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Executive functions and psychiatric symptoms in drug-refractory juvenile myoclonic epilepsy

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ABSTRACT

Purpose: The pattern of executive dysfunction reported in juvenile myoclonic epilepsy (JME) resembles that of patients with cluster B personality disorders. This study examined whether executive dysfunction and maladaptive behavior reported in patients with JME are related.
Method: Sixty patients with drug-refractory JME were administered tests of intellect, memory, and executive dysfunction. Anxiety, depression, personality traits, impact of epilepsy, and perceived cognitive effects of antiepileptic drugs were measured.
Results: Half of the cohort exhibited moderate to severe anxiety symptoms. The patients performed most poorly on naming ability and inhibition switching. Duration of epilepsy exacerbated poor performance on inhibition switching. Females presented with pathological scores for neurotic and introvert traits and males for introvert traits. Abnormal personality traits and psychiatric disorders were associated with worse intellectual and executive functioning. People with extreme Eysenck Personality Scale — Brief Version (EPQ-BV) scores demonstrated the greatest level of executive impairment. Furthermore, the same degree of dysfunction was not seen in any individual with unremarkable EPQ-BV scores.
Conclusion: This study indicates that specific patterns of executive dysfunction are related to maladaptive behavior in JME. Distinct behavioral patterns may be used to identify functional and anatomical differences between people with JME and for stratification to enable gene discovery.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalized epilepsy with onset occurring during adolescence and is lifelong in most individuals. Standard diagnostic magnetic resonance imaging is unremarkable, and 40% of members of an expert panel stated that cognition must be intact to make the diagnosis [1]; despite this, impairments in executive function are consistently demonstrated in JME [2–6]. The executive dysfunctions found are similar to those reported in patients with cluster B personality disorders [7,8]. Moreover, researchers have described structural and functional abnormalities in the frontal lobes of patients with JME [9–11], which have also been reported in patients with personality disorders [12,13].

Janz and Christian described the personality of people with JME as typically "*characterised by unsteadiness, lack of discipline, hedonism, and an indifference to their disease*" [14]. Subsequent research has investigated the psychiatric comorbidities in JME and has found high incidence of anxiety and personality disorders [9,15,16].

It has been proposed that JME is not one disorder but several subtypes [17], and past research has attempted to categorize patients with JME into these subgroups [18]. We have chosen to focus our study on the fifth of patients who do not adequately respond to sodium valproate, the anticonvulsant of choice. Research has revealed different levels of neuropsychological dysfunction, psychiatric disorders, and different personalities in patients with JME [15,19]. De Araujo Filho et al. proposed that the distinct patterns of behavior could be partially explained by the localization of seizure foci and the recruitment of broader networks implicated in epileptogenesis.

1.1. Aims of the study

The study aimed to address whether the executive dysfunctions and maladaptive behavior reported in people with juvenile myoclonic epilepsy are related. In addition, we examined the proportion of affective symptoms, personality traits, and executive dysfunctions in a sample of patients with drug-refractory juvenile myoclonic epilepsy.

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2. Materials and methods

2.1. Subjects

Sixty people with drug-refractory JME were assessed as part of the multicenter MRC-funded refractory juvenile myoclonic epilepsy cohort (ReJuMEC) study. Participants were recruited from outpatient appointments in epilepsy clinics in the Untied Kingdom. Patients were classified as having drug-refractory epilepsy if they experience ≥1 seizure per month despite prior or current exposure to a dose of at least 1000 mg of sodium valproate. The definition of drug-refractory epilepsy varies greatly in the literature [20] and has not been defined in JME research. The criteria used were based on a combination of the knowledge of sodium valproate being effective in 85–90% of the patients with most becoming seizure-free [21], the criteria used by others [22,23] and clinical experience of members of the ReJuMEC group. Exclusion criteria included abnormal brain MRI scan, alcoholism, a history of drug abuse, and/or neurological disorder besides epilepsy. In addition, none of the patients had experienced a generalized tonic–clonic seizure within the 24 h prior to the neuropsychological assessment. Ethical approval was granted by the North West 1 Research Ethics Committee — Cheshire, and written informed consent was obtained from all patients. Please see Table 1 for the demographic and clinical characteristics of the current sample.

2.2. Neuropsychological battery

Participants were given a clinical interview, and a detailed history was obtained from their clinical records. A standardized comprehensive battery of neuropsychometric tests was chosen to enable the evaluation of intellectual ability, language functioning, verbal and nonverbal memory, and executive functions. For a detailed description of the battery used, please refer to Thomas et al. [24].

