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The electrophysiological "delayed effect" of focal interictal epileptiform discharges. A low resolution electromagnetic tomography (LORETA) study

^{*1}Clemens Béla M.D., Ph.D.; ¹Piros Pálma M.D.; ¹Bessenyei Mónika M.D.; ²Varga Edit, M.D.; ³Puskás Szilvia, M.D., ³ Fekete István, M.D., Ph.D.

¹ Kenézy Hospital Ltd., Department of Neurology, Debrecen, Hungary

² Kenézy Hospital Ltd., Department of Pediatrics, Debrecen, Hungary

³ University of Debrecen, Medical and Health Science Center, Department of Neurology, Debrecen, Hungary

* Corresponding author: Dr. Clemens Béla, Kenézy Kórház Kft., Neurológia, Bartók Béla út 3., 4031, Debrecen, Hungary.

TEL: ++36 52 511 777

Fax: ++36 51 511 729

E-mail: bela.clemens@yahoo.com

Abstract

Collating the findings regarding the role of focal interictal epileptiform discharges (IEDs) on CNS functions raises the possibility that IEDs might have negative impact that outlasts the duration of the spike-and wave complexes. The aim of this study was the electrophysiological demonstration of the "delayed effect" of the IEDs. 19-channel, linked-ears referenced, digital waking EEG records of eleven children (aged 6-14 years, eight with idiopathic, three with cryptogenic focal epilepsy, showing a single spike focus) were retrospectively selected from our database. A minimum of twenty (preferably, thirty), 2-second epochs containing a single focal spike-and-wave complex were selected (Spike epochs). Thereafter, Postspike-1 (Ps1), Postspike-2 (Ps2) and Postspike-3 (Ps3) epochs were selected, representing the first and second seconds (Ps1), the third and fourth seconds (Ps2) and the fifth and sixth seconds (Ps3) after the Spike epoch, respectively. Interspike epochs (Is) were selected at a distance at least ten seconds after the Spike epoch. *Individual analysis*: the frequency of interest (FOI = the individual frequency of the wave component of the IEDs), and the region of interest (ROI = the site of the IEDs) were identified by reading the raw EEG waveform and the instant power spectrum. Very narrow-band LORETA (low resolution electromagnetic tomography) analysis at the FOI and ROI was carried out. Age-adjusted, Z-transformed LORETA "activity" (= current source density, amperes / meters squared) was compared in the Spike, Ps1, Ps2, Ps3 and Is epochs. Findings: the greatest (uppermost pathological) Z-scores and the greatest spatial extension of the LORETA-abnormality were always found in the Spike epochs, followed by the gradual decrease of activity in terms of severity and spatial extension in the Ps1, Ps2, Ps3 epochs. The lowest (baseline) level and extension of the abnormality was found in the Is epochs. *Group analysis*: average values of activity across the patients were computed for the temporal decrease of the abnormality. Findings: a clear tendency for the decrease of abnormality was demonstrated. *Conclusion*: the "delayed effect" of the IEDs was demonstrated electrophysiologically and quantified. The method may be utilized in the individual assessment of the effect of IEDs on cortical activity, the degree and temporo-spatial extension of the abnormality.

Key words

Epilepsy, spike, delayed effect of the spike, EEG, LORETA

1. Introduction

The electroencephalographic term interictal epileptiform discharge (IED) means spikes and sharp waves usually followed by a slow wave (Chatrian et al, 1974). The attribute "interictal" indicates that, unlike ictal EEG patterns, IEDs are not accompanied by seizure symptoms. However, IEDs are not always clinically silent because even a single, focal spike-and-slow wave complex might interfere with attentional, motor, sensory and cognitive processes (Shewmon and Erwin 1988a-c). The designation "nociferous cortex" implies that IEDs themselves impair neurological functions; in fact, the spiking cortex gives rise to a greater degree of cerebral dysfunction than the abolition of the same part of the cortex (Penfield, 1952). In a recent summary of the IED-related dysfunction the author concluded that "focal IED should not be assumed as clinically benign" (Fisch, 2003). As a corollary, "EEG treatment", that is, abolition of the IEDs with antiepileptic drugs has been a matter of increasing interest (Guerrini et al, 2002; Binnie, 2003; Pressler et al, 2005; Jaseja, 2006).

