Clinical correlates of memory complaints during AED treatment

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Abstract

Objectives: To investigate clinical correlates of memory complaints (MC) during antiepileptic drug (AEDs) treatment in adults with epilepsy with special attention to the role of depression, **using user-friendly standardised clinical instruments which can be adopted in any outpatient setting.**

Materials & methods: Data from a consecutive sample of adult outpatients with epilepsy assessed with the Neurological Disorder Depression Inventory for Epilepsy (NDDIE), the Adverse Event Profile (AEP) and the Emotional Thermometer (ET) were analysed.

Results: From a total sample of 443 patients, 28.4% reported MC as "always" a problem. These patients were less likely to be seizure free (18.3% vs. 34.3%; $p<0.001$), had a high number of previous AED trials (4 vs. 3; $p<0.001$) and high AEP total scores (49 vs. 34.2; $p<0.001$). There was no correlation with specific AED type or combination. Depression was the major determinant with a 2-fold increased risk (95%CI 1.15-3.86; $p=0.016$). When depression was already known and under treatment, patients with MC were less likely to be in remission from depression despite antidepressant treatment (11.9% vs. 1.6% $p<0.001$). Among patients without depression, those reporting MC presented with significantly high scores for depression (3.3 vs. 2; $t=3.07$; $p=0.003$), anxiety (4.5 vs. 2.7; $t=4.43$; $p<0.001$), anger (3 vs. 2; $t=2.623$; $p=0.009$) and distress (3.8 vs. 2.2; $t=4.027$; $p<0.001$) than those without MC.

Conclusions: Depression has to be appropriately treated and full remission from depression should represent the ultimate goal as sub-threshold or residual mood and anxiety symptoms can contribute to MC.

Key words: adverse events, antiepileptic drugs, antidepressant drugs, epilepsy, depression, memory

Introduction

The issue of cognitive complaints in epilepsy is still challenging for clinicians especially when in the context of treatment emergent adverse events of antiepileptic drugs (AEDs). Patients with epilepsy report a degree of subjective impairment in cognitive functioning ranging between 44% for difficulties in learning and psychomotor retardation, to 59% for sleepiness or tiredness (1, 2). Most importantly, 63% of patients perceive that AEDs prevent them from achieving activities or goals (1). It can be challenging for clinicians to understand whether cognitive complaints represent an underlying cognitive problem especially when reported in the context of side effects of medications.

The presence of memory deficits in people with epilepsy is well recognized. In fact, people with epilepsy seek help for memory problems more often than for any other problem (3) and according to the NICE Guidelines, memory complaints (MC) represent one of the indications for a neuropsychological assessment (4). Several studies have revealed discrepancies between subjective MC and the objective results of neuropsychological tests showing that patients who have MC often perform within normal limits on standardized memory tests and emotional factors, such as depression and anxiety, have to be considered (5-16). It seems evident that spontaneous complaints of memory difficulties may overestimate the incidence of the actual impairment (17, 18).

Mood and anxiety disorders represent the most frequent psychiatric comorbidities in patients with epilepsy and reasons for such a close link are both biological and psychosocial (19). In addition, difficulties in concentrating and remembering represent specific symptoms of depression, reflecting a specific dysfunction in frontal lobe activity (20, 21). It is, therefore, important to investigate the role of such comorbidities in patients with MC during AED treatment. **The aim of the present study was to investigate clinical correlates of MC during AED treatment in adult patients with epilepsy with special attention to the role of depression, using user-friendly standardised clinical instruments which can be adopted in any outpatient setting.**

Material & methods

Data from a consecutive sample of patients with an established diagnosis of epilepsy attending the epilepsy outpatient clinics of 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 complete the Neurological Disorder Depression Inventory for Epilepsy (NDDIE) (22), the Adverse Event Profile (AEP) (23) and the Emotional Thermometer (ET) (24). 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.

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 has been found to be a very practical and user-friendly screening instrument in an outpatient setting.

The AEP 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.

The ET is a new screening instrument made up of seven visual analogue scales validated in patients with epilepsy. For the screening of depression in epilepsy, the ET showed a sensitivity of 85.1%, a specificity of 78.8%, a PPV of 0.463 and a NPV of 0.961.

MC have been identified using the specific subscale of the AEP. Groups were compared for age, gender, age of onset and duration of the disease, epilepsy diagnoses, AEDs treatment and combinations, seizure frequency, current depression (defined by a positive NDDIE screening), AEP and ET scores.

Frequencies of categorical demographic and clinical variables were analysed using the $\chi 2$ analysis or Fisher's exact test. Continuous demographic and clinical variables, AEP and ET scores were compared using the Student's t-test for independent samples. Correlations were tested using a bivariate two-tailed parametric correlation procedure (Pearson's coefficient). A logistic regression model was then constructed with age and gender as potential confounders. The alpha error was set at

0.05. All statistical analyses were 2-tailed and conducted using the Statistical Package for Social Sciences (Version 15 for Windows, SPSS Inc. Chicago, IL).

