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Psychiatric comorbidities in patients from seven families with autosomal dominant cortical tremor, myoclonus, and epilepsy

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ABSTRACT

Objective: The objective of this report was to assess the psychiatric comorbidity in a group of patients affected by autosomal dominant cortical tremor, myoclonus, and epilepsy (ADCME).
Methods: Reliable and validated psychodiagnostic scales including the BDI (Beck Depression Inventory), STAI-Y1 and 2 (State-Trait Anxiety Inventory – Y; 1 and 2), MMPI-2 (Minnesota Multiphasic Personality Inventory – 2), and QoLIE-31 (Quality of Life in Epilepsy Inventory – 31) were administered to 20 patients with ADCME, 20 patients with juvenile myoclonic epilepsy (JME), and 20 healthy controls.
Results: There was a higher prevalence of mood disorders in patients with ADCME compared to patients with JME and healthy controls, particularly depression ($p = 0.035$ and $p = 0.017$, respectively) and state anxiety ($p = 0.024$ and $p = 0.019$, respectively). Trait anxiety was not different from JME ($p = 0.102$) but higher than healthy controls ($p = 0.017$). The myoclonus score positively correlated with both state (rho: 0.58, $p = 0.042$) and trait anxiety (rho: 0.65, $p = 0.011$). These psychiatric features were also often associated with pathological traits of personality: paranoid (OR: 25.7, $p = 0.003$), psychasthenia (OR: 7.0, $p = 0.023$), schizophrenia (OR: 8.5, $p = 0.011$), and hypomania (OR: 5.5, $p = 0.022$). Finally, in patients with ADCME, decreased quality of life correlated with these psychiatric symptoms.
Significance: Patients with ADCME show a significant psychiatric burden that impairs their quality of life. A comprehensive psychiatric evaluation should be offered at the time of diagnosis to detect these comorbidities and to treat them.

1. Introduction

Autosomal dominant cortical tremor, myoclonus, and epilepsy (ADCME) is a familial condition characterized by cortical myoclonus tremor associated with rare generalized seizures [1]. In the past, different acronyms (BAFME, FAME, FEME, FCTE, and ADCME) have been used to describe the same clinical entity even if genetically heterogeneous [1]. Clinically, this condition is characterized by adult onset, autosomal dominant inheritance, cortical tremor (action and postural, continuous, arrhythmic, mainly distal, fine twitches of the hands), myoclonus (distal, segmental, arrhythmic, erratic myoclonic jerks of the upper limbs), and rare generalized tonic–clonic seizures (GTCS) [2]. This condition is also characterized by peculiar neurophysiological findings including an EMG pattern of irregular, arrhythmic, and high frequency (10/s) myoclonic jerks, a jerk-locked averaging positive–negative biphasic premyoclonic spike, giant somatosensory-evoked potentials, and enhanced long-latency C-reflex response [2]. Some of these

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electrophysiological features may be masked by antiepileptic drugs (AEDs). A pathophysiologic mechanism has not been elucidated yet, but chronic excitation of the cerebello-thalamo-cortical circuits involving the basal ganglia has been demonstrated through a H-MR spectroscopy study [3]. The cerebellar involvement has also been shown by postmortem histological studies [4]. To date, about 70 families from Japan and Europe have been described, and genetic studies have disclosed four different loci (8q24, 2p11.1q12.2, 5p15.31-p15, 3q26.32-3q2) [5,6,7,8]. In Italy, the same haplotype (2p11.1-q12.2) was shown to cosegregate with the disease phenotype in five apparently unrelated families from the region 'Campania' [9,10]. All the subjects belonging to these families presented with a homogeneous phenotype with adult onset and stable symptoms responsive to antimyoclonic agents such as levetiracetam [10,11]. This condition has often been described as benign with a mild phenotype and a lower rate of GTCS [12]. However, a recent follow-up study of three of these families with "classical" presentation and 2p11.1-q12.2 linkage disclosed a gradual progression with age of the myoclonus severity and mild cognitive impairment, together with slowing of the background activity on EEG [13]. In the same study, the authors also reported a relatively high frequency (>40% of the cases) of psychiatric features, namely anxiety and depression. These data were also consistent with the 37.5% of cases affected by a psychiatric disorder of variable severity, reported by Licchetta et al. [10]. All these findings suggest a more complex phenotype of this condition, including psychiatric aspects. The aim of this study was to assess and characterize the psychiatric comorbidities of this condition.

