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The integrity of corpus callosum and cluster B personality disorders: A quantitative MRI study in juvenile myoclonic epilepsy

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ABSTRACT

Evidence suggests increased prevalence of cluster B personality disorders (PD) among patients with juvenile myoclonic epilepsy (JME), which has been associated with worse seizure control and more psychosocial dysfunctions. A preliminary voxel-based morphometry study demonstrated corpus callosum (CC) volume reduction in patients with JME and cluster B PD, particularly in the posterior midbody and isthmus. In this study we aimed to follow up these results with region of interest analysis. Sixteen JME patients with cluster B PD, 38 JME patients without any psychiatric disorder, and 30 demographically matched healthy controls submitted to a psychiatric evaluation and a magnetic resonance imaging scan. The total and regional callosal areas were obtained from the midsagittal slice using a semi-automated program. Psychiatric evaluation was performed through SCID-I and -II. Significant reductions in the posterior region of the CC were observed in the JME with PD group relative to the other groups. These data support previous findings of callosal reductions in cluster B PD, as well as a possible involvement of CC in patients with JME and such personality characteristics.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a well defined type of idiopathic generalized epilepsy (IGE) that comprises 5–11% of patients with epilepsy. JME is characterized by myoclonic jerks and generalized tonic–clonic seizures (GTCS) and typical findings of generalized 4–6 Hz spike and wave or poly-spike and wave discharges in the electroencephalogram (EEG) (Commission, 1989; Schmitz and Wolf, 1995). Recent studies using a variety of neuroimaging techniques have found evidence of frontal lobe dysfunction among JME patients (Betting et al., 2006; Gelisse et al., 2001; Koepp, 2005; Woermann et al., 1998; Woermann et al., 1999). Neuropsychological evaluation of these patients confirmed those findings (Devinsky et al., 1997; Pascalicchio et al., 2007), that could be related to pathophysiologic mechanisms involved in the generation of epileptic activity in this epileptic syndrome (Bernasconi et al., 2003; Haki et al., 2007; Savic et al., 2000. Savic et al., 2004; Simister et al., 2003). Other studies, however, suggest more widespread network abnormalities in the brain of JME patients, possibly including the frontal lobes, hippocampus and corpus callosum (CC) (Tae et al., 2006).

Previous studies involving JME patients have highlighted difficulties in their treatment, which were attributed to specific psychological and personality traits including emotional instability and immaturity, unsteadiness, lack of discipline, hedonism, frequent and rapid mood changes and indifference towards their disease (Janz, 1985; Janz and Christian, 1994; Simonsen et al., 1976; Trimble, 2000; Trimble et al., 2000). Recent studies support these observations, finding a high frequency of psychiatric disorders among JME patients; particularly anxiety and mood disorders, as well as mild to moderate cluster B personality disorders (PD), such as histrionic, passive–aggressive and borderline (De Araújo Filho et al., 2006; Perini et al., 1996; Sengoku et al., 1997; Trinka et al., 2006). Patients with these personality characteristics also present a worse seizure control and greater psychosocial

Abbreviations: JME, juvenile myoclonic epilepsy; IGE, idiopathic generalized epilepsies; GTCS, generalized tonic–clonic seizures; EEG, electroencephalogram; CC, corpus callosum; PD, personality disorders; VBM, voxel-based morphometry; ROI, regions of interest; ILAE, International League Against Epilepsy; DSM, Diagnostical and Statistical Manual of Mental Disorders; AED, antiepileptic drug; VPA, valproate; TPM, topiramate; LTG, lamotrigine; CNZ, clonazepam; PHT, phenytoin; CBZ, carbamazepine; OXC, oxcarbazepine; CLB, clobazam; PB, phenobarbital; MRI, magnetic resonance imaging; MANOVA, multivariate analysis of variance; DTI, diffusion tensor imaging; WM, white matter.

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dysfunction (De Araújo Filho et al., 2007). Recently, a voxel-based morphometry (VBM) study demonstrated gray and white matter structural abnormalities in JME patients with cluster B PD, mainly in the thalamus, frontal lobe and CC (De Araújo Filho et al., 2009).

The CC is the major connecting fiber bundle in the human brain and the most important interhemispheric connection pathway (Rüsch et al., 2007; Tae et al., 2006). In addition, it is the primary white matter tract in the brain and is frequently involved in neurologic and psychiatric diseases (Rüsch et al., 2003; Rüsch et al., 2007; Tae et al., 2006). Structural callosal abnormalities in patients with cluster B PD have been found, particularly involving the genu, posterior body and isthmus (Rüsch et al., 2003; Rüsch et al., 2007; Tebartz van Elst et al., 2001). To the best of our knowledge, there is one region of interest (ROI) and a single VBM study that evaluated the CC or the white matter structure in JME patients (De Araújo Filho et al., 2009; Tae et al., 2006). The ROI study reported reduced rostrum and rostral midbody callosal areas in JME patients when compared to controls (Tae et al., 2006) while the VBM study reported reduced posterior callosal regions in JME with cluster B PD (De Araújo Filho et al., 2009). Given the evidence of callosal abnormalities in JME patients (Grewal et al., 2007; Tae et al., 2006) and in patients with cluster B PD (De Araújo Filho et al., 2009), in this study we follow up the previous callosal VBM results with ROI analysis. We hypothesized that JME patients with cluster B PD would present reduced posterior callosal midsagittal areas in comparison to JME patients without psychiatric disorders and healthy controls (Fig. 1).

