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Changes in current-source density of interictal spikes in benign epilepsy of childhood with centrotemporal spikes following treatment with oxcarbazepine

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ABSTRACT

Purpose: The aim of this study was to detect clinical variables associated with the extent of change of the irritative zone in benign epilepsy of childhood with centrotemporal spikes (BECTS) after oxcarbazepine monotherapy.
Method: BECTS patients receiving oxcarbazepine monotherapy were retrospectively reviewed. Changes in current-source density (CSD) of the maximum negative points of interictal spikes prior to the start of oxcarbazepine treatment were compared with CSD following oxcarbazepine treatment for 6–12 months. CSD was measured using low-resolution brain electromagnetic tomography (LORETA). Patients were divided into two groups based on the change in CSD: increased-extent or decreased-extent. Comparisons were made between the groups based on the age of onset, seizure frequency before treatment, time interval between seizure onset and treatment start, time interval between the two EEGs, oxcarbazepine dosage at the follow-up electroencephalography, occurrence of daytime seizures, and seizure control.
Results: Fourteen patients were enrolled. Seven patients were in the decreased-extent group and six in the increased-extent group; one patient was excluded because she did not demonstrate any change in CSD. We found that seizure control differed significantly between the two groups: seizures were well-controlled in six out of seven patients in the decreased-extent group (85.7%), but in only one of six patients (16.7%) in the increased-extent group ($p = 0.03$). The other variables did not differ between the groups.
Conclusion: Seizure control may be associated with the extent of changes in the neuronal irritative zones of BECTS patients. We suggest that changes of CSD extent may be used as an imaging modality to evaluate clinical improvement in BECTS patients.

1. Introduction

Benign epilepsy of childhood with centrotemporal spikes (BECTS) is the most common idiopathic childhood focal epilepsy.[1] Morphologically similar centrotemporal spikes may be observed in various other clinical syndromes,[2] but the electroencephalographic (EEG) finding of centrotemporal spikes plays a decisive role in the diagnosis of BECTS in children with normal neurodevelopment.[3] Centrotemporal spikes are characterized by focal surface negative spikes with relatively prolonged duration, high amplitude, and bluntness.[4] These spike characteristics suggest that BECTS are generated by an extensive neuronal pool[4] and possesses relatively low epileptogenicity.[5]

Although the interictal spikes in BECTS have distinctive neurophysiological characteristics, the relationship between these discharges and the degree of seizure-control in a particular patient has yet to be clarified.[4] Furthermore, no correlation has been noted between the intensity of spike discharges in the EEG and the frequency, length, or duration of clinical seizures; or between an atypical morphology of interictal spikes and seizure frequency in previous studies.[6–8] In particular, the persistence of EEG abnormalities long after clinical seizure remission and extreme discrepancies characterized by very rare seizures on the one hand but high EEG activity on the other common. Clinical

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experience suggests that the EEG often remains relatively unchanged even after treatment has effectively stopped seizures.[1,9] These findings suggest that it is difficult to anticipate the clinical manifestations of BECTS based on the visual characteristics of interictal spikes. Having said that, a computer-based assessment[10] of interictal spikes in childhood partial seizures, including BECTS, demonstrated that the achievement of seizure control using antiepileptic medication is associated with changes in epileptic spike configuration, including decreases in spike amplitude and duration. The authors hypothesized that such changes in spike morphology may be caused by critical reductions in the epileptogenic neuronal pool, however they did not have the proper instruments to demonstrate this.[10]

Since that study was published, remarkable advances in functional imaging techniques have been made, and researchers now have the ability to observe neuronal activity and obtain 3-dimensional data in a non-invasive manner, for instance by using EEG current-source analysis. Low-resolution brain electromagnetic tomography (LORETA) is one of these functional imaging methods. It uses EEG measurements based on electrophysiological and neuroanatomical constraints.[11] LORETA can demonstrate 3-dimensional distributions of electrical neuronal activity, with maximum similarities of orientation and strength between neighboring neuronal populations.[11] Therefore, it may be an excellent tool for investigating the epileptogenic neuronal pools that correspond to interictal epileptic abnormalities. To date there are only few studies investigating the electrophysiological characteristics of BECTS using current-source analyses of EEG, and a current-source analysis using LORETA may be helpful for investigating the relationship between current-source changes of interictal spikes and seizure control. Thus, the purpose of this study was to investigate the relationship between distributional changes in irritative neuronal areas and seizure control in BECTS patients. A number of clinical factors were also analyzed to evaluate whether these factors are influenced by the extent of change in the irritative area following treatment.

