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Selective medial temporal volume reduction in the hippocampus of patients with idiopathic generalized tonic—clonic seizures

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Summary
Background: Different subtypes of idiopathic generalized epilepsy may indicate different mechanisms and outcomes, suggesting that it is necessary to use a 'pure sample' of a single subtype.
Methods: A volumetric study, in conjunction with cognition assessments, was performed in a pure sample of patients with idiopathic generalized tonic—clonic seizures (IGE-GTCS; 15 males and 15 females) matched with normal control subjects (15 males and 17 females). The volumetric measurements were focused on the hippocampus and its surrounding structures, including the amygdala, the parahippocampal gyrus, the entorhinal cortex and the perirhinal cortex. The Wechsler Adult Intelligence Scale-Revised in China was administered to assess cognitive status.
Results: A volume reduction was found only in the hippocampus, with a more severe effect on the left side than the right side. The total number and frequency of seizures had significant negative correlations with multiple cognitive measures. Furthermore, the hippocampal volume reduction was significantly correlated with some aspects of cognitive impairment.

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Conclusion: These findings suggest that compared with the other medial temporal structures, the hippocampus may be more vulnerable to the neuropathology of IGE-GTCS. The observation that cognitive deterioration was correlated with an increased frequency and total number of seizures highlights the critical importance of preventing seizures from recurrence.

Introduction

According to the International League against Epilepsy, idiopathic generalized epilepsy (IGE), with its etiology unknown other than a potential hereditary predisposition, differs from symptomatic epilepsies and syndromes, and given that all seizures are initially generalized, it also differs from partial or focal seizures. Thus, the various subtypes of IGE are classified mainly by the age of onset and the clinical features manifested as generalized tonic–clonic, myoclonic, or absent seizures (CoCaTotILA, 1989). Although a characteristic electroencephalogram (EEG) strongly supports the diagnosis of IGE, and different patterns of abnormalities in the EEG are suggestive for the discrimination of different subtypes, there is a lack of consensus with regards to these potential diagnostic criteria given the inconsistencies that occur when the EEG is applied to cases with overlapping features; thus, an accurate classification and outcome prediction still heavily depend on the clinical features(CoCaTotILA, 1989; Nordli, 2005). It seems that IGE, a group of seizure symptoms currently defined descriptively, may comprise different phenotypes, and has different clinical features among its subtypes, thereby indicating potentially different mechanisms and outcomes (Panayiotopoulos, 2002). In view of this point, using a 'pure sample' of a single subtype should be more informative for detecting this syndrome (Savic et al., 2004; Zifkin et al., 2005). This study was designed to critically examine idiopathic generalized tonic–clonic seizures (IGE-GTCS), with the major purpose of exploring the anatomical basis of its cognitive alterations.

Cognitive impairment is a major complication of epilepsy and has been associated with the etiology, seizure type, seizure frequency, age at onset, duration, severity, antiepileptic drugs, epilepsy surgery, and psychological variables (Hamed, 2009; Motamedi and Meador, 2003). Among the various seizure types, generalized seizures are more likely to impair cognitive functions (such as attention, short-term memory and information processing) than focal seizures (Bhise et al., 2010). The frequency of IGE-GTCS has been suggested to be the strongest predictor of cognitive decline (Thompson and Duncan, 2005). It was reported that despite intelligence levels largely in the normal range, patients with IGE performed remarkably worse in short-term memory and psychomotor performance (Bhise et al., 2010; Hommet et al., 2006). Further, GTCS may be the most significant predictor of short-term memory deficits (Thompson and Duncan, 2005). However, compared with focal seizures, such as temporal lobe epilepsy, IGE-GTCS has received significantly less attention with respect to the anatomical basis of its cognitive impairments. Based on the demonstrated characteristic memory deficits in IGE-GTCS, it is reasonable to consider the medial temporal lobe as a target.

The medial temporal lobe consists of several critical memory-related structures, including the hippocampus, the amygdala, and the surrounding hippocampal areas (such as the entorhinal, perirhinal, and parahippocampal cortices). As a major brain structure which underlies memory formation and plays an important role in spatial memory and navigation (Kolb and Whishaw, 1996), the hippocampus has recently attracted some attention in the field of IGE research. Animal experimental studies have demonstrated that the hippocampus is sensitive to the pathophysiology of GTCS, and repeated GTCS induced neuronal loss in the hippocampus (Cavazos et al., 1994; Kotloski et al., 2002; Sutula et al., 1995). However, the results from a very limited number of magnetic resonance imaging (MRI) volumetric studies which measured the hippocampal volume of patients with IGE-GTCS were inconsistent (Betting et al., 2006; Ciumas and Savic, 2006), possibly due to the differences in the sample characteristics and volumetric methods. Furthermore, the relationship between hippocampal volume and cognitive alterations remains unclear. The other medial temporal lobe structures, such as the amygdala and the entorhinal, perirhinal, and parahippocampal cortices, are all anatomically and/or functionally connected with the hippocampus; these regions are currently theorized to be critical for memory storage and long-term memory (Kolb and Whishaw, 1996). However, these regions have rarely been studied in the context of IGE-GTCS. Thus, whether the damage to the hippocampus by IGE-GTCS is a specific neurobiological change among the medial temporal lobe structures also remains unknown.

Using high-resolution three-dimensional MRI and consecutive coronal 1-mm thick slices, the aims of the present study were to evaluate the volumetric changes of the hippocampus and its surrounding structures and to determine their relationships with the cognitive alterations in patients with IGE-GTCS. Based on the results from experimental animal studies, the central role of the hippocampus in memory-related cognitive functions, and the characteristics of IGE-GTCS related cognitive deficits, we predicted that: (1) the patients with IGE-GTCS would show reduced hippocampal volumes; (2) the volume reduction of the hippocampus would correlate with some cognitive alterations (such as short-term memory and psychomotor performance) and some aspects of the clinical characteristics (such as illness duration and seizure frequency); and (3) the other surrounding structures would be volumetrically less damaged or undamaged.

Methods

Subjects

The participants included 30 patients with IGE-GTCS (15 males and 15 females) and 32 healthy controls (15 males and