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Cognitive impairment in adults with epilepsy: the relationship between subjective and objective assessments of cognition.

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Abstract

Aim

To assess the relationship between objective measures of cognition and subjective perception of cognitive functioning reported by patients with epilepsy and their care givers.

Methods

100 patients with epilepsy attending hospital neurology outpatient clinics and their care givers were enrolled in this study. The Epitrack® (version 1) brief cognitive screening tool was used to measure objective impairment, the ABNAS questionnaire (A-B Neuropsychological Assessment Schedule) to assess subjective cognitive performance, and a version of the ABNAS designed to be completed by caregivers (C-ABNAS) to document caregivers' views. Patient anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) and considered as covariates. Patients with an uncertain diagnosis of epilepsy or likely severe comorbid mood or anxiety disorders were excluded.

Results

Data from 82 patients was analysed after exclusion of patients with uncertain diagnoses or likely mood and anxiety disorders. Fifty-nine (72%) had a degree of objective cognitive impairment. Fifty of these 59 patients (85%) had 'high' ABNAS scores concordant with the objective assessment and 43 (73%) had high C-ABNAS scores matching the abnormalities

detected by objective screening. Of the 23 (28%) patients without objective cognitive impairment, seven (30%) had concordantly low ABNAS scores and 10 (43%) had concordantly low C-ABNAS scores. Patient memory impairment was more often reported by patients themselves than by caregivers (p=0.011). Carers were significantly more likely to rate patients as having impaired motor co-ordination than patients themselves (p=0.016).

A small part of the variance of the Epitrack score was predicted by the C-ABNAS. Objective cognitive performance did not predict ABNAS or C-ABNAS scores.

Conclusions

Self- or caregiver report questionnaires identify patients with epilepsy and objective cognitive impairment more accurately than patients with objectively intact cognition. Objective tests of cognition, self-report and carer report of cognitive functioning are largely independent of each other and provide complimentary information. ~~Those without objective evidence of cognitive impairment may nevertheless perceive themselves as having memory dysfunction; it is these patients therefore who benefit most from both subjective and objective assessments of cognition, including carers' assessments, in order to establish the nature of their symptoms.~~ None of these assessment measures can be used as a reliable proxy for another, each contributes individually to a comprehensive assessment of cognition and all must be used in conjunction with measures of mood and anxiety.

1. Background

Patients with epilepsy (PWE) experience a broad range of subjective cognitive impairments affecting domains such as memory, attention and word finding ability. In a survey conducted by the International Bureau for Epilepsy, 45% of responders felt that their thinking was slowed or that they had difficulties with new learning (2004; Mounfield et al. 2004).

However, several studies have shown that there is poor correlation between subjective and objective measures of cognitive function in these patients. (Thompson and Corcoran 1992; Perrine et al. 1995; Elixhauser et al. 1999). These discrepancies could be attributable to problems with the ecological validity of objective tests (their correlation with everyday cognitive performance). There may also be confounders affecting patients' self-reporting of symptoms, namely limited insight into their own cognitive problems, anxiety or depression. What is more, it is likely that physicians' and patients' understanding of cognitive function differ conceptually, and that this difference is not adequately accommodated by current neuropsychological tests (Helmstaedter and Elger 2000).

A major factor limiting clinicians when assessing cognitive function objectively is the time required to perform an assessment. Epitrack® is an objective fifteen minute screening tool for cognitive impairments in PWE and was developed as a tool that is particularly sensitive to cognitive problems originating from antiepileptic drug treatment, as demonstrated by two monotherapy studies (Helmstaedter and Witt 2008; Helmstaedter and Witt 2010). Whilst Epitrack scores appear to reflect the complexity of antiepileptic drug regimens as well as seizure control (Helmstaedter 2005), the degree of correlation between the Epitrack

score and self-reported cognitive functioning remains unclear. Assessment of 247 untreated PWE revealed that, where Epitrack detected impairment in attention and executive functions~~memory deficits~~ in 47.8%, only 25.1% of patients complained of these symptoms (Witt and Helmstaedter 2012).

The relationship between Epitrack and caregivers' perceptions of memory has not previously been assessed. Given that patients may both under- and over-report cognitive symptoms (Hall et al. 2009) the question is whether family, friends or caregivers could be better judges of the patient's objective cognitive impairment than the patient him/ herself.

