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A comprehensive neuropsychological description of cognition in drug-refractory juvenile myoclonic epilepsy

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ABSTRACT

The study of juvenile myoclonic epilepsy is important in that: it is common and heterogeneous; the etiology is unknown; and patients report broad cognitive problems. We utilized a broad battery of neuropsychometric tests to assess the following: intellectual function, memory, language and naming, executive function, the impact of epilepsy, and antiepilepsy drug side effects. Sixty people with drug-refractory JME were interviewed, and performance was profoundly impaired across the range of tests. Impairments included the following: full-scale IQ (89, $p < 0.001$); processing speed (86, $p < 0.001$); visual memory (immediate and delayed) more affected than verbal memory; verbal fluency and inhibition ($p < 0.001$); and self-reported drug side effects ($p < 0.001$). Eighty-three percent of patients exhibited frank executive dysfunction, which was moderate to severe in 66%. Regression modeling confirmed that an early age at onset and the need for polytherapy were associated with poorer cognitive outcomes. This study confirms previous reports of executive dysfunction in a larger cohort and with greater statistical rigor. We also identified a high prevalence of neurotoxicity symptoms such as fatigue and poorer functioning across intellectual and memory tests than had previously been reported.

1. Introduction

Juvenile myoclonic epilepsy (JME) is both the most typical and atypical of the genetic generalized epilepsies (GGEs). It is a common electroclinical syndrome that accounts for 5 to 10% of all epilepsies [1]. It is characterized by the following: i) the age at seizure onset; ii) the triad of absence seizures, generalized tonic–clonic seizures, and epileptic myoclonus — of which only myoclonus needs to be present; iii) a tendency for lifelong seizures with an early morning preponderance; and iv) typically, the improvement of seizure control in 80% of individuals with the use of sodium valproate. The atypical features include the following: i) an inconsistency as to how cases are defined [2]; ii) despite the evidence from twin studies and family aggregation studies [3], no convincing gene for this genetic epilepsy has been identified [4]; iii) despite being classified as a generalized epilepsy, focal EEG features are seen in a third of cases [5], and there are focal patterns of neuropsychological deficits [6]; and iv) there is variation in terms of response to antiepileptic drugs and long-term consequences between individuals [7]. There is a current consensus that JME is a heterogeneous epilepsy syndrome, considering response to antiepileptic drugs, long-term consequences, and the presence of psychiatric and cognitive comorbidities [8–10].

1.1. Neuropsychological performance

It is not uncommon for people with JME to describe 'real-world problems' with planning and sequencing in the context of a preserved IQ [11–14]. These difficulties were recognized in the definitive descriptions of JME by Janz and Christian in 1957 [15]. Impulsivity and greater novelty seeking are also recognized in JME, particularly when seizure control is poor [16]. There is growing evidence of executive function deficits from studies of individuals with predominantly drug-responsive JME [6,17].

1.2. Hypothesis and aims

There is a growing consensus of subtle executive function deficits from studies of individuals with predominantly drug-responsive JME [6,18]. These findings are consistent with advanced imaging studies, which implicate functional abnormalities in the frontal cortex and thalamus. Consistency within neuropsychological studies has been hampered, however, by the following: i) inadequate sample sizes, ii) clinical heterogeneity between cases, iii) atypical performance in 'control' populations, and iv) the utilization of only a limited number of neuropsychological tests.

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Considering the heterogeneity of this syndrome, studies on the subgroup of drug-refractory JME are necessary because of the notable heterogeneity of this syndrome. We, therefore, undertook a comprehensive study of cognition in people with drug-refractory JME. These individuals are most likely to use clinical services and represent the cohort with the greatest social burden. We hypothesized that there would be no differences in cognitive performance between these individuals and standardized control means after correcting for multiple comparisons.

