and management was compliant with the Good Clinical Practice statement in accordance to the Declaration of Helsinki.

Data analysis and statistical methods

The following variables were included: age, gender, ethnicity (Caucasian, African, Asian, mixed, others), duration of the epilepsy, drug treatment for epilepsy, LAEP score which was dichotomised as <44 and ≥45 (a LEAP score of ≥45 is considered an unacceptable burden

[13]), presence of seizures in the last 6 months dichotomised as present or not present, presence of depression according to NDDI-E, using more than one AED was coded as polytherapy. LAEP items were also included individually in the analysis.

Initially, patients with and without injuries were compared for clinical and demographic variables. The Chi-square and Fisher's exact tests were used to analyse qualitative variables. Mann–Whitney U test was applied to compare quantitative variables between two groups. Individual LAEP items were also compared in the two groups adopting an alpha error corrected for multiple comparisons (0.05/19 = 0.0026).

Subsequently, a two-step cluster analysis with the previously identified variables was conducted in the group of patients with injuries to identify specific subgroups. Cluster analysis is an exploratory data analysis tool aimed at sorting different objects into groups in a way that the degree of association between two objects is maximal. Cluster groups were determined automatically by SPSS on basis of the best fit. Model fit indicated by the average silhouette of cohesion and separation was 0.5, which is considered as good [14].

All statistical analyses were performed using SPSS version 22.0 for Windows.

RESULTS

Data from 407 patients (243 female) were analysed. The mean age was 43.09 years +/- 15.75. Three hundred twenty-five patients were Caucasian, 35 were African, 33 were Asian, 8 were mixed and 6 were from other nationalities. Seventy-one patients (17.4%) had at least one injury since last appointment (injury (+) group). The remaining 336 patients (82.5%) did not suffer any injuries since last appointment (injury (-) group). Tables 1 and 2 summarise the data of both groups.

When both groups were compared in the descriptive analysis, the injury (+) group included more patients having seizures ($p<0.001$), using multiple anti-epileptic drugs ($p=0.01$), having a higher LAEP score ($p<0.001$), having depression according to the NDDI-E screening ($p=0.002$), having the side effects of restlessness ($p=0.002$), upset stomach ($p<0.001$), difficulty in concentration ($p<0.001$), trouble with gums ($p<0.001$), dizziness ($p<0.001$), depression ($p=0.01$), memory problems ($p=0.01$), and disturbed sleep ($p<0.001$) (tables 1 and 2).

A two-step cluster analysis including all associated variables showed that a high LAEP score (>45) identified two groups of patients: 53.5% of the injury (+) group with a high adverse event total score and the remaining 46.5% with no side effects (Table-3).

DISCUSSION

In this study, we identify further risk factors associated with injury in people with epilepsy. In our sample, 17.4% epilepsy out-patients reported an injury since their last review (typically 6 months). This is higher than rates reported in other studies. Epidemiological studies report a relative risk of 2.9 for injuries in patients with generalised tonic-clonic seizures [15] and a 5% chance per year of visiting an emergency department with a seizure-related injury [16]. However, other injuries such as mechanical falls were not reported. The Rest-1 study [2], found only 24% of injuries seizure related. In the remaining 76% other precipitants may have been present. Little is known about the potential role of AEDs side effects.

As compared to the injury (-) group, patients with injury since last appointment were more likely to have a higher LAEP score (≥45), to be on a polytherapy, to have suffered seizures in the last 6 months and a positive screening for depression. Looking at the individual LAEP items in the two populations, patients with injuries are more likely to have high scores for global cognitive slowing (i.e. memory problems, difficulties in concentrating), coordination

problems (i.e. dizziness) and sleep problems (i.e. disturbed sleep and upset stomach). Interestingly enough, they also reported more problems with gums as compared with injury (-) patients potentially suggesting a high proportion of patients on phenytoin. However, in our dataset the most frequently used anti-epileptic drug was Levetiracetam (42.3%) followed by Lamotrigine (28.2%), Valproate (23.9%), Carbamazepine (23.9%), Pregabalin (7%) and Topiramate (5.6%).

Another interesting finding comes from the cluster analysis in the group of patients with injury that revealed two cluster groups. Both groups are characterised by a similar pattern of concomitant factors like the presence of uncontrolled seizure, polytherapy and depression. However, the difference is a total LAEP score of more than 45. In fact, in 53.5% of patients, a LAEP≥45 represents the most important predictor having the highest importance (importance=1), suggesting that these patients present a significant burden of side effects (more than 45 is usually considered an unacceptable burden). It is possible to speculate that these accidents might be due to drug toxicity causing both, side effects and injuries. In the other group, the total burden of side effects does not seem to be relevant and other factors, still unidentified, play a role. It seems evident that further studies on this subject are needed.

The association between depression and injuries is another interesting finding of our study. Depression represents one of most commonly reported psychiatric comorbidities of epilepsy [17] being reported in up to one third of patients [18]. Patients with psychiatric comorbidities are also more likely to be drug refractory [19] and it is possible that the association with injuries reflects just the increased chances of having uncontrolled seizures. However, epidemiological studies showed that patients with epilepsy have three times increased suicidality risk as compared to the general population with even higher rates in patients with epilepsy and depression [19-22]. It is reported that patients with epilepsy have higher incidences of home, street and work accidents, even without seizures [2]. One explanation

proposed is the reduced attentional processes and information-processing speed with frequent interictal EEG epileptiform discharges occurring in the absence of obvious clinical seizure activity [23, 24]. Those deficits may contribute to injury mechanism. However, these may be due to psychomotor slowing due to AEDs or even due to depression itself.

