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Decrease of global current source density predicts successful treatment in absence and juvenile myoclonic epilepsies

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ABSTRACT

Objective: To investigate relationship between treatment efficiency and EEG background activity changes in absence epilepsy (AE) and juvenile myoclonic epilepsy (JME) patients.
Patients and methods: EEGs of 31 patients were analysed before treatment and after six months of treatment. Three minutes of artifact-free waking EEG background activity (without epileptiform potentials) were analysed for each patient in both conditions. All the EEG samples were processed to LORETA (Low Resolution Electromagnetic Tomography). Average of all the voxel-wise current source density (CSD) values within the 0.5–8.0 Hz frequency range was computed for each EEG. Fischer's exact test was used to investigate association between the global CSD changes and the therapeutic outcome.
Results: Tight connection was demonstrated between seizure freedom and decreased CSD, and between persisting seizures and increased CSD ($p < 0.001$).
Significance: An EEG-based biomarker that predicts successful drug treatment was described.

1. Introduction

Epilepsy is a great group of CNS disorders, affecting about 0.5–1 per cent of the total population. Treatment is mainly based on anticonvulsive drugs. Syndrome-oriented drug selection is the generally accepted approach nowadays. However, recommendations and guidelines are based on population outcome measures of drug trials and do not consider inter-individual biological variability of the patients. Therefore, efficiency of the drug in the individual setting cannot be confidently predicted. Delay of finding the actually effective drug can result in recurring seizures and the biological and psychological sequels of them. There is a need for biomarkers that predict therapeutic response of the individual patient. However, no reliable methods are available at present (Engel et al., 2013).

Prior pharmaco-EEG findings suggest that individual solution to this problem might be possible. "A consistent EEG pattern produced by a compound is paralleled by an equally consistent pattern of behavioral changes" is principle of pharmaco-EEG (Künkel, 1982). CNS-active drugs cause EEG changes that are opposite to EEG differences that emerge between patients and healthy controls (Saletu et al., 2002). The latter conclusion resulted from investigation of patients with mental abnormalities. By analogy, we postulated that treatment-related normalization of abnormal EEG background activity can predict therapeutic efficiency of anticonvulsive compounds. As an additional increment, drug-induced EEG changes might highlight large-scale neurophysiological mechanisms of seizure control (Margineanu, 2010).

In prior articles we demonstrated abnormally increased current source density (CSD) of resting-state EEG background activity in untreated idiopathic generalized epilepsy (IGE) patients as compared to healthy controls (Clemens et al., 2012, 2016). Successful treatment with valproate (VPA) or lamotrigine (LTG) abolished the seizures and caused statistically significant reduction of CSD in IGE patients (Clemens et al., 2007, 2008). The results suggested that the above-mentioned pharmaco-EEG principle might be valid for IGE syndromes as well. However, we had no definite proof for parallel clinical and EEG changes because group effects and not individual effects were investigated. Furthermore, pharmacoresistant patients were not included.

The aim of the present study was to evaluate effects of drug treatment on seizure control and EEG background activity on individual basis. Patients with idiopathic absence epilepsy (AE) and juvenile myoclonic epilepsy (JME) were investigated. These

Abbreviations: AE, absence epilepsy; CSD, current source density; CZ, clonazepam; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; LEV, levetiracetam; LORETA, low resolution electromagnetic tomography; LTG, lamotrigine; VPA, valproate.

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syndromes belong to the IGE category. AE and JME are ideal for pharmaco-EEG studies because within-syndrome phenotypic variability is small (as compared to the very heterogeneous group of focal epilepsies) and seizure frequency is high.

2. Patients and methods

2.1. Patients

Design of the present investigation was approved by Research Ethics Committee of Kenézy Gyula Hospital. Clinical and EEG data stemmed from routine evaluation and follow-up of AE and JME patients who were enrolled without any restriction. No investigation or treatment were indicated, delayed or missed for study purposes. Diagnosis and treatment of the AE and JME patients followed generally accepted principles (Panayiotopoulos, 2005) and were carried out by epilepsy expert neurologists. Baseline evaluation included general, neurological, laboratory and EEG examinations.

Baseline EEG (EEG1) was recorded in the drug-free condition. Drug treatment started with one of the recommended drugs, chosen on individual basis. Administration of valproate in females of childbearing age was discussed with the patients. The daily dose was increased gradually until seizures disappeared or ineffectiveness (at maximal tolerated doses) was ascertained. The patients were regularly controlled. Seizure frequency, adverse events and other complaints were entered into the patient files. Given that absences and myoclonia may run unnoticed by patients and their parents, control EEG (preferably, video-EEG) was recorded and repeated if necessary.