Results

From a total sample of 443 patients, 126 (28.4%) rated "always", 112 (25.3%) "sometimes", 48 (10.8%) "rarely" and 157 (35.4%) "never" for MC. Demographic and clinical variables are shown in **Table 1**. MC subscale correlated with age (r=0.132 p<0.001) but the extent of the correlation was quite weak; it did not correlate with age at onset or duration of the epilepsy. Still, MC subscale correlated with number of previous AED trials (r= 0.196 p<0.001) but again the extent of the correlation was quite weak. Comparing patients who rated "always" vs. the remaining group, patients with MC were less likely to be seizure free (18.3% vs. 34.3%; Chi-square = 11.215; df=1; p<0.001), had a higher number of previous AED trials (4 vs. 3; t=4.037; p<0.001) and a higher load of adverse events in general as demonstrated by the high AEP total score (49 vs. 34.2; t=12.387; p<0.001). There was no difference in age, gender, ethnicity, duration and age of onset of the epilepsy, epilepsy diagnosis. There was no difference in terms of AEDs regimen (polytherapy vs. duo-therapy vs. monotherapy). There was no difference in AED combinations. There was no association with a specific AED (i.e. topiramate, levetiracetam, lamotrigine) apart from pregabalin (PGB). In fact, there were significantly more patients on PGB among those with MC as compared to those who did not (11.1% vs. 0.3%; Chi-Square=32.120; df=1; p<0.001). However, it is important to acknowledge that the total number of patients on PGB, in our sample, was very small, namely 15.

Patients with MC were more likely to be on antidepressant drug treatment (19% vs. 7.3%, Chi-square=13.220; df=1; p=0.001) and to be currently depressed as defined by the NDDIE (48.4% vs. 12.3%; Chi-square=67.265; df=1; p<0.001). The association with depression was further supported by the correlation between the MC subscale and NDDIE total score (r=0.586; p<0.001). In addition, patients with MC presented high scores not only for depression but also for anxiety (6 vs. 2; t=7.419; p<0.001), anger (4 vs. 1; t=7,471; p<0.001) and distress (5 vs. 2; t=7.107; p<0.001) as measured with the ET.

A subsequent regression analysis in the whole sample resulted in a reduced model where only depression and total AEP score were significantly associated with MC (**Table 2**).

Finally, analysing separately patients with and without current depression (as defined by the NDDIE), patients with MC and depression were less likely to be in remission from depression despite the antidepressant drug treatment (Not in remission 11.9% vs. In remission 1.6%; Chi-square=22.308; df=1; $p<0.001$) while, in the subgroup of patients without depression, subjects with MC still presented significantly elevated scores for depression (3.3 vs. 2; t=3.07;p=0.003), anxiety (4.5 vs. 2.7; t=4.43; $p<0.001$), anger (3 vs. 2; t=2.623; p=0.009) and distress (3.8 vs. 2.2; t=4.027; $p<0.001$) (**Figure 1**).

Discussion

Previous authors have suggested a relationship between MC and emotional distress in patients with epilepsy (5-16) and similar results have been found in general medical conditions (25-28). **The novelty of this study is the delineation of MC in a large sample of patients with epilepsy using user-friendly standardised clinical instruments which can be adopted in any outpatient clinic in a real life setting.** Previous studies in epilepsy were conducted in small groups of patients using clinical scales (e.g. Beck Depression Inventory) that can be strongly affected by adverse events of AEDs in general and cognitive adverse events in particular (22). On the contrary, the NDDIE has been developed in order to minimize the impact of adverse events when screening for depression. In fact, in the original NDDIE validation study, AEP scores did not affect the whole model (22). Our results clearly suggest that depression has to be actively considered and appropriately treated in patients with MC during AED treatment. The prevalence of depression in our sample (22.6%), as identified with the NDDIE, is quite in line if not even lower than that reported by the majority of studies conducted in tertiary epilepsy centres (22, 29, 30). The link between MC and depression is easy to understand. Firstly, mood disorders are associated with neuropsychological deficits per se (31). Secondly, patients with depression often believe that their cognitive problems are caused by external factors, such as the drug they have to take, instead of by internal factors such as their mood state or the epilepsy (2). **From our data, it is impossible to understand whether MC represent just biological symptoms of depression or patients with depression are more likely to complain of**

memory problems. Other authors showed that a past history of depression is associated with cognitive complaints during treatment with AEDs (32, 33). **Further studies using objective neuropsychological measures for memory in this group of patients are needed.** However, our results bring further evidence about the importance of a full remission from depression in patients with epilepsy and the role of sub-threshold mood and anxiety symptoms in patients with MC. In our sample, 24% of depressed patients in the group of subjects with MC were not in remission from their mood disorder despite a first line antidepressant treatment at a correct dosage vs. 12% of depressed patients in the comparison group. Obviously, not all these patients could be considered as having a drug resistant depression as probably some of them had only recently started on the antidepressant treatment.