2. Methods and materials

2.1. Participants

Sixty patients with drug-refractory JME were assessed as part of the multicenter MRC (Medical Research Council)-funded refractory juvenile myoclonic epilepsy cohort (ReJuMEC) study. Ethical approval was granted by the NorthWest (Cheshire) and the South West Wales Research Ethics Committees; written informed consent was obtained from all patients. Participants were recruited from outpatient appointments with epilepsy specialists in the United Kingdom. Patients were classified as having drug-refractory epilepsy if they experience one or more myoclonic, absence, or tonic–clonic seizures per month despite prior or current exposure to a dosage of at least 1000 mg/day of sodium valproate. Care was taken to identify individuals who do not adhere to prescribed medication; these individuals were excluded. Exclusion criteria included abnormal MRI brain scan, alcoholism, a history of drug abuse, and a neurological disorder besides epilepsy. Patients were provided with seizure diaries which documented seizure occurrence and frequency. In addition, none of the patients had experienced a generalized tonic–clonic seizure within the 24 h of the neuropsychological assessment.

2.2. Neuropsychological battery

Participants were given a clinical interview, and their medical files were studied to obtain detailed histories. A standardized battery of neuropsychological tests was administered to each participant. The battery was chosen to evaluate key areas of neuropsychological functioning including the following.

2.2.1. Intellectual functioning

All subtests from the WAIS-III [17] were administered from which full-scale IQ (FSIQ), verbal IQ (VIQ), performance IQ (PIQ), working memory (WM), and processing speed (PS) index scores were obtained. Scaled scores were calculated using WAIS–WMS writer software for each of the subtests for comparison [19].

2.2.2. Memory

All subtests from the WMS-III [20] were administered from which general memory, working memory, immediate memory, visual immediate and delayed, auditory immediate and delayed, and auditory recognition delayed memory index scores were obtained. Scaled scores were calculated using WAIS–WMS writer software for each of the subtests for comparison [21].

2.2.3. Language and fluency

The verbal fluency test from the Delis–Kaplan Executive Function System (D-KEFS) [21] was used; it not only contains subtests analogous to the FAS test but also assesses semantic fluency. In addition, the Boston Naming Test (BNT) was used to assess visual naming ability.

2.2.4. Attention and executive functions

The color-word interference task from the D-KEFS was used to assess control of inhibition, perseveration, mental flexibility, and attention. Working memory was tested using the WMS-III.

2.2.5. Questionnaires

The Aldenkamp–Baker Neuropsychological Assessment Scale (ABNAS) was included to assess the patients' perceived level of cognitive effects of their AEDs [22,23]. The Impact of Epilepsy Scale (IES) was employed to assess the current daily functioning of people with epilepsy, including their relationships with friends and family, social life, employment, health, self-esteem, plans for the future, and standard of living.

2.3. Statistical analysis

Means and standard deviations (SDs) were 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. Participants' scores were compared with the standardized means using one sample t-tests. To analyze the ABNAS, where these means were not available, a clinical sample was chosen for comparison [23]. To control for and assess the impact of education, intellectual functioning scores were correlated with years in education using Pearson's R correlation coefficients. To reduce the likelihood of making Type I errors, the significance level was set at $p < 0.01$ for all t-tests.

To determine the impact of contributory factors (age at onset of epilepsy, duration of epilepsy, types of seizures, number of AEDs and ABNAS) on the neuropsychological profile of the sample, bivariate correlation and regression analyses were conducted. Standard linear regression was chosen to assess the predictive power of all the variables and to identify which factors significantly contributed to the explanation of variance in cognition.

2.4. Severity of executive dysfunction

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 [16,24], a z-score of ≤ -1 (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. As naming ability was measured by only one test, a z-score of ≤ -1 on the Boston Naming Test was categorized as dysfunction in relation to naming ability. Low scores in two domains equated to a mild dysfunction, three or four scores to moderate dysfunction, and all five to severe executive dysfunction. The executive function tests were divided into the following six domains:

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

3. Results

3.1. Clinical features

Sixty patients with drug-refractory JME were recruited. The median age at seizure onset was 12 years (IQR = 8–15), while the median duration of epilepsy was 21 years (IQR = 10–30.5). Ninety-six percent of patients had at least one generalized convulsion, and 70% had absence