2. Patients and methods

2.1. Patients

Patients with a clinical and electrophysiological diagnosis of ADCME, from seven families followed in two Italian epilepsy centers (Napoli and Bologna), were enrolled in this study (haplotype: 2p11.1q12.2). All the patients presented with hand tremor and myoclonus. Two control groups were also enrolled: healthy subjects and patients with a diagnosis of juvenile myoclonic epilepsy (JME) according to the current classification of the International League Against Epilepsy [14]. Routine blood tests, neurological examination, and electroencephalography were performed for each subject. A neurologist with a special expertise in epilepsy evaluated the epilepsy history including the number of seizures, AEDs, and the myoclonus score by using the Unified Myoclonus Rating Scale (UMRS) for each patient with ADCME.

Patients were excluded if they had a generalized tonic-clonic seizure in the previous month, had been admitted to the hospital for acute disease in the previous three months, or were under treatment with a drug known to have psychiatric effects (this did not include antiepileptic treatment).

Informed consent was signed by all participants or their legal guardian if the patient was younger than 18 years old. Ethical approval was obtained from Federico II University Ethic Committee.

2.2. Psychiatric evaluation

Psychiatric evaluation included a specialist consultation, drug history, and a battery of psychiatric tests: BDI (Beck Depression Inventory) to evaluate depression symptoms, STAI-Y1 and 2 (State-Trait Anxiety Inventory — Y; 1 and 2) to evaluate anxiety, and MMPI-2 (Minnesota Multiphasic Personality Inventory — 2) to evaluate personality disorder. In addition, the validated Italian version of QoLIE-31 (Quality of Life in Epilepsy Inventory — 31) was administered to evaluate subjects' quality of life [15].

2.3. Statistical analysis

Data were analyzed using Stata/IC 11.1 (Stata, Texas, USA). The following continuous variables were evaluated: age, education, myoclonus score, seizure frequency, number of AEDs, BDI, QoLIE-31, STAI-S, and STAI-T scores. These were described using median and interquartile range (IQR), or mean and standard deviation (SD), according to the normality of the distribution. Gender, exposure to each AED, and MMPI-2 subscales (elevated or low scores) were considered as binary variables and described by percentages. All the demographic factors and psychometric scores were compared among the three groups. Kruskal–Wallis rank test, Wilcoxon rank-sum test, or one-way analysis of variance (ANOVA), for continuous variables, and Pearson χ^2 or Fisher exact tests, for categorical variables, were used.

Spearman correlation analysis was used to identify relationships between the neuropsychological scores and the myoclonus score in the group with ADMCE, after Bonferroni correction for age.

Binary STAI-S and STAI-T scores with a cutoff of 40 (indicating moderate to severe anxiety) were considered as outcome variables in logistic regression analysis. The association between the distinct underlying conditions of the three groups and the anxiety scores was evaluated using the univariate logistic regression analysis. Any factors with a p-value ≤ 0.05 were eligible for addition into multivariate analysis. Multivariate logistic regression analysis with backward stepwise selection was then performed to determine the optimal combination of clinical factors needed to predict the anxiety level. Statistical significance was set at the 0.05 level. Before univariate logistic regression analysis was conducted, collinearity between the different predictor variables was checked using the variance inflation factors and the tolerance. Collinearity was assumed to be present if variance inflation factors were higher than 10, and tolerance was lower than 0.1 [16]. If collinearity was present, the risk factor with the highest correlation with the outcome was used for the multivariate analysis. An analogous process was followed to build a linear regression model considering BDI score as a dependent variable.

3. Results

A total of 60 subjects were included in the analysis: 20 with ADCME, 20 with JME diagnosis, and 20 healthy controls.

All the 20 patients with ADCME were from the Campania region in the south of Italy: nine belonged to three families from Naples with linkage to 2p11.1-q12.2 that have already been reported [11,17,18], four belonged to a previously reported family from Caserta with the same linkage [10], and seven belonged to three other unreported families from Naples.

At the time of the evaluation, all except two patients with ADCME were under treatment with one or more AEDs including valproate, levetiracetam, and clonazepam. None of the patients at the time of recruitment into this study had a known psychiatric diagnosis or was under the care of a mental health professional. All patients in this study had a negative family psychiatric history. None of the patients was under treatment with antidepressants. Three patients were experiencing three to four seizures per year; all the remaining patients were seizure free.

Table 1 shows the demographic and clinical characteristics and the psychometric scores among the three groups. There was no difference among the three groups regarding gender and education. Age was different among the three groups ($p < 0.001$, Kruskal–Wallis): in particular, cases with ADCME were older than cases with JME ($p < 0.001$, Wilcoxon), while there was no significant difference of age between cases with ADCME and healthy controls ($p = 0.291$, Wilcoxon).

Epilepsy duration and GTCS frequency were not statistically different between cases with ADCME and cases with JME ($p = 0.053$ and $p = 0.474$, respectively, Wilcoxon). Subjects with ADCME were more exposed to benzodiazepines ($p = 0.031$, Fisher exact), and subjects