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Temporal current-source of spikes suggests initial treatment failure in childhood absence epilepsy

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ABSTRACT

Purpose: In addition to the frontal lobe, the temporal lobe may also be involved in typical absence seizures. However, few studies have addressed the relationship between this involvement and drug responsiveness in childhood absence epilepsy (CAE). In this study, we observed the current-source distribution (CSD) of generalized spike-and-wave discharges (GSWDs) and investigated the relationship between temporal lobe involvement in the CSD and responsiveness to initial antiepileptic drug (AED) in CAE.

Method: Seventeen consecutive patients with CAE were retrospectively enrolled in the study. Patients were divided into an initial-response group and an initial-failure group, according to their responsiveness to the initial AED treatment. For each patient, the spike peak CSD of an averaged GSWD was obtained from the initial electroencephalogram. We compared the incidence of temporal involvement in the CSD between the two groups. We also compared clinical variables, including age of onset, gender, type and dose of first AED, time to cessation of clinical seizures, and seizure-free status.

Results: The initial-response and initial-failure groups contained 12 and five patients, respectively. Temporal lobe involvement was more frequent (80% vs. 17%, $p = 0.03$), and time to cessation of clinical seizures was more prolonged (median 2.5 months vs. 8 months, $p < 0.01$) in the initial-failure than in the initial-response group. None of the other variables studied differed between groups.

Conclusion: Initial AED failure was associated with temporal involvement in the CSD of CAE patients. This electrophysiological information may be helpful in clinical practice by estimating the efficacy of initial AED treatment in AED-naïve CAE patients in advance.

1. Introduction

Childhood absence epilepsy (CAE) is a prototype of idiopathic generalized epilepsy (IGE), and characterized by typical absence seizures [1]. Generalized spike-and-wave discharges (GSWDs) of 3 Hz frequency is an electrographic pattern of CAE [2]. However, cortical involvement of the GSWDs is not truly generalized [3–8]. The GSWDs associated with typical absence seizures are predominantly localized to the frontal cortex, as assessed by visual inspection [3]. Studies using other modalities such as current-source analysis or depth EEG recording have demonstrated similar results [4–8]. In addition, the idea that a focal cortical source may play a leading role in absence seizure generation is widely accepted [9]. This idea suggests that a focal cortical area initiates the paroxysmal oscillations and triggers thalamic involvement [10]. These findings suggests that the frontal lobe are hyperexcitable, and have epileptogenicity related to absence seizures and/or GSWDs.

Although there are some common locations for epileptic cortices, individual variation in regional susceptibility of the cortex may lead to variability in the localization and size of generators for GSWDs [11]. Differences among individuals with respect to IGE generators may result in inconsistent responses to the same antiepileptic drugs [12–14]. The generators of typical absence seizures primarily localize to the frontal lobe, as mentioned above [3–8]; however, recent evidence suggests that some generators may also exist in the temporal lobe [15,16]. There

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is clear evidence of involvement of the temporal lobe circuitry in atypical absence seizures based on clinical and experimental studies [17,18]. Despite this, temporal lobe involvement in the generation of typical absence seizures has had little recent attention. Furthermore, certain clinical aspects of atypical absence seizures differ somewhat from those of typical absence seizures [19]. Typical seizures are usually associated with idiopathic epilepsies and respond well to treatment with antiepileptic drugs (AEDs) [20]. Atypical absence seizures, on the other hand, are invariably associated with severe symptomatic or cryptogenic epilepsies, and tend to be refractory to AED medication [19]. Based on the clear association of both temporal lobe involvement and drug refractoriness with a typical absence seizures [17,18], we hypothesize that temporal involvement in seizure generation may be an indicator of drug refractoriness.

Although the long-term prognosis of CAE is excellent in general, 20–71% of patients with CAE experience treatment failure with the initial antiepileptic drugs [20,21]. A poorer prognosis is often reported for CAE patients in whom the first antiepileptic drug (AED) treatment failed [22]. The initial AED failure may therefore be an early indicator of the long-term prognosis for CAE patients. We hypothesized that temporal involvement in seizure generation may be associated with initial treatment failure in patients suffering from typical absence seizures. We investigated the relationship between temporal lobe involvement in the current-source distribution (CSD) of spikes and failure of the initial AED in CAE. To define the CSD of patients with CAE, we employed a distributed model of current-source analysis of GSWDs.