The mechanism and the evolution of the IED-related deficit symptoms are not clearly understood. Some symptoms like transient abolition of muscle tone (Rubboli et al, 1995), increased reaction time (Shewmon and Erwin, 1988a), and transient impairment of cognitive functions (Aarts et al, 1984; Binnie and Marston, 1992; Aldenkamp et al, 2005) are strictly time-locked to the IEDs. However, other investigators described fluctuating neurological symptoms, disturbed speech and cognitive impairment that were related to the presence of frequent IEDs but not strictly time-locked to them. Drug treatment that abolished the spikes caused significant clinical improvement within a short time period (Hirsch et al, 1990; Metz-Lutz et al, 1999; Baglietto et al, 2001; Massa et al, 2001; Dalla Bernardina et al, 2002). Thus, a "delayed effect" of the IEDs might be deductively postulated as an explanation for the lack of the precise temporal coincidence between the IEDs and the time course of the above mentioned symptoms. We are not aware of any explicit hypothesis addressing this delayed effect albeit a few possible mechanisms have been conceived (Holmes and Lenck-Santini, 2006). The delayed effect might be due to oscillations that survive the spike-and-wave complex. Conventional visual EEG analysis confirms slow EEG oscillations after a single spike in some patients but not in all. However, quantitative assessment of the impact of these oscillations on physiological cortical activity is not possible by visual analysis. Our hypothesis was that IED-related abnormal oscillations follow the spike-and-slow wave complex, and the time course and spatial distribution of this phenomenon may be characterized in a quantitative way by source analysis.

2. Patients and methods

2.1. Patients and EEG recording

The design of this retrospective study was approved by the Research Ethics Committee of Kenézy Kórház Ltd. Our computerized Epilepsy & EEG database was retrospectively searched for epileptic children who fulfilled the following criteria: registered in the 2002 to 2007 time period; idiopathic or cryptogenic, localization-related epilepsy of childhood as defined by the international classification (ILAE 1989); age of onset between 6 and 14 years; no treatment at EEG evaluation; EEG carried out at a day without prior seizure; a retrievable waking EEG record that was recorded in our laboratory

with the usual technique. This means the use of the same digital EEG equipment, the 10-20 electrode system, recording from 19 active electrodes against the linked ears reference, impedances < 10 kOhm, filters set at 0.1 and 33.6 Hz, 128 per second sampling, 2^{12} bit on-line analog-digital conversion. EEG traces that did not fit the general quality criteria for quantitative EEG analysis (Nuwer et al, 1994) were excluded with the remarkable difference that the presence of IEDs was not an exclusion criterion. Only the "eyes closed" portion of the EEG records showing a single spike focus and IEDs of "medium frequency" were analyzed because very rare or too frequent spiking did not permit the application of the study design presented below and in Fig-1.

2.2. Quantitative EEG analysis

Epoch selection and computing the Fast Fourier Transform (FFT) were done with the NeuroGuide software (<http://www.appliedneuroscience.com>). As the first step, at least twenty (preferably, thirty) 2-second epochs of EEG activity each containing a single spike-and slow complex were selected as presented in Fig-1 (Spike epochs). Thereafter, 2-second epochs immediately following the Spike epochs were selected (Postspike-1 epochs, Ps1), followed by the selection of Postspike-2 (Ps2) and Postspike-3 (Ps3) epochs each of 2 seconds. Finally, 2-second epochs that were located at least 10 seconds from the last Spike epoch (Interspike epochs, Is) were selected. Files selectively containing the Spike, Ps1, Ps2, Ps3, and Is epochs for each patient were processed separately. FFT values of the selected epochs were averaged for every file, and the results were converted to ".lor" files in order to transfer the data to the allied LORETA (low resolution electromagnetic tomography) software.