A number of questionnaires have been designed to assess cognitive function subjectively; these measures tend to focus on the impact of cognitive difficulties on everyday function. One example is the A-B Neuropsychological Assessment Schedule (ABNAS), which was originally designed by Aldenkamp and colleagues as the "Neurotoxicity Scale" (Aldenkamp et al. 1995). It has been validated as a measure of patient-perceived cognitive function against the computerised Fepsy neuropsychological battery (Aldenkamp et al. 2002), although not against a clinician administered tool such as EpiTrack. The ABNAS has previously been used to assess the scope of cognitive complaints in a number of PWE, including in those following a first seizure (Velissaris et al. 2009). In its original form, the ABNAS does not take account of caregivers' perceptions of the patient's cognitive functioning.

1.1 Study Objectives

In this study we compare cognitive performance as measured by EpiTrack, a well-validated objective measure of executive function and working memory, with that described by the ABNAS questionnaire. We relate both forms of assessment to that delivered by friends / family members / caregivers of PWE on a version of the ABNAS questionnaire adapted for completion by third parties. We then consider the effects of epilepsy-related variables on these three measures of cognitive functioning.

2. Methods

2.1 Study Design

A cross sectional analysis of data from 100 PWE and their caregivers (friends/relatives) was performed. Consecutive PWE attending the adult outpatient neurology clinics at the Royal Hallamshire Hospital, Sheffield (RHH) and the University Hospitals Coventry and Warwickshire, Coventry (UHCW) were invited to participate. Patients completed the EpiTrack ® version 1 test procedure administered by a psychologist immediately prior to their outpatient consultation. Patients also completed the ABNAS questionnaire. Caregivers (friends/ relatives) independently completed a version of the ABNAS questionnaire (C-ABNAS, modified for the purpose of this study).

2.2 Inclusions

Patients were aged 18 years and over. Patients were only included if their diagnosis of epilepsy had been made by a neurologist with a special interest in seizure disorders. Subjects had to be accompanied by a caregiver who knew them sufficiently to be able to answer questions about their cognitive functioning via the modified ABNAS questionnaire (C-ABNAS).

2.3 Exclusions

Patients with clinically uncertain diagnoses of epilepsy or patients in whom there was a suspicion of additional psychogenic nonepileptic seizures or other types of paroxysmal disorders were excluded. Patients who were unable to complete the self-report questionnaires without assistance (for example, those with significant learning disability) and patients identified as severely anxious or depressed with a score of 16 or more on

either the anxiety or depression subset of the Hospital Anxiety and Depression Rating Scale (HADS) were also ineligible for inclusion.

2.4 Regulatory Approvals

The South Yorkshire research ethics committee approved the study. All patients and caregivers gave written informed consent prior to their participation in the study.

2.5 Group size calculation

Prior to the study we established that a minimum of 44 patients was required to detect a correlation of at least 0.5 between the assessment measures with 90% power at a significance level of 5%. 100 patients were recruited to allow for loss to exclusions.

2.6 Measures

Objective cognitive functioning

Patients completed the Epitrack® version 1, which assesses attention, executive function and working memory (Helmstaedter 2005). Results are summed to give a total score, corrected for age. The maximum score is 45 points; those scoring those scoring 27 to 25 points are classified as unimpaired, those between 26 and 28 (between -1 and -2 SD below the mean) as mildly impaired and those scoring below 26 points as significantly impaired (>2 SD below the mean). The Epitrack ® has been shown to be sensitive to epilepsy type, seizure control, and especially antiepileptic treatment choice and drug load (Witt et al. 2013).

Subjective cognitive functioning

Patients were asked to complete the ABNAS (Aldenkamp et al. 1995). This comprises 24 statements across five domains: fatigue, slowing, memory, concentration, motor coordination and language, with an overall score from 0 – no symptoms reported to 72 – severe symptoms. A cut off of above 15 (“high”) has previously been established to identify those with significant subjective symptoms (Aldenkamp and Baker 1997; Brooks et al. 2001).

Caregiver-reported cognitive functioning

Caregivers / friends / relatives completed adapted modified version of the ABNAS, the caregiver ABNAS (C-ABNAS). This involved the replacement of the first person statements on the original ABNAS with third person statements (eg. "He/she has difficulties remembering names of people"). Response options and scoring were identical to the original ABNAS.

