EEG background activity is abnormal in the temporal and inferior parietal cortex in benign rolandic epilepsy of childhood: A LORETA study

M. Besenyei\textsuperscript{a}, E. Varga\textsuperscript{b}, I. Fekete\textsuperscript{c,∗}, S. Puskás\textsuperscript{c}, K. Hollódy\textsuperscript{d}, A. Fogarasi\textsuperscript{e}, M. Emri\textsuperscript{f}, G. Opporists\textsuperscript{f}, S.A. Kis\textsuperscript{f}, B. Clemens\textsuperscript{a}

\textsuperscript{a} Kenézy Hospital Ltd., Department of Neurology, Debrecen, Hungary
\textsuperscript{b} Kenézy Hospital Ltd., Department of Pediatrics, Debrecen, Hungary
\textsuperscript{c} University of Debrecen, Medical and Health Science Center, Department of Neurology, Debrecen, Hungary
\textsuperscript{d} University of Pécs, Medical and Health Science Center, Department of Pediatrics, Pécs, Hungary
\textsuperscript{e} Epilepsy Center, Bethesda Children's Hospital, Budapest, Hungary
\textsuperscript{f} University of Debrecen, Institute of Nuclear Medicine, Debrecen, Hungary

Received 29 June 2011; received in revised form 18 August 2011; accepted 20 August 2011

\textbf{KEYWORDS}
Benign rolandic epilepsy; EEG; LORETA; Attention; Language

\textbf{Summary}
\textit{Introduction:} Benign rolandic epilepsy of childhood (BERS) is an epilepsy syndrome with presumably genetic-developmental etiology. The pathological basis of this syndrome is completely unknown. We postulated that a developmental abnormality presumably results in abnormal EEG background activity findings.

\textit{Patients and methods:} 20 children with typical BERS and an age- and sex-matched group of healthy control children underwent EEG recording and analysis. 60 × 2 s epochs of waking EEG background activity (without epileptiform potentials and artifacts) were analyzed in the 1–25 Hz frequency range, in very narrow bands (VNB, 1 Hz bandwidth). LORETA (Low Resolution Electromagnetic Tomography) localized multiple distributed sources of EEG background activity in the Talairach space. LORETA activity (current source density) was computed for 2394 voxels and 25 VNBs. Normalized LORETA data were processed to voxel-wise comparison between the BERS and control groups. Bonferroni-corrected \(p < 0.05\) Student's \(t\)-values were accepted as statistically significant.

\textit{Results:} Increased LORETA activity was found in the BERS group (as compared to the controls) in the left and right temporal lobes (fusiform gyri, posterior parts of the superior, middle and inferior temporal gyri) and in the angular gyri in the parietal lobes, in the 4–6 Hz VNBs, mainly at 5 Hz.

\textsuperscript{∗} Corresponding author at: University of Debrecen, Medical and Health Science Center, Department of Neurology, Móricz Zsigmond krt. 22, 4032 Debrecen, Hungary. Tel.: +36 52 415 176; fax: +36 52 453 590.
\textit{E-mail address: prof.fekete@yahoo.com} (I. Fekete).

0920-1211/5 — see front matter © 2011 Elsevier B.V. All rights reserved.

Please cite this article in press as: Besenyei, M., et al., EEG background activity is abnormal in the temporal and inferior parietal cortex in benign rolandic epilepsy of childhood: A LORETA study. Epilepsy Res. (2011),
Discussion: (1) Areas of abnormal LORETA activity exactly correspond to the temporal and parietal cortical areas that are major components of the Mirsky attention model and also the perisylvian speech network. Thus the LORETA findings may correspond to impaired attention and speech in BERS patients. (2) The LORETA findings may contribute to delineating the epileptic network in BERS.

Significance: The novel findings may contribute to investigating neuropsychological disturbances and organization of the epileptic network in BERS.

© 2011 Elsevier B.V. All rights reserved.

Introduction

Benign epilepsy of childhood with rolandic spikes (BERS) was first realized as a self-limited epilepsy syndrome with rare, localization-related seizures, no neuro-psychiatric symptoms, characteristic rolandic spike-and-slow EEG discharges (RS), and excellent outcome (Beaussart, 1972). Later, neuropsychological investigations disclosed impaired performance in functional domains including attention, memory, language, visuo-spatial orientation and executive functions in 28–53% of these children (Chahine and Mikati, 2006). Some of the disturbances are related to the laterality of the epileptic focus and the amount and spatial distribution of the RSs while others are not (Massa et al., 2001; Fonseca et al., 2007; Nicolai et al., 2007). As to the etiology of the cognitive disturbances, the very rare and brief seizures in BERS are by no means responsible for them. Furthermore, RSs and neuropsychological disturbances were found in persons who had no seizures at all (van der Meij et al., 1993). It became gradually clear that the essence of the BERS phenotype is not epilepsy but a developmental encephalopathy that may present with or without seizures (Doose and Baier, 1989; Panayiotopoulos, 2005). The biological marker or endophenotype of this condition is the RS that is inherited as an autosomal dominant trait. The first genome-wide linkage scan carried out in typical BERS patients disclosed that the gene responsible for the RSs encodes the Elongator Protein Complex 4. The mutation of this gene might result in widespread abnormality of neurodevelopment (Strug et al., 2009).