LORETA is a recently developed method to localize multiple distributed cortical sources of bioelectric activity in the three-dimensional space (Pascual-Marqui et al, 1994). In other words, LORETA demonstrates the synchronously activated neuronal populations underlying EEG activity by computing their cortical localization from the scalp distribution of the electric field. This is called solving the inverse problem of the EEG. The LORETA inverse solution is based on existing neuroanatomical and physiological knowledge and a mathematical constraint called the smoothness assumption (Pascual-Marqui, 2002a). 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, according to the Talairach Brain Atlas digitized at Montreal Neurological Institute (Talairach and Tournoux, 1988). The grey matter compartment was subdivided in 2394 voxels, which allows a spatial resolution of 7 millimeters. LORETA computes a physically existing dimension, current density (amperes / meters squared) for each voxel. For the sake of brevity, this is called "activity" in this paper. The consistency of LORETA with physiology and localization has been validated for a lot of normal and pathological conditions (Pascual-Marqui et al, 2002b). The accuracy of LORETA in localizing IEDs has been addressed in a few papers. Intracranial EEG and functional MRI confirmed the LORETA-defined localization of IEDs (Seeck et al, 1998). LORETA-MRI fusion disclosed considerable topographical overlap between the epileptogenic lesion and the IEDs (Sgouros et al, 2001). Using 22 scalp electrodes and intracranial leads LORETA found the highest current density in the area where intracranial EEG detected IEDs (Lantz et al, 1997). Using 21 scalp electrodes LORETA localized correctly IEDs to the mesial temporal structures in 14/19 patients in whom the localization was confirmed by simultaneous foramen ovale recordings and the good results of amygdalo-hippocampectomy. There was no clear LORETA solution in the remaining 5 cases but no LORETA solution was clearly incorrect (Zumsteg et al, 2005). Using 23 to 29 scalp electrodes LORETA localized a distinct EEG abnormality, small sharp spikes, in the same sub-lobar area than did intracranial EEG recordings (Zumsteg et al, 2006). However, the LORETA method has its limitations.

Comprehensive evaluation of its localizing accuracy and the scientific background of LORETA were discussed in recent papers (Zumsteg et al, 2005; Grova et al, 2006; Plummer et al, 2008).

Given that the main source of IED-related deficit is the slow wave component of the focal spike-and-slow complex, very narrow band LORETA analysis (with the resolution of 1 Hz) was focused to the frequency of interest (FOI) and the region of interest (ROI). FOI and ROI were first estimated by evaluating the raw EEG trace and the instant power spectrum of the averaged spike epochs. The main negative phase of the spikes was fitted to the middle of the spike epoch. (Fig-2). As the next step, FOI (= the frequency of the wave component of the IEDs) and ROI (= the site of maximum LORETA abnormality in the averaged Spike epochs at the site of the IEDs) were precisely determined from the LORETA solution. The ROI was anatomically localized in the three-dimensional space by specifying the position of the voxel on the Z-axis of the Talairach coordinate system, the number of the Brodmann-area, and the anatomical name of the gyrus. Measurement was carried out at the selected FOI and ROI (Fig-3). In this study we used age-adjusted, Z-transformed LORETA values of activity the derivation of which was described in the LORETA Normative EEG Database (Thatcher et al, 2005). The use of statistical mapping was reported to be superior to the raw LORETA results in localization studies (Zumsteg et al, 2005). The degree of abnormality (Z-score) within the ROI was compared among the Spike, Ps1, Ps2, Ps3 and Is epochs for each patient thus demonstrating the severity and time course of the abnormality. Picture-montages were created for each patient in order to assess the spatial changes of the abnormality across the Spike, Ps1, Ps2, Ps3 and Is epochs (Figures 4. and 5). The anatomical extension of the abnormality could be semi-quantitatively estimated from these LORETA series. Finally, the Z-scores of the Spike, Ps1, Ps2, Ps3 and Is epochs were averaged across the patients in order to assess the average degree of temporal decrease of the abnormality.

3. Results

3.1. Temporal diminution of the IED-related abnormality

The data of the patients, the EEG localization of the IEDs and the findings are given in Table-1. All the patients displayed maximum abnormality in the Spike epochs that showed a marked tendency to diminish in the Ps1, Ps2, Ps3 epochs and reached the minimum value in the Is epochs. This tendency was found in the children with idiopathic partial epilepsy with rolandic spikes (BERS) and in cryptogenic epilepsy alike. However, the individual time course of the decrease of the abnormality differed from patient to patient. As to show the average tendency the data of the patients were averaged. Paired t-tests showed statistically considerable difference between the Spike and Ps1 epochs ($p < 0.0001$), between Ps1 and Ps2 ($p = 0.004$) but not between Ps2 and Ps3 ($p = 0.276$) and Ps3 and Is epochs ($p = 0.070$). The reliability of the findings was supported by the high test-retest and split-half reliability values. These reliability measures for the 19 derivations were averaged and the average values were always above 90 per cent for the Spike, Ps1, Ps2, Ps3 and Is epochs.