Coexisting mood symptoms

Patients completed the Hospital Anxiety and Depression (HADS) rating scale (Zigmond and Snaith 1983) which was used as a screening tool to identify those with significant mood symptoms. It comprises 14 questions across two subsets- anxiety and depression. Within each subset scores range from 0-7 no significant symptoms to 16- 21- severe symptoms. We used a cut-off score of ≥ 8 for each of the anxiety and depression subsets as a marker of likely psychopathology and excluded those with a score of ≥ 16 in either subset. The HADS scale is described in detail elsewhere and has been extensively validated across a range of subgroups of PWE (Andrewes et al. 1999; Moss et al. 2009; Salas-Puig et al. 2009).

2.7 Clinical data

Seizure frequency was determined by self-report and verified by recourse to seizure diaries when available. Antiepileptic drug (AED) treatment details were obtained from patient's clinical records. In keeping with previous critical reviews of the cognitive risks associated with different AEDs (Ortinski and Meador 2004), these drugs were subdivided into three cognitive risk categories: Levetiracetam and lamotrigine were included in the low risk category; valproate, carbamazepine, oxcarbazepine, phenytoin, pregabalin in an intermediate risk category; and clobazam, topiramate, zonisamide and phenobarbital in a high risk category. Patients were categorised according to their AED associated with the greatest cognitive risk.

2.8 Statistics

Given that the C-ABNAS was used in this study for the first time, the internal consistency of the questionnaire was assessed using Cronbach's alpha. An alpha level of ≥ 0.70 was considered as indicative of an acceptable level of internal consistency. Stepwise backwards linear regressions were calculated to determine the contributions of the available variables to models explaining Epitrack, ABNAS and C-ABNAS scores. The following variables were entered in these models: Epitrack, ABNAS and C-ABNAS scores, seizure frequency, epilepsy syndrome, gender, epilepsy centre, HADs anxiety and depression scores, AED number, AED cognitive risk category). The significance of the linear regression models was tested by ANOVA. Two-sided p-values of <0.05 were considered statistically significant.

3. Results

Thirty-nine patients from RHH and 43 patients from UHCW met the inclusion criteria for the study. Of the 18 patients excluded from the study, two were excluded because of uncertainty regarding the diagnosis of epilepsy. The remaining 16 had HAD anxiety or depression scores above the threshold for exclusion ~~threshold for~~from this study (see table 1 for more detailed demographic and clinical information about the patients in this study). ~~44 (53.9%) of patients were male. 63 (76.7%) had a focal epilepsy. 45 (54.8%) of patients had frequent (> 1/month) seizures (table 1).~~

3.1 Objective measures of cognitive impairment

All but one of the 82 patients were prescribed AEDs. 59 of the 82 patients (72%) had a degree of cognitive impairment, as measured by Epitrack, The proportion of those experiencing 'significant' cognitive impairment on Epitrack ® was 34% of those prescribed monotherapy, 64% of those prescribed two AEDs and 71% of patients prescribed three or more AEDs. Considering AED cognition risk score, a higher proportion of those prescribed AEDs with a risk score of 3 experienced significant cognitive impairment compared with those prescribed AEDs with a risk score of 1 or 2 (p=0.021) (fig 1).

3.2 Subjective measures of cognitive impairment

Sixty-seven (81.7 %) of the patients scored themselves as 'high' on the ABNAS indicating self-perceived cognitive dysfunction. Fifty-six (68.5%) of the caregivers scored patients in this range on the C-ABNAS. The C-ABNAS, a modification of the ABNAS designed to capture

caregiver's observations, was found to be internally consistent with a Cronbach's alpha of 0.95.

Significantly more patients prescribed polytherapy self-reported~~experienced~~ subjective cognitive impairment (p =0.002). The trend was not reflected in the ~~inconsistent when considering~~ caregiver scores ~~(~~as measured by the C-ABNAS (figure 1).