2. Methods

2.1. Subjects

All patients included in this study were followed up in the outpatient clinic of a tertiary center (Epilepsy Section of the Universidade Federal de São Paulo, Brazil), from July 2005 to July 2007. After the Ethical Committee approval, advantages and risks for participation were explained and informed consent was obtained. The inclusion criteria for the patients group were the presence of electroclinical diagnosis of JME based on ILAE classification (Commission, 1989) and participation in treatment in our unit for at least six months. JME patients had typical EEG showing generalized 3–6 Hz spike and wave or poly-spike and wave activity maximum in frontocentral regions. We excluded patients with clinical illnesses besides epilepsy or receiving any other pharmacological treatment other than antiepileptic medication.

2.2. Psychiatric evaluation

A clinical and socio-demographic questionnaire including age, gender, years of education, duration of epilepsy, neurological and psychiatric family antecedents, previous psychiatric treatment, type and frequency of seizures, occurrence of status epilepticus and drug treatment was applied. Patients and controls were submitted to a psychiatric evaluation through the Brazilian versions of Schedule Clinical Interview for Diagnostical and Statistical Manual of Mental Disorders (DSM), axes I and II (SCID-I and SCID-II, respectively) (First et al., 1998; Spitzer et al., 1989). These are psychiatric instruments based on DSM and have been used internationally to evaluate psychiatric disorders. Axis I refers to the evaluation of most psychiatric diseases (e.g.; mood disorders, anxiety and psychotic disorders), while axis II refers to the evaluation of all types of PD. The Brazilian version of SCID-II based on DSM-IV is not validated. Therefore, we performed the evaluation of axis II disorders using the SCID-II version based on DSM-III-R (Diagnostical and Statistical Manual of Mental Disorders, 3rd edition, revised) criteria. The evaluation of axis I disorders was performed using SCID-I version based on DSM-IV (Diagnostical and Statistical Manual of Mental Disorders, 4th edition) criteria. Patients with both axis I and II psychiatric diagnoses, with alcohol or drug misuse or with any axis II diagnosis other than cluster B were excluded.

2.3. Procedures

Sixteen patients with JME who fulfilled only the criteria for diagnosis of a cluster B PD based on DSM-III-R (histrionic, borderline and passive–aggressive) were included, and compared to 38 JME patients without any psychiatric diagnosis. The control group consisted of 30 age and sex-matched healthy volunteers who also had been evaluated by the same psychiatrist (GMAF). None of them had presented any seizures, antihistamine administration or alcohol consumption within 72 h prior to the psychiatric evaluation. Adequate treatment was defined by the use of therapeutic doses of a first-line antiepileptic drug (AED) for generalized epilepsies, in monotherapy or in association with other drugs, such as valproate (VPA), topiramate (TPM), lamotrigine (LTG) and clonazepam (CNZ). Inadequate treatment was defined by the use of non-recommended drugs for this type of epileptic syndrome, like phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), clobazam (CLB) and phenobarbital (PB). The number and types of seizures, like myoclonia, absences or GTCS were also compared to investigate seizure control in

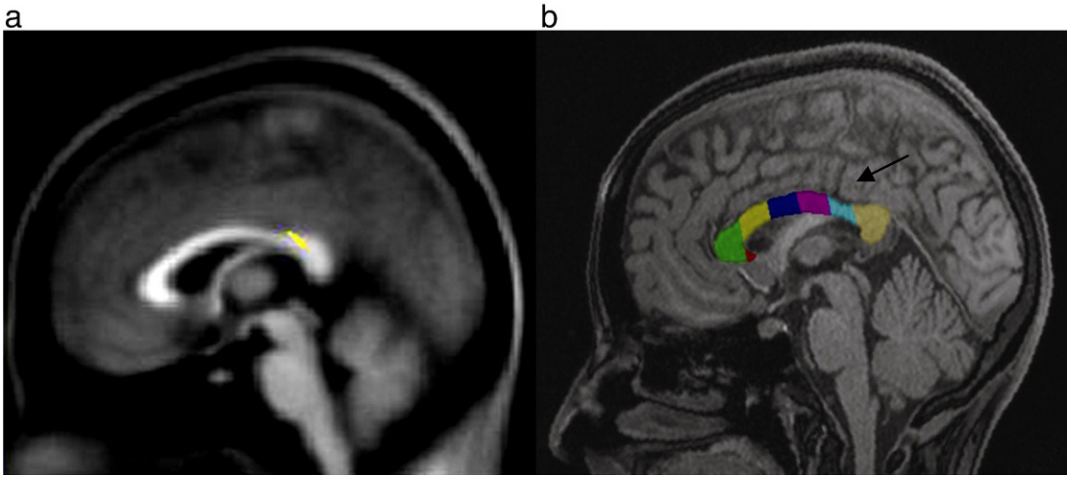

Fig. 1. Midsagittal view of the corpus callosum. a. VBM results showing reduced posterior callosal volume (arrow) in JME patients with PD in comparison to controls. b. Follow-up ROI analysis showing reduced callosal subregion (cyan) in JME patients with PD in comparison to JME patients without PD and healthy controls.