3.2. Spatial extension of the abnormality

LORETA always lateralized the maximum of the abnormality to the hemisphere of the spike focus. There was no striking discrepancy between the LORETA solution and the conventional EEG localization of the IEDs. The LORETA series that were composed for each patient showed that the spatial extension of the abnormality was the greatest in the Spike epochs and showed an overall

tendency for gradual spatial shrinking in the Ps1, Ps2, Ps3 and Is epochs as demonstrated by the two exemplars (Figures 4, 5). The Z-score helps to estimate the extension and the time course of the abnormality on the individual basis.

4. Discussion

4.1. The importance and the assessment of "synchronization"

The IED-related derangement of cortical functions is mainly due to the wave component of the discharge. The wave represents surround inhibition, the temporo-spatial distribution of which determines the local and remote deficit symptoms including cognitive impairment (Prince and Wilder, 1967; Shewmon and Erwin, 1988c). Every EEG reader knows that the waves interrupt normal brain rhythms for a longer time period (several hundred milliseconds) than the spikes. In addition, the wave is time-locked to the decrease of the very fast (100 to 500 Hz) oscillations that are involved in normal information processing (Urrestarazu et al, 2006). Earlier studies disclosed that the disruptive effect of a single IED is directly proportional to the voltage of the wave but not the spike (Shewmon and Erwin, 1988c). This observation and the direct relationship between the spatio-temporal amount of the spike-wave series and the severity of the deficit symptoms in the long run (Metz-Lutz et al, 1999; Baglietto et al, 2001; Massa et al, 2001) are independently derived findings but lead to the same conclusion: *the greater the degree of neuronal synchronization over time and space the greater the cortical dysfunction*. As to avoid confusion in this paper "synchronization" refers to the synchronous activation of great cortical neuronal masses (Nunez, 1995), the result of which is reflected by the increase of the voltage of the EEG signal (Pfurtscheller and Lopes da Silva, 1999). This relationship highlights why LORETA is an appropriate method to assess IED-related synchronization: "the LORETA inverse solution corresponds to the three-dimensional distribution of electric neuronal activity that has maximum similarity (i.e., maximum synchronization) in terms of strength and orientation between neighbouring neuronal populations" (Pascual-Marqui, 2002a). The use of 2-second epochs was predetermined by the software; however, it was a lucky choice because this time frame was sufficient to include all component of the IED including some possible pre-spike events (Hawco et al, 2007), and the complete IED.

4.2. The delayed EEG effect

Our findings confirmed the hypothesis that the delayed EEG effect lasts for at least a few seconds beyond the duration of the IED, and the characteristics of the decreasing oscillation can be quantitatively assessed in space and time. Its neuronal basis is not known but several mechanisms exist that can generate and sustain rhythmic phenomena in epileptically functioning neuronal ensembles (de Curtis and Avanzini, 2001; McCormick and Contreras, 2001). Numerically, the degree and time course of the delayed EEG effect refers to the investigated cohort of patients with medium spike frequency. It is possible that more frequent IEDs or long series of them result in more delayed normalization of cortical activity thus resulting in less transient CNS dysfunction. This possibility is supported by another, IED-related phenomenon, the decrease of axonal firing of hippocampal neurons that outlasts the IED for about 2 seconds but even for longer periods after clusters of spikes (Zhou et al, 2007). As far as we know, no other electrophysiological phenomena that outlast the entire spike-and-wave complex have been described yet.

4.3. Spatial assessment of the abnormality

The localization of the IED-related dysfunction can be visualized by means of quantitative EEG methods, magneto-encephalography and functional magnetic resonance imaging (fMRI). The latter method greatly contributed to the understanding the complexity of the IED-related abnormality, the involvement of subcortical structures (that remain hidden for scalp EEG), and differentiate between areas of increased and decreased activity. EEG-fMRI co-registration seems to be particularly promising (Grova et al, 2008); however, going into details is beyond the scope of this paper. LORETA localized the abnormality concordantly to the raw EEG waveform and the EEG-spectrum thus increasing the number of the papers validating the LORETA method (Pascual-Marqui et al, 2002b). In this paper we investigated the localization of the sum of the IED-related, spatially distributed abnormality in 2-sec time frames; this task fundamentally differs from the efforts to localize the sources of spikes in BERS (or any other epilepsy syndrome) and must not be confused with them. Not surprisingly the maximum spatial extension of the abnormality was found in the Spike epochs and a gradual shrinking of it was seen in the subsequent epochs. The exact neuronal mechanism for this spatial decrease is not known but the role of decreased intracortical synchronization seems to be probable (Chagnac-Amitai and Connors, 1989; de Curtis and Avanzini, 2001). Finally, even the Is epochs show some degree of focal abnormality, as compared to the remaining parts of the cortical mantle. This is in accord with a recent intracranial EEG study demonstrating that locally increased synchronization in the interictal state is characteristic to the epileptic cortex in focal epilepsy (Schevon et al, 2007).