There was a significant difference between the number of patients (ABNAS) versus their caregivers (C-ABNAS) reporting moderate/ serious symptoms in both the memory and motor coordination domains of this questionnaire. A higher proportion of patients rated themselves as having memory impairment (p=0.011). A higher proportion of carers rated the patients as having impaired motor coordination (p= 0.016, ~~).~~see table ~~(~~table 2 for further details).~~appendix)~~

3.3 Concordance between objective and subjective measures of cognition

Overall, concordance between objectively measured cognitive performance and patient or caregiver report was modest. When objectively measured cognitive performance (Epitrack) was impaired, concordance of objective scores was greater with patient reported cognition (ABNAS) than caregiver reports (C-ABNAS). However, when objective cognitive performance (Epitrack) was unimpaired, concordance with objective scores was greater between caregiver reports (C ABNAS) than patient self-report (ABNAS) (see table 3~~2~~).

~~3.4 Relationship between mood symptoms and cognitive impairment~~

~~There were significant correlations between HADS anxiety and depression scores and all three cognitive assessment measures (appendix). Correlation was greatest between the HADS and ABNAS scores.~~

3.~~4~~5 Modelling cognitive impairment

The relative contribution of each measure to a model predicting subjective and objective cognitive impairment is shown (figure 2a-c). Of all variables available, the Epitrack score was predicted by the C-ABNAS- score (p=0.006) and AED cognitive risk category (p=0.035). The backward stepwise linear regression model of the Epitrack explained 13.1% of the variance (F=5.965, p=0.004). The ABNAS score was predicted by depression (p=0.001), C-ABNAS- (p=0.002), anxiety (p=0.032) and AED cognitive risk category (p=0.071). The ABNAS model explained 28% of the variance (F=22.153, p<0.001). The C-ABNAS score was predicted by ABNAS (p<0.001), anxiety (p=0.019), gender (p=0.036) and seizure frequency (p=0.047). The C-ABNAS model explained 31% of the variance (F=13.518, p<0.001).

4. Discussion

Cognitive functioning is one of the greatest concerns of PWE, has significant effects on adherence with medical epilepsy management (Witt et al. 2013), and influences the decision-making process about medical and surgical treatments for epilepsy ~~surgery~~ (McIntosh et al. 2001). The single best measure of cognitive function in epilepsy remains unclear. This study assesses the relationship between well-validated objective and subjective measures of cognitive functioning. It also considers the relative value of third-party (caregiver/family/friend) reports of cognitive functioning.

The main finding of this study is that the concordance between subjective and objective measures of cognitive function is moderate; objective impairment measured by Epitrack matched self-reported impairment on ABNAS scores in only 63% of subjects. Caregiver-reported impairment matched poor objective cognitive functioning even less well than patient -reported impairment. Unimpaired objective cognitive functioning was identified with even lower accuracy by patient or caregiver report than objectively impaired functioning.

Conversely, subjective cognitive impairment is often not observable objectively; 70% of those without objective cognitive impairment still reported significant subjective symptoms.

The relatively weak relationship between objective and subjective (or caregiver-rated) measures of impairment became clearer in the regression models: Objective cognitive impairment (as measured by Epitrack) did not contribute to the models of self-reported or caregiver reported cognitive impairment at all. Only the caregiver assessment contributed to the multivariate model. Despite the fact that we captured a wide range of clinical, demographic and reported measured variables in this study, the modelling of the Epitrack scores only explained a very modest proportion of the variance of subjectively reported cognitive impairment (13.1%). In part the lack of concordance between EpiTrack, self-and caregiver-reported cognitive function may, at least in part, be explained by the fact that the ABNAS asks about domains of cognition which EpiTrack does not formally assess, such as other aspects of memory than working memory. We have not attempted to correlate single items or domains of ABNAS or caregiver ABNAS with EpiTrack. It is possible that items asking about mental slowing or concentration could correlate more closely with the kinds of cognitive functions captured by EpiTrack than the total ABNAS scores.

The contribution which both depressive and anxiety symptoms make to patient- or caregiver-perceived cognitive dysfunction is striking. This cross-sectional study does not tell us about the direction of the relationship between mood and cognitive symptoms. It may be that mood disorders cause symptoms of cognitive dysfunction or that cognitive dysfunction (not captured by objective testing) can cause symptoms of anxiety and depression. The relationship between mood and cognitive symptoms may also be mediated by other factors, such as the well-documented interdependent relationships with antiepileptic drug therapy and seizure frequency (Elixhauser et al. 1999; Meador 2002; Marino et al. 2009). This may

well have been relevant in our refractory population recruited in a specialist epilepsy clinic, with 60% prescribed polytherapy.

