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Generalized epilepsy syndromes and callosal thickness: Differential effects between patients with juvenile myoclonic epilepsy and those with generalized tonic-clonic seizures alone

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ABSTRACT

Purpose: The definition of two well-studied genetic generalized epilepsy syndromes (GGE) – juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures alone (GTCS) – suggests the absence of structural cerebral abnormalities. Nevertheless, there are various reports of such abnormalities (especially in JME), where effects mainly occur within thalamus and mesial prefrontal regions. This raises the question of whether JME is particularly linked to midline structure abnormalities, which may also involve the corpus callosum.
Method: We studied callosal morphology in a well-matched sample of 22 JME patients, 15 GTCS patients, and 42 controls (CTL) for all of whom we obtained T1-weighted data on a 3 T MRI scanner. More specifically, we measured callosal thickness at 100 equidistant points across the callosal surface, and subsequently compared the three groups (JME, GTCS, and CTL) against each other.
Results: Significant differences between JME patients and controls were observed within the callosal genu, anterior midbody, and isthmus, with thinner regions in JME patients. There were no significant differences between GTCS patients and controls, and also not between JME patients and GTCS patients.
Conclusion: The present outcomes point to callosal abnormalities in JME patients suggesting an impairment of interhemisperic communication between prefrontal, motor, parietal and temporal cortices. These findings further support the notion that structural aberrations are present and differentiated across GGE syndromes, with significant callosal deviations from normality in JME.

1. Introduction

Juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic clonic seizures alone (GTCS) are two classic generalized epilepsy syndromes. Formerly subsumed as idiopathic generalized epilepsy syndromes, the updated classification of epilepsies according to the International League Against Epilepsy now subsumes JME and GTCS under genetic generalized epilepsy syndromes (GGE), aiming at a more concrete categorization of epilepsies (Berg et al., 2010). In this new classification, the definition of JME and GTCS is mainly based on seizure semiology and electroencephalography (EEG) findings, and supposes an absence of structural abnormalities (https://www.epilepsydiagnosis.org/syndrome/jme-imaging.html, https://www.epilepsydiagnosis.org/syndrome/egtcsa-imaging.html). Importantly though, while inspecting magnetic resonance imaging (MRI) data from JME and GTCS patients on the individual level does not always seem to reveal anatomical abnormalities, significant structural deviations are often observed when data are analyzed on the group level (Ciumas and Savic, 2006; Focke et al., 2014; Kim et al., 2012, 2015; Koepp et al., 2013; Liu et al., 2011; O'muircheartaigh et al., 2011; Seneviratne et al., 2014; Tae et al., 2006, 2008). Thus, further revisions might seem appropriate with respect to the definition of JME and/or GTCS.

Based on data from MRI-based volumetry and spectroscopy, as well as positron emission tomography (PET) measurements of a

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dopamine transporter, it was previously suggested that JME and GTCS represent two epilepsy syndromes with different underlying anatomical substrates (Ciumas and Savic, 2006; Ciumas et al., 2010; Savic et al., 2004) and several independent studies supported this notion (Kim et al., 2012; Koepp et al., 2013; O'muircheartaigh et al., 2011; Vulliemoz et al., 2011). Interestingly, structural differences in the JME populations have been found primarily in the mesial frontal cortex and the thalamus (Ciumas and Savic, 2006; Ciumas et al., 2010; Helms et al., 2006; Koepp et al., 2013). Findings from a number of imaging studies (Ekmekci et al., 2016; Focke et al., 2014; Kim et al., 2012, 2015; Liu et al., 2011; O'muircheartaigh et al., 2011; Tae et al., 2006) suggest that such structural differences extend into the corpus callosum (CC). More specifically, it was reported that JME patients show a reduced fractional anisotropy (FA) in callosal fiber tracts compared to healthy controls (Ekmekci et al., 2016; Focke et al., 2014; Kim et al., 2012, 2015; Liu et al., 2011; O'muircheartaigh et al., 2011) or smaller callosal sections (Tae et al., 2006), which altogether may suggest an impaired myelination of callosal axons (Beaulieu, 2002). Furthermore, impaired structural connectivity could also be in line with data on the cognitive profile of JME patients demonstrating cognitive dysfunction in JME, possible due to altered network in the anterior cortices (Pascalicchio et al., 2007; Vollmar et al., 2011; Wandschneider et al., 2012).