Our results should be considered bearing in mind the following limitations. First, the seizure type was not recorded. Second, causes of the injuries were not recorded and it was not possible to distinguish between "seizure-related" and "seizure-unrelated" injuries. Third, the type of injury was not recorded. Fourth, presence of injury since last appointment without a specific date, whereas NDDI-E and LAEP refer to the last two weeks prior to the appointment. Hence, we can't differentiate if higher LAEP scores occur as a result or cause of injury. Additionally, retrospective self-reporting via questionnaires bares some limitations. Recall of injuries seems to be reliable but when more detailed information is requested the level of recall accuracy might decline [25]. The effect of adoption of a single question for injuries compared to a structured questionnaire may have influence on recall bias as well.

CONCLUSION

In conclusion, we suggest that individuals presenting with injuries should be evaluated for the side effect burden of anti-epileptic drugs and precautions should be taken. To avoid further injury, focusing on side effects of anti-epileptic drugs, following up their essential minimum dosages and blood levels, deciding the suitable earliest time for discontinuing or change of AED, and being aware of drug-drug interactions would be substantial. Further prospective studies with more detailed and ideally prospectively recorded injury via a structured questionnaire are needed to ascertain which type of drug choice and interactions mostly cause injuries.

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Table 1: Demographics and clinical characteristics

	No injury since last appointment N=336 (82.5%)	**Injury since last appointment N=71 (17.4%)**	**P value**
Age,mean, (SD)	43.4 (16.2)	41.2 (13.3)	0.28
Gender,female, n, (%)	196 (58.3%)	47 (66.2%)	0.22
Duration of epilepsy, mean, (SD)	17.8 (14.4)	19.4 (12.4)	0.40
Presence of seizures (≥1 in 6 months), n, (%)	212 (63.1%)	66 (93%)	**<0.001**
Presence of polytherapy,n, (%)	147 (43.8%)	43 (60.6%)	**0.01**
LAEP >45, n, (%)	92 (27.3%)	37 (52.1%)	**<0.001**
Depression according to NDDIE screening, n, (%)	70 (20)	27 (38)	0.002

***P≤0.05** statistically significant; **SD** standard deviation

Table 2: Severity and presence of side effects among injury (+) and injury (-) groups

	No injury since last appointment N=336 (82.5%)	Injury since last appointment N=71 (17.4%)	P value
SE Unsteadiness, mean, (SD)	2.0 (1.073)	2.45 (1.169)	0.003
SE Tiredness, mean, (SD)	2.87 (1.086)	3.17 (1.082)	0.014
SE Restlessness, mean, (SD)	1.98 (1.087)	2.46 (1.193)	**0.002**
SE Agression, mean, (SD)	1.86 (1.014)	2.00 (1.108)	0.403
SE Nervousness/Agitation, mean, (SD)	2.10 (1.097)	2.39 (1.236)	0.064
SE Headache, mean, (SD)	2.16 (1.072)	2.61 (1.177)	0.003
SE Hair Loss, mean, (SD)	1.59 (1.061)	1.61 (1.021)	0.518
SE Problems of Skin, mean, (SD)	1.72 (1.056)	1.86 (0.975)	0.122
SE Blurred Vision, mean, (SD)	1.60 (0.944)	1.94 (1.182)	0.023
SE Upset Stomach, mean, (SD)	1.74 (0.983)	2.34 (1.121)	**<0.001**
SE Difficulty in Concentration, mean, (SD)	2.16 (1.116)	2.76 (1.165)	**<0.001**
SE Trouble with Gums, mean, (SD)	1.62 (0.964)	2.17 (1.183)	**<0.001**

SE Shakey Hands, mean, (SD)	1.87 (1.105)	2.11 (1.153)	0.079
SE Wieght Gain, mean, (SD)	1.84 (1.130)	1.87 (1.120)	0.666
SE Dizziness, mean, (SD)	1.88 (1.025)	2.52 (1.286)	**<0.001**
SE Sleepiness, mean, (SD)	2.36 (1.153)	2.72 (1.173)	0.016
SE Depression, mean, (SD)	1.97 (1.129)	2.49 (1.252)	**0.001**
SE Memory Problems, mean, (SD)	2.45 (1.196)	2.96 (1.259)	**0.001**
SE Disturbed Sleep, mean, (SD)	2.31 (1.158)	2.87 (1.230)	**<0.001**

*** p<0.0026 (Bonferroni's correction 0.05/19)**; **SD** standard deviation

Table 3: Two-step cluster analysis of injury (+) group

	Cluster 1 (53.5% n=38)	Cluster 2 (46.5% n=33)
LAEP >45,%,(n), (loi)	97.3% (n=37), (1)	0% (n=0), (1)
Depression according to NDDIE screening, %, (n), (loi)	65.7% (n=25), (0.43)	6.1% (n=2), (0.43)
SE dizziness, %, (n), (loi)	50%, (n=19), (0.39)	34% (n=11), (0.39)
SE depression, %, (n), (loi)	55%, (n=21), (0.32)	45% (n=15), (0.32)
SE disturbed sleep, %, (n), (loi)	73.6%, (n=28), (0.37)	55% (n=18), (0.37)
SE difficulty in concentrating, %, (n), (loi)	57.8%, (n=22), (0.30)	58% (n=19), (0.30)
SE memory problems, %, (n), (loi)	73.6%, (n=28), (0.21)	58% (n=19), (0.21)
SE restlesness, %, (n), (loi)	42.1%, (n=16), (0.27)	43% (n=14), (0.27)
SE upset stomach, %, (n), (loi)	44.7%, (n=17), (0.24)	40% (n=13), (0.24)
Presence of seizure,%, (n), (loi)	97.3%, (n=37), (0.06)	87.8% (n=29), (0.06)
Presence of polytherapy,%, (n), (loi)	65.7%, (n=25), (0.03)	54.5% (n=18), (0.03)

***loi** level of importance