Unfortunately, very little is known about the structure and neurophysiological characteristics of this encephalopathy. Its microscopic morphology and spatial extension is unknown because no gold standard neuropathological data and no conclusive neuroimaging findings exist (van Bogaert et al., 1998; Lundberg et al., 1999; Boxerman et al., 2007). EEG, magnetoencephalography (MEG), and functional MRI localized the cortical generators of the RSs into the pre- and postcentral cortex (Baumgartner et al., 1996; Boor et al., 2007; Patarayia et al., 2008). However, the authors did not analyze EEG background activity. The aim of the present study was anatomical localization of the cortical generators of abnormal EEG activity in BERS patients. The scientific rationale for this approach is that the elements of the anatomical and physiological basis of EEG background activity: cerebral grey and white matter microstructure, connectivity and related metabolism (Robinson et al., 2004) are genetically strongly determined (Zietsch et al., 2007). As a corollary, a developmental encephalopathy probably gives rise to EEG abnormalities that inform us about its localization and electrophysiological characteristics. Given the developmental nature of the abnormality and the rule that genetic determination of EEG background activity refers to both hemispheres we hypothesized a bilateral EEG abnormality, disregarding the laterality of the RSs in the analyzed record. In fact, RSs frequently shift back and forth between the left and right central areas.

Patients and methods

Patients

The study design was approved by the Research Ethics Committee of Kenézy Hospital Ltd. The patients were prospectively sorted out of those who were referred to one of the collaborating Epilepsy Outpatient Services at Debrecen, Budapest or Pécs because of one or more epileptic seizures. Evaluation included a detailed medical history, pediatric and neurological investigations, routine blood analysis, EEG. Cranial MRI at 1.5 T field was carried out in some of the patients depending on the decision of the investigator. The children who fulfilled the generally accepted diagnostic criteria for BERS (ILAE, 1989) were potential candidates for this study. In order to collect typical BERS cases, patients with atypical clinical and EEG features (Wirrel et al., 1995) were excluded. The children contacted the specialist a few days or weeks after the first or second seizure. Minimal interval between the last seizure and EEG investigation was 6 days. EEG was always carried out in the untreated state. Patients with very frequent spikes that disturbed EEG background activity were excluded. EEG records that did not meet the requirements of quantitative EEG analysis (Nuwer et al., 1994) were excluded as well. Drug treatment was initiated on individual basis.

EEG recording and epoch selection

EEG recordings were carried out in the morning, after a night of sufficient sleep, in a semi-isolated room, with the same type of digital equipment, by trained personnel, according to recommended standards for quantitative EEG studies (Nuwer et al., 1994). 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 the EEG derivations the filters were set at 0.1 and 33.6 Hz, sampling rate was 128 per
second, 12 bit on-line digitization was used. 30 min EEG was recorded in the waking-relaxed, eyes-closed condition. The state of vigilance was controlled by the EEG technician who gently aroused the child when the posterior alpha rhythm disappeared.

The "best" 60 epochs (each 2 s, a total of 2 min EEG activity) were selected for analysis. Epoch selection and analysis was done blindly. Our standard epoch selection protocol includes: (1) the presence of continuous physiological alpha activity with alpha voltage maximum in posterior regions, (2) the absence of artifacts, epileptiform potentials, and other nonstationary elements, and (3) the absence of patterns indicating drowsiness or arousal. This electrographic definition of the relaxed-waking state refers to a narrow range of vigilance level (Bente, 1979). Epochs within the 6-s post-RS period were not included because the delaying electrophysiological effect of the RSs may interfere with EEG background activity (Clemens et al., 2009). Two reproducibility measures were used to minimize the effect of short- and long-term variability within the samples. Only samples with at least 95% of average split-half reliability and test—retest reliability (calculated as the average of the 19 channels) entered further analysis. All steps of sampling and data analysis were the same for the patients and the controls. Final control of the selected epochs was done by the senior author, by means of the NeuroGuide software Version 2.5.6 (http://www.appliedneuroscience.com/) that allowed transmission of the samples to the joined LORETA (Low Resolution Electromagnetic Tomography) software.

LORETA analysis

LORETA is a recently developed 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 the smoothness assumption. LORETA computes the inverse solution within a three-shell spherical head model including scalp, skull, and brain. The brain compartment of this model was restricted to the cortical grey matter and hippocampus. The grey matter compartment is subdivided in 2394 voxels, which allows a spatial resolution of 7 mm. LORETA computes current source density (amperes/meters squared) for each voxel. For the sake of brevity, this is called "activity" in this paper as usual in the LORETA literature. The voxel-wise LORETA activity values are projected to a structural MRI image. Localization follows the Talairach coordinate system (Talairach and Tournoux, 1988). The consistency of LORETA with physiology and localization has been validated for a lot of normal and pathological conditions (Pascual-Marqui et al., 2002). Comprehensive evaluation of the LORETA method is available in reviews, for example, activity in the 1 Hz VNB was the average of the 0.5 and the 1.0 Hz values. Localization is given in anatomical terms, specifying the lobe, the gyrus and the Brodmann area (BA) of the abnormality.