If it is clear that all three measures of cognitive function are complementary, can a relative weight be placed on each of these measures? Assessment of mood is often viewed as an essential screening tool; it is likely to influence a patient's perception of their cognitive function and their perception of the likely efficacy of changes to their epilepsy management (for example, changes to AEDs). If the patient feels that their cognition is unimpaired, asking for a carer's response may be additionally helpful. Although carers often detect changes in performance, they may be more likely to detect changes in *physical*, rather than mental function.

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5. Limitations

We have used a cross sectional design to study our sample population. It may well be that the measures of cognitive functioning used here would have performed differently in a longitudinal study, for instance involving the application of the measures before and after the introduction of a particular drug. The findings of our study may not be readily generalizable to patients with epilepsy in general: the study population was drawn from specialist epilepsy clinic in two clinical neuroscience centres. Our data demonstrate that we were dealing with a patient population, which was significant impacted by relatively refractory seizure disorders. The C-ABNAS measure used here was developed for this study. Although the Crohnbach's alpha levels of all subscores of this measure were acceptable, there is no previous experience with this questionnaire and no information on test re-test reliability. The EpiTrack which was used as an objective measure of cognition in this study does not capture all domains of cognitive function covered by the ABNAS. It may be that we could have identified closer correlations between objective and subjective measures if we had combined EpiTrack with more extensive objective tests, for instance of memory functions. However, more extensive cognitive testing would not have been replicable in a routine outpatient clinic setting.

~~That's very good so far. A point I miss and which might be detected by the informed and careful reader is, that EpiTrack assesses functions which are only poorly covered by the ABNAS, its only mental slowing and concentration which overlap (detailed anyalysis might have provided better correlations). Memory is not covered with ET??. We may skip this but this is surely one factor which can explain missing correlations. Apart from this I think that~~

clinically it is interesting that caregivers reports are influence by seizures and that subjective and objective assessment picked up some part and may be different treatment side effects.

For the discussion I think it is important that EpiTrack is a short screening butit is valid only for a certain, still very important, cognitive domain. It therefore may miss problems patients see. And for the subjective measures we don't know whether there might be an objective performance or test which might reveal the objective basic for this. (see Juri Witts and my publication on long delayed recall and subjectively complained memory.

I think that a good point can be made, and you mention this in the introduction, that there is no time and no money for doing extended evaluations. Thus which combination of short screenings would provide the best and most reliable overview. In addition the decisive question is what we really need to know for treatment and what the clinical consequences of the assessment might be. (there are not too many: change reduce AED, introduce antidepressants, send to psychotherapy, counseling etc.) Maybe we should mention this more explicitly?

6. Conclusion

Assessment of cognition ideally requires a triad of subjective, objective and carer reports. Subjective measures assess different facets of performance compared with objective tests and are particularly subject to influence by co-existing mood symptoms. The subjective ABNAS assessment tool was the most sensitive measure of cognitive dysfunction in this study, but it was not closely correlated with the objective measure of cognitive function used here, the Epitrack. In fact, only caregiver-reported cognitive functioning and not patient-reported functioning contributed to a model of objective cognitive test performance. Mood and anxiety symptoms strongly influence patient or caregiver report of

cognitive symptoms but did not ~~affect~~ correlate with~~to~~ objective cognitive function in this study. Treatment-related variables such as the choice of an AED associated with a greater risk of cognitive dysfunction affected objective and questionnaire based cognitive functioning scores. Exclusive reliance on self-reported cognitive problems may cause clinicians and patients to continue treatments with significant adverse effects on cognitive function. Conversely, subjective report may cause the physician to change a successful therapy which objectively does not harm cognition. S~~o s~~ubjective report or simply asking ~~the~~ patient or caregivers about cognition can provide initial clues about potential cognitive side effects of treatment ~~reveal valuable information for the beginning~~, however, this study demonstrates that ~~but if there is doubt,~~additional objective assessment can yield important additional information with likely effects on ~~can provide the guidance for~~ treatment choices.

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Disclosures and Conflicts of Interest

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

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