In the quest for a further clarification of the underlying neurobiology of JME and its singularity in relation to other GGE syndromes, we set out to investigate whether the CC is altered in JME and/or GTCS patients compared to healthy controls. For this purpose, we employed a well-established MR-based method to analyze the thickness of the CC with a high regional specificity (i.e., at 100 locations across the callosal surface). We hypothesized that there would be aberrations in callosal morphology primarily among JME patients but less so in GTCS patients, with main effects confined to anterior callosal sections, as suggested by previous brain imaging and neuropsychological data from this population (Focke et al., 2014; Kim et al., 2012, 2015; Liu et al., 2011; O'muircheartaigh et al., 2011; Tae et al., 2006).

2. Methods

2.1. Subjects

Our study included 37 consecutive GGE patients, recruited at the Karolinska University Hospital (Stockholm, Sweden). All of these patients were treated at this hospital from the year of their seizure onset and thus well-known to the neurologists in charge. Only patients whose seizure phenomenology was reliably assessed were included in the study. Specifically, the individual clinical data, in particular with regard to seizure type and frequency were collected on site by the neurologist who recruited patients for the study. The seizure semiology was confirmed by relatives. When needed, clinical data (e.g., comorbidity, age at disease onset) were also retrieved from the patients' journals or in telephone interviews when the journals were unclear. The diagnosis of the respective syndrome was based on seizure history, seizure semiology as described by relatives or recorded during hospitalization, and scalp EEG recordings showing bursts of generalized spike and wave and/or polyspike and wave activity without any specific lateralization. Brain imaging data from all patients were obtained using high-resolution MRI according to the standardized epilepsy protocol (for details see below).

Twenty-two patients were diagnosed with JME (mean ± SD age: 31.72 ± 8.91 years, 15 females) with a mean ±SD epilepsy duration of 18.18 ± 9.15 years, at the time of the MRI acquisition. All of these patients had a late childhood or teenage onset of awakening myoclonic jerks, often in the upper but sometimes also in the lower extremities. Twenty JME patients also experienced occasional GTCS and four also rare absences. Seventeen JME patients were on monotherapy with one antiepileptic drug (AED), where 10 patients received valproate. Five JME patients received a combination of two AEDs. Fifteen patients were diagnosed with GTCS alone (mean ± SD age: 33.86 ± 12.38 years, 6 females) with a mean ±SD epilepsy duration of 21.13 ± 12.02 years at the time of their MRI. While these 15 patients presented mainly with a pubertal onset of primarily GTCS, four of them experienced occasional absences in childhood or early adolescence. The majority of patients with GTCS reported seizures on awakening, although some experienced them at random. Eleven GTCS patients were on AED monotherapy with six patients receiving valproate; the remaining four patients were on a combination of two AEDs. In addition, the study sample also included 42 healthy subjects (mean ± SD age: 30.93 ± 8.8 years, 20 females) with no history or heredity for epilepsy and normal MRI of the brain as deemed by a radiologist. The study was approved by the local ethical committee at the Karolinska Institute (Stockholm, Sweden), and written consent was obtained from all study participants.

The three groups were matched for demographic variables, and particular care was taken to match the two patient groups for clinical characteristics. As shown in Table 1, sub-sample size dif-

Table 1
Demographic and clinical data. ICV: intracranial volume in cm^3.

	JME	GTCS	Control	Significance (F | p) JME vs. GTCS
Number of subjects	22	15	42	n/a
Number of females (%)	15 (68%)	6 (40%)	20 (47%)	
Age at MRI (mean ± SD)	31.72 (8.91) years	33.86 (12.38) years	30.92 (8.80) years	n/a
Intracranial Volume (mean ± SD)	1457.1 ± 112.9 cm^3	1601.2 ± 151.6 cm^3	1608.2 ± 141.3 cm^3	n/a
Age at epilepsy onset (mean ± SD)	13.54 ± 2.78 years	12.73 ± 4.09 years	n/a	1.593|0.215
Duration of epilepsy at MRI (mean ± SD)	18.18 ± 9.15 years	21.13 ± 12.02 years	n/a	0.790|0.380
Total GTCS seizures at MRI (mean ± SD)	14.72 ± 18.03 years	15.80 ± 14.59 years	n/a	0.862|0.360
Antiepileptic drug monotherapy (yes / no)	17-May	11-Apr	n/a	0.277|0.602

n/a = not applicable.