Remission and recovery are main goals of the acute treatment of depression and avoiding recurrence is the main objective of long-term treatment. Remission applies when all symptoms go away and when remission lasts for 6 to 12 months the patient is then considered in a recovery state. In general terms, it is estimated that the percentage of response to one treatment or a combination of therapeutic interventions is up to 90% of patients with depression and among these subjects about 50% may recover within 6 months and up to 75% in 2 years (34). To date, there are no data on remission and recovery rates in patients with epilepsy and depression. Our data bring further evidence on the urgent need of prospective studies addressing this specific issue.

The role of sub-threshold mood and anxiety symptoms is the second important point raised by our study. Even in patients that were not depressed according to the NDDIE, those with MC presented with higher scores for mood, anxiety, anger and distress (**Figure 1**). Although these scores per se were not in the pathological range, they obviously suggest the sub-threshold or residual mood and anxiety symptoms play a role in MC even when a screening for depression is negative. Previous authors pointed out to the role of sub-threshold mood and anxiety symptoms in quality of life of patients with epilepsy (35). Our data support the view that these symptoms are implicated in MC during AED treatment and should get clinical consideration.

Other clinical variables identified by our study worth further discussion. The association with poor seizure control and the total number of previous AED trial may suggest that patients with more severe, drug-refractory syndromes are more likely to complain of memory problems than those who are well controlled. This finding would be in keeping with previous studies emphasizing the role of the underlying epileptic syndrome for cognitive problems (36). In this regard, it is interesting to note that even newly diagnosed untreated patients with epilepsy seem to be cognitively compromised even before they start AEDs, independently by the underlying cause, with memory and psychomotor speed being the most severely affected domains (37). The lack of an association with the AED regime (either monotherapy or polytherapy) is in keeping with a major role played by disease-related variables rather than by treatment-related ones, as already suggested by other authors regarding treatment emergent adverse effects of AEDs in general (38). The association between MC and depression has to be discussed in such a light. Whether patients with epilepsy and depression configure a specific endophenotype characterized by poor response to treatment and increased risk of treatment emergent adverse events has to be further explored.

Our results should be considered bearing in mind the following limitations. First, the retrospective nature of this study. However, the cross-sectional data on which it is based was collected prospectively as part of a previous study aimed at identifying relevant variables using user-friendly instruments that can be adopted in any outpatient settings. **Neuropsychological tests represent the gold standard for memory assessment in epilepsy but our data bring further evidence on the need for a multidisciplinary approach and a routine screening for depression in patients with epilepsy and MC, depicting a pragmatic way for neurologists to approach the problem of MC in a busy outpatient setting.** Second, our results may not be representative of the general population of patients with epilepsy as they come from a tertiary referral centre where more severe and drug-refractory cases are present. Third, the NDDIE and ET represent well-known screening instruments for a depressive episode but they are not diagnostic of a specific categorical diagnosis per se and a subsequent formal psychiatric assessment is needed in order to clarify whether the depressive episode

is part of a major depressive disorder, a bipolar disorder or a persistent depressive disorder. However, an eloquent disquisition about the underlying psychopathological picture was not our aim.

Further prospective studies in specific subpopulation of patients with epilepsy are urgently needed in order to develop tailored treatment approaches and management plans.

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Conflicts of interest

MM received consultancy fees from UCB Pharma, Eisai and Pfizer. He has also received supports from Special Products Ltd and is currently serving as Associate Editor of Epilepsy & Behavior. HRC has served as a paid consultant for Special Products Ltd and Eisai Europe Ltd, and received speaker honoraria/support from UCB Pharma, and Glaxo-Smith-Klein Ltd. Details at www.whopaysthisdoctor.org. TJvO received a research grant, travel grants and consulting fees from UCB pharma, travel grants from Eisai, Novartis, Biogen-Idec, consulting fees from UCB, Eisai, Genzyme, Biogen-Idec and Novartis. DAL received hospitality from Eisai and UCB.

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Table 1. Demographic and clinical variables in patients in the study sample.

	N = 443 (%)
Gender	
Males	179 (40.4%)
Females	264 (59.6%)
Age, years mean +/- SD	43.1 +/- 15.6
Age at onset, years mean +/- SD	24.6 +/- 17.8
Diagnosis	
Focal	285 (64.3%)
Generalised	138 (31.1%)
Unclassified	20 (4.6%)
Seizure free	132 (29.8%)
AED therapy	
Monotherapy	213 (48.1%)
Duotherapy	160 (36.1%)
Polytherapy	70 (15.8%)
Total n AED trial, mean +/- SD	3.2 +/- 2.3

Table 2. Logistic regression model for memory complaints (adjusted OR for age and gender).

Variable	Wald	OR	95%CI	P value
Number of AED trial	2.086	1.08	0.97-1.20	n.s.
AEP Total score	39.654	1.08	1.06-1.11	<0.001
Depression	5.776	2.10	1.15-3.86	0.016
Seizure freedom	0.732	0.77	0.42-1.40	n.s.

Figure Legend: Figure 1. Emotional Thermometer (ET) scores in patients with memory complaints (MC) with and without depression (Black=MC; Light grey=noMC; *t=3,075 p=0.003; **t=4,430 p<0.001; §t=2,623 p=0.009; §§t=4,027 p<0.001).