Group comparison

The BERS patients group was compared to an age- and sex-matched group of control children selected from our own normative EEG database. Control children were clinically healthy, without any developmental, neurological and psychiatric illness in medical history. Their waking EEG records were within normal limits, no pathological slow wave activity or irritative potentials were found. EEG was recorded and post-processed in the same way for the patients and controls. The normalized LORETA data underwent voxel-wise Student’s t-statistics. Given that not the voxel-based current source density values but rather the sensors (electrodes) are independent (Grave de Peralta Menendez et al., 2004), Bonferroni’s correction for multiple comparisons was used as to emphasize and visualize the statistically significant group differences at the corrected \( p < 0.05 \) level.

Results

20 children were enrolled (9 males and 11 females, aged 6.1—12.3 (average: 8.7) years). They had one to three, non-provoked rolandic seizures. Clinical findings were normal. We could not carry out neuropsychological investigations, but the lack of significant problems in school performance and behaviour argued against clinically significant cognitive disturbances. All the patients showed EEG background activity within normal limits. RSs were found in all records. Immediate activation of RSs was seen in all patients when the first EEG signs of drowsiness occurred. 18 children displayed RSs with voltage maximum in the T3/T4 derivations, two children in the C3/4 leads. 10 children had right-sided, 7 had left-sided and 3 had bilateral-independent RSs. The characteristic dipolar field at the main negative phase of the RS was demonstrable in all cases.

LORETA results

Statistically significant differences emerged in the 4—6 Hz VNBs only. The abnormality was the greatest at 5 Hz. The patient group showed increased LORETA activity (as compared to the controls) in the temporal lobes and in the angular gyri in the parietal lobes. In infero-superior direction (Fig. 1): left and right fusiform gyri, BA 27; posterior parts of the left and right inferior and middle temporal gyri (BA 37). Right-sided abnormality was found in the following four slices: in the posterior parts of the right inferior, middle and superior temporal gyri (BA 22, 37). Upwards from this level, symmetrically increased activity emerged in the posterior parts of the middle and superior temporal gyri (BA 39) and the angular gyri (BA 39).

**Discussion**

This is the first study to demonstrate the cortical sources of abnormal EEG background activity in BERS patients. The importance of our findings is valorized by the fact that other imaging methods did not detect consistent abnormalities in BERS (van Bogaert et al., 1998; Lundberg et al., 1999; Boxerman et al., 2007). LORETA specified cortical areas characterized by abnormally synchronized, mainly cortico-cortical neuronal input. However, increased EEG synchronization is related to altered neuronal output (Denker et al., 2011), indicating disturbed connectivity between the affected areas and the rest of the hemisphere.

Children with typical BERS are prone to general memory difficulty and impaired phonological awareness (Northcott et al., 2005), the latter being perhaps related to impaired preattentive sensory processing (Fiedler et al., 2006). Attention, a prerequisite of all cognitive activities, is frequently impaired in BERS. The posterior part of the superior temporal gyrus, the fusiform gyrus, the inferior parietal lobe, frontal cortical areas and subcortical structures form the anatomical basis of the Mirsky attention model that was applied to the attention deficit findings in BERS (Kavros et al., 2008). Granger causation analysis of intracranial EEG data disclosed that the posterior part of the superior temporal gyrus governs sensory processing in the perisylvian speech network (Gow et al., 2009). Our LORETA results disclosed abnormal cortical function exactly in the posterior part of the superior temporal gyrus, fusiform gyri and inferior parietal cortex that are involved in the Mirsky model of attention. Thus we suggest that causal relationship exist between the LORETA abnormalities and the

---

above-mentioned neuropsychological disturbances. Parallel neuropsychological and EEG-LORETA investigations may improve our understanding regarding the localization, temporal evolution and final resolution of these symptoms.

To date, localizing efforts were limited to establishing the cortical generators of the RRs within the perirolandic cortex in BERS (Baumgartner et al., 1996; Boor et al., 2007; Patarea et al., 2008). However, contemporary concepts of the epileptic focus are not based on epileptiform EEG abnormalities exclusively. The “epileptogenic zone” (Lüders et al., 1993) and the “epileptic network” (Spencer, 2002) are complex concepts aiming to delineate the anatomical substrate of the brain that is responsible for its seizure-generating property. The LORETA abnormality described in this study may contribute to improved understanding the epileptic network in BERS. Finally, we suggest that forthcoming, sophisticated MRI investigations should be guided towards the temporal and parietal areas highlighted in this study.

**References**