After six months of treatment and follow-up, each patient was categorized as “responder” or “refractory”. Responders were seizure-free as reported by the patients and/or parents and confirmed by EEG. In cases of persisting seizures the patient were labelled as refractory for the applied drug. Alternative monotherapy or bitherapy was introduced in these cases. Importantly, EEG2 was recorded in refractory patients as well. All clinical and EEG data were stored as specified by data archiving protocol of Kenézy Gyula Hospital. Official identification data of the patients remained hidden in the course of the investigation as each patient had a code number.

2.2. EEG recording and conventional EEG analysis

EEGs were recorded in board-certified EEG laboratory, in a semi-isolated room in the morning, after a night of sufficient sleep, with the same digital EEG equipment. Silver-silver chloride electrodes were placed according to the 10–20 System, fixed by appropriate adhesive and conductive gel. Impedances did not exceed 10 kOhm. 21-channel EEG was recorded from standard scalp sites and the earlobes against Fpz sampling reference. EEG was recomputed against a mathematical linked ears reference. Additional bipolar derivations were used to differentiate between EEG and eye movement potentials and to detect myogenic activity. In EEG derivations filters were set at 0.1 and 33.6 Hz, sampling rate was 256 per second, on-line digitization was 12 bit. 30 min resting EEG was recorded in the waking-relaxed, eyes-closed condition, followed by 3 min of technician-controlled hyperventilation and intermittent light stimulation. The EEG technician controlled the state of vigilance and gently aroused the child when the posterior alpha rhythm disappeared. Control EEGs were preferably carried out with simultaneous video recording. Seizures and seizure-like events were noted by the technician.

Conventional EEG evaluation included assessment of background activity, proper description of transient and paroxysmal events, presence or lack of corresponding seizure phenomena, effects of hyperventilation and intermittent light stimulation.

2.3. Epoch selection

The “best” 90 epochs (each 2 s, a total of 3 min EEG) of resting-state EEG activity were selected for quantitative analysis by means of the NeuroGuide software Version 2.8. (www.appliedneuroscience.com). Our standard epoch selection protocol included: 1. presence of continuous physiological alpha activity with voltage maximum in posterior regions, 2. absence of artifacts, epileptiform potentials and other nonstationary elements, 3. absence of patterns indicating drowsiness or arousal. This electrographic definition of the relaxed-waking state refers to a narrow window of vigilance level (Bente, 1979). We used two reproducibility measures to minimize the effect of short- and long-term variability within the samples. Each sample showed at least 95 percent split-half and test-retest reliability (calculated as the average of the 19 channels). The selected epochs were revised by the senior author. NeuroGuide facilitated transmission of the samples to Low Resolution Electromagnetic Tomography (LORETA) software.

2.4. LORETA analysis

LORETA is a widely used method to localize multiple distributed cortical sources of EEG activity in the three-dimensional space (Pascual-Marqui et al., 1994).

In other words, LORETA demonstrates the synchronously activated EEG generators by computing their cortical localization from the scalp distribution of the electric field. The LORETA inverse solution is based on existing neuroanatomical and physiological knowledge and a mathematical constraint called smoothness assumption. The cortical grey matter compartment (including the hippocampi) is subdivided in 2394 voxels. LORETA computes CSD (ampers/meters squared) for each voxel. From the technical point, amount of CSD is color-coded for each voxel and projected onto a MRI brain template developed at Montreal Neurological Institute. Three-dimensional localization of the voxels is given according to the Talairach coordinates system. As to neurophysics and computation, CSD is an estimate of primary (transmembrane) neuronal currents that are main driving forces of EEG generation. Computing CSD means generating the second spatial derivative of the scalp potential field. CSD computation by LORETA includes mathematical correction for influence of electrically inhomogenous conducting media (cerebrospinal fluid, meninges, skull and scalp) on scalp-recorded EEG. Advantages of the LORETA method (over scalp EEG) are source localization of the EEG generators, reference-independence and eliminating some of volume conduction effects (Pascual-Marqui et al., 2009). Amount of CSD is frequently called “activity” in the LORETA literature. Consistency of LORETA with physiology and localization has been validated in physiological and pathological conditions (Pascual-Marqui et al., 2002). Comprehensive evaluation of the LORETA method is available in reviews (Plummer et al., 2008; Pascual-Marqui et al., 2009).

The goal of most LORETA studies is to localize maximal CSD abnormalities that are relevant to the clinical question. In this study we ignored the localisation issue and computed average CSD that reflects global amount of primary cortical outward currents (Pascual-Marqui et al., 2009). We computed average of all the voxel-wise CSD values within the 0.5–8.0 Hz frequency spectrum. So, a single CSD value characterized the patient’s global electrical abnormality in the untreated condition and another CSD value in the treated condition.

Neurophysiological and empirical evidence justified to deal with global cortical abnormality. Experimental studies (Timofeev and Steriade, 2004; Paz and Huguenard, 2015) and prior LORETA