2.2.1. Attention and executive functions

The color–word interference task from the D-KEFS and zoo map, key search, and rule shift from the Behavioural Assessment of Dysexecutive Syndrome (BADS) were used to assess control of inhibition, perseveration, mental flexibility, planning ability, and attention.

2.3. Severity of executive dysfunctions

Executive function tests were divided into six executive functions, and the z-scores of each of the tests were calculated. In concordance with previous research [25,26], a z-score of ≤− 1.00 (one or more standard deviations below the manual means) on at least one test within each of the six domains was categorized as dysfunction in relation to that domain. If two domains met these criteria, the patient was assessed as having mild executive dysfunction; if three or four domains met the criteria, the patient was assessed as having moderate dysfunction; and if five or more domains met the criteria, the patient was assessed as having severe dysfunction. The six domains were as follows:

- Working memory, mental control of auditory–visual stimuli, and attention span: assessed using the digit span and letter–number sequencing.
- Visual working memory, mental control of visual–spatial stimuli, and attention: assessed using the digit–symbol coding and spatial span.
- Verbal fluency: assessed using letter fluency and category fluency.
- The ability to switch between categories: assessed using category switching and category accuracy.
- The ability to inhibit responses to visual–verbal stimuli: assessed using the color–word interference test (verbal inhibition and inhibition switching).
- Naming ability: assessed using the Boston Naming Test.

2.4. Questionnaires

The Eysenck Personality Questionnaire — Brief Version (EPQ-BV) [27,28] was administered to examine the presence of personality traits in JME and whether these traits are related to clinical variables, cognitive impairment, and executive dysfunction. The EPQ-BV is a 24-item short version of the EPQ-R, which was developed from the original Eysenck and Eysenck's EPQ (1975). It is a self-report questionnaire that measures two personality dimensions, namely, extroversion (E) and neuroticism (N). The EPQ-BV was chosen over other measures because of its brevity, Likert scale, and good retest reliability and validity [27].

The Hospital Anxiety and Depression Scale (HADS) [29], the Aldenkamp–Baker Neuropsychological Assessment Scale (ABNAS), and the Impact of Epilepsy Scale (IES) were also performed. The HADS is an assessment of an individual's level of anxiety and depression. The ABNAS is a subjective assessment of symptoms of neurotoxicity such as fatigue, whereas the IES to record how disruptive epilepsy has been to the individual's life.

2.5. Statistical analysis

Means and standard deviations were calculated for the demographic and clinical characteristics and reported for continuous data that met the normal distribution. If data were considered skewed from the normal distribution, the median and interquartile ranges were reported. One-sample t-tests (Wilcoxon signed-rank test if skewed) were conducted based on the means and standard deviations given by the assessment manuals to compare the cohort's performance with standardized norms. To reduce the likelihood of making a Type I error, the significance level was set at $p < 0.01$ for all t-tests. Bonferroni correction was not applied as this would have provided too conservative an alpha statistics estimate, increasing the likelihood of making a Type II error.

Those scoring the highest levels of mood symptoms (HADS) and personality traits (EPQ) were identified. A quirk of the normative values provided by Sato for the EPQ-BV is that males and females are analyzed separately [28]; one-sample t-tests were employed (as above). Pearson's correlation analyses were conducted between intellectual functioning, executive functioning, HADS scores, and EPQ-BV scores. Clinical variables and psychometric test scores identified from the Pearson correlation were investigated further with independent sample t-tests. Mann–Whitney U test was used for skewed data. Hierarchical regression was performed to assess the contribution of anxiety and neuroticism on test scores.

3. Results

3.1. Affective symptoms

49% of the patients scored in the moderate to severe range for anxiety symptoms and 16% for depressive symptoms. Nine (24%) people had mild anxiety; 15 (41%) people had moderate anxiety; and three (8.1%) had severe anxiety symptoms. In contrast, seven (19%) people had mild depressive symptoms; five (14%) had moderate depressive symptoms; and one (2.7%) had severe depressive symptoms.

Higher anxiety scores were significantly correlated with poorer function on tests of vocabulary, similarities, information, picture completion, verbal IQ, performance IQ, full-scale IQ, and letter fluency. Independent t-tests revealed significantly poorer function on the WAIS subtests vocabulary ($p = .004$) and information ($p = .010$). People with high anxiety scores had, on average, 2.77 points lower on vocabulary ($d = 1.02$) and 2.40 points lower on the information subtest ($d = 0.89$) compared with people with drug-refractory JME and less extreme HADS anxiety scores. Anxiety remained a significant independent predictor of performance on the information subtest when correlated clinical and demographic characteristics (duration of epilepsy and years of education) were controlled for and explained 19% ($p = .003$) of the