The shortcoming of the study is suboptimal spatial sampling due to the limited number of electrodes, which is usually criticized in 19-channel LORETA studies. Nevertheless, we do not think that this resulted in significantly inaccuracy in this study. Resting EEG rhythms (in particular, slow rhythms) are generated by largely distributed cortical sources that can be accurately investigated by the standard 10-20 system (Nunez, 1995; Babiloni et al, 2006). Comparative studies disclosed that LORETA analysis results in very similar localization of the generators with 19 and 46 electrodes provided that they are evenly distributed on the scalp (Michel et al, 2004). In our study the good signal to noise ratio improved the accuracy of localization. Albeit some mislocalization and blurring the extension of the abnormality may be inherent to LORETA, this mainly refers to smaller sources (Zumsteg et al 2005). In any case, the potential localization inaccuracy of the method does not interfere with our main findings. Finally, the LORETA normative database (that permits the assessment of the abnormality in terms of age-related deviations from $Z=0$ for each voxel) is constructed for 19 standard deviations and inserting further derivations is not possible.

Only the anatomical distribution at the frequency of the wave was investigated in this study. However, the complex, mutual interdependence of the physiological oscillations at diverse frequencies in the brain (Buzsáki and Draguhn, 2004) implies that IEDs may cause interference with some other oscillations underlying cognition and other cortical activities. The present findings suggest that LORETA might be a useful method to investigate the anatomical distribution of the effect of disturbing transient events on normal cerebral activities.

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6. Legends to Figures

Fig-1. EEG record, spontaneous waking activity of patient No.10. Occipital alpha rhythm, left temporal (T3) spike focus. The spike epoch (highlighted in pink) contains the spike-and-slow wave complex. Postspike1, Postspike2, Postspike 3 epochs are labelled with black, blue, and violet colors, respectively, just above the time axis. Interspike epochs are not present in the figure because they are located at least 10 seconds from the last spike epoch.

Fig-2. EEG record of patient No.10. with instant power spectrum of the averaged spike epochs: absolute power (top) and Z-score of absolute power (bottom). The spectra reflect the average of the 30 spike epochs. The frequency of interest is about 3 - 4 Hz as estimated by the duration of the slow wave and the first major peak of the Z-spectrum for T3 and F7 derivations. Color-coding is the same for the traces and the spectrum thus allowing the identification and estimation of the Z-value for any trace and frequency.

Fig-3. Three-dimensional LORETA probability maps of a patient. X, Y, Z coordinates of the Talairach coordinate system and the frequency of interest are presented. The latter is a very narrow band variable, the average of the activity (ampers / meters squared) measured at 3.5 and 4 Hz in this example. The cursor (not present in this figure) can be moved from voxel to voxel and the corresponding amount of activity (Z-score) and its precise localization is given in a window. The color scale ranges from $Z=0$ (white) to the maximum value ($Z=1.55$, maximum red).

Fig-4. Patient No.2., 9 years old. Spatial extension of the abnormality in the Spike, Postspike1, Postspike2, Postspike3 and Interspike epochs. The color threshold was set at $Z=2$, that is, only the voxels with $Z>2$ values are displayed in red, according to the color scale. FOI = frequency of interest, the individual frequency of the wave component of the IEDs. ROI= the region of interest, the cortical site of the IEDs.

Fig-5. Patient No.3., 7 years old. Spatial extension of the abnormality in the Spike, Postspike1, Postspike2, Postspike3 and Interspike epochs. The color threshold was set at $Z = \pm 1$. FOI = frequency of interest, the individual frequency of the wave component of the IEDs. ROI= the region of interest, the cortical site of the IEDs.

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