2. Methods

2.1. Subjects

Children, newly diagnosed with epilepsy, who met the diagnostic criteria for BECTS, were recruited retrospectively from January 2009 to August 2013 at Gyeongsang National University Hospital. The diagnosis of BECTS was based on the following criteria: seizure onset between the ages of 4 and 14 years, blunt high-voltage centrotemporal or mid-temporal spikes or sharp-wave focus on EEG scans, a normal neurological examination, the absence of brain lesions and compatible seizure semiology. Of the newly diagnosed BECTS patients, only those who had undergone at least two EEG recordings were included in the study: the first EEG immediately following the diagnosis of BECTS and the start of oxcarbazepine (OXC) monotherapy (baseline) and the second EEG during the maintenance phase of treatment, 6–12 months after drug initiation (post-treatment). To minimize the effect associated with the use of different antiepileptic drugs (AED), only BECTS patients undergoing OXC monotherapy were included. Patients were excluded if (1) there was inadequate data, or they were unavailable for follow-up, (2) they experienced breakthrough seizures due to low compliance with OXC, (3) they were receiving polytherapy or taking AEDs other than OXC, or (4) they had an inadequate EEG follow-up interval.

During the study period, a total of 28 patients were newly diagnosed with BECTS. Within this group, 14 patients were excluded for different reasons (1) unavailability for follow-up ($n = 4$); (2) breakthrough seizures due to poor compliance with OXC treatment ($n = 3$); (3) polytherapy or AED medication other than OXC ($n = 3$); and (4) inadequate EEG follow-up interval ($n = 4$). Ultimately, 14 patients were enrolled in the study.

2.2. EEG recording

EEG recordings were taken for a minimum of 30 min in each patient, with the majority of recordings obtained during the waking state. A 32-channel digital EEG machine (Comet® EEG machine; Grass-Telefactor; West Warwick, Rhode Island, USA) was used in conjunction with 25 electrodes placed on the scalp according to the International 10-20 System (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, F9, F10, T9, T10, P9, P10, Fz, Cz, and Pz). The sampling rate was 400 Hz, and two EEGs from each patient were analyzed.

2.3. EEG analysis using LORETA

Brain Electrical Source Analysis (BESA; V. 5.1; MEGIS; Grafelfing, Germany) software was used to select epochs for data processing. After the visual selection of typical interictal spikes, 20 EEG segments of 1 s epochs, including 500 ms before and 500 ms after the maximum positive point of the spikes, were obtained. These 20 epochs were averaged to one spike for each set of EEG data in each patient. Thus, one averaged spike was obtained from the baseline EEG, and another was obtained from the post-treatment EEG for each patient.

Two LORETA images corresponding to the positive peak of the averaged spikes were obtained from each patient to identify the anatomical distribution and extent of the current source of the averaged spikes. LORETA is a distributed model that adapts a depth weighting to compensate for the drawbacks of the minimal norm approach.[11,12] The area with the highest current density is the location of current source.[13] To objectively define the distribution of the current source, percentiles were used to determine the threshold of significance. Because the probability distribution for the current source suggested that the 95th percentile would be reasonable, a current-source distribution over the 95th percentile was considered the threshold of significance.[14] Therefore, we calculated a LORETA value of mean +2 standard deviations among all LORETA values in each EEG, and considered this the threshold value of LORETA 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), and LORETA represents a total of 2394 voxels at 7-mm spatial resolution.[11] For quantitative analysis, the voxels for the current-source density (CSD) of the averaged spikes of the baseline and post-treatment EEGs were enumerated and compared. The complete EEG data were analyzed by an investigator (SJ). The investigator who undertook the LORETA analysis did not have access to any clinical information regarding the patients during the entire analytic process.

2.4. Acquisition of clinical information and statistical analysis

Clinical data were acquired by means of a chart review and parental documentation. Clinical factors included age of onset, seizure frequency before treatment, time interval between seizure onset and treatment start, time interval between the two EEGs, AED dosage at the follow-up EEG, and seizure control. Seizure occurrence was measured according to parental documentation, and seizure frequency at baseline was defined as seizure number per month. Patients were categorized as "well-controlled" if they had been seizure-free during the time interval between the baseline and post-treatment EEGs (at least six months), and as "poorly-controlled" if they had experienced a recurrence of a seizure or seizures during the same time interval.

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