2. Methods

2.1. Subjects

Children who were newly diagnosed with epilepsy and who met the diagnostic criteria for CAE were recruited retrospectively from January 2008 to January 2014 at Gyeongsang National University Hospital and Samsung Changwon Hospital. This retrospective study was approved by the institutional review boards of both hospitals (GNUH-2014-12-028, SCMC-2015-016). The diagnosis of CAE was based on the criteria proposed by Panayiotopoulos and reviewed by Loiseau et al. [23] The criteria for inclusion were (1) seizure onset between 4 and 10 years; (2) normal neurological state and development; (3) absence seizures as the initial type of seizures; (4) very brief typical absence seizures occurring many times per day; and (5) epileptiform discharges of bilateral, symmetrical, and synchronous discharge of regular 3 Hz SWCs with normal or mildly abnormal background activity. The criteria for exclusion were: (1) atypical clinical features, such as generalized tonic clonic seizures or myoclonic jerks, before or during the active stage of absence, absences with marked eyelid or perioral myoclonus, stimulus-sensitive absences; and (2) atypical EEG features, such as discharge fragmentation and multiple spikes, irregular and multiple spike and slow-wave discharges with marked variations in the intradischarge frequency, predominant brief discharges of 3–4 Hz spike-waves of <4 s, or fixed 'lead in' anomaly in the frontal region on EEG.

During the study period, a total of 24 patients were newly diagnosed with CAE, according to the inclusion criteria. Among them, seven patients were excluded for the following reasons: (1) atypical clinical features, according to our exclusion criteria ($n = 2$); (2) atypical EEG features, according to our exclusion criteria ($n = 2$); (3) patient unavailable for EEG before AED medication ($n = 1$); (4) patient unavailable for drug responsiveness assessment ($n = 2$). Ultimately, 17 patients were enrolled in the study. The median age of onset was 8 years (range, 5–10 years), and the median treatment period was 3.0 years (range, 1.2–6.5 years). Patients were divided into two groups according to responsiveness to initial antiepileptic drug (AED) treatment: an initial-response group and an initial-failure group. Initial failure of AED treatment was defined as the inability to attain complete seizure control with the optimal dose of the first appropriate AED.

2.2. EEG recording and collection of average spikes

Scalp EEGs were recorded for a minimum of 30 min in each patient, according to the International 10–20 system, with 25 or 19 channels, depending on the clinical setting of each hospital. A 32-channel digital EEG machine (Comet® EEG machine; Grass-Telefactor; West Warwick, RI, USA) was used in each hospital. Sampling rates were 400 or 200 Hz, depending on the clinical setting. We analyzed an EEG recording taken before AED medication, and selected artifact-free EEG segments of 500 ms before and 500 ms after the spike peak points of typical 3 Hz GSWDs. We obtained an averaged spike of 18–50 GSWDs from each patient. Because the numbers of typical spikes varied in each EEG, the numbers of spikes averaged also varied. The filter setting was 1.6–30 Hz. Brain Electrical Source Analysis (BESA; V. 5.1; MEGIS; Grafelfing, Germany) software was used to select epochs for data processing.

2.3. eLORETA images and localization of the current-source distribution

Exact low-resolution brain electromagnetic tomography (eLORETA, Key Institute for Brain-Mind Research; Zürich, Switzerland), a functional image modality expressing current-source distribution (CSD) in three-dimensional brain images of 6239 voxels, with a space resolution of 5 mm [24], was used to obtain CSD images. eLORETA images corresponding to the positive peak of the averaged spike were obtained from each patient to identify the anatomical distribution and extent of the current-source of the averaged spike. To objectively define CSD, percentiles were used to determine the threshold of significance. Because the probability distribution for the current-source suggested that the 95th percentile would be suitable, a current-source distribution above the 95th percentile was designated as the threshold of significance.[25] Therefore, we calculated an eLORETA value of mean + 2 standard deviations among all eLORETA values in each EEG and considered this the threshold value of eLORETA images in each EEG. The neuronal cortex has been modeled as a collection of volume elements (voxels) in the digitized Talairach atlas (provided by the Brain Imaging Center, Montreal Neurological Institute). eLORETA analysis was performed on the complete EEG data by an investigator (SJ) who did not have access to any patient clinical information during the entire analytic process. The location of the CSD in each patient was identified from the eLORETA images.

2.4. Acquisition of clinical data

Clinical data were acquired by retrospective review of medical records. Clinical variables included age of onset, age at initial EEG recording, gender, type of initial AED, presence or absence of response to initial AED treatment, time interval to achievement of ultimate seizure control, drug dosage at the time of determination of the success or failure of the first AED, and seizure freedom. Successful response to initial AED was defined as complete seizure control with the first AED. Patients were divided into two groups according to responsiveness to initial AED treatment: the initial-response group and the initial-failure group. Initial failure of AED treatment was defined as a lack of complete seizure control with an optimal dose of the first appropriate AED. Seizure control was defined as the absence of clinical absence seizures. The clinical