Seizure 2002; **11**: 320–324
doi:10.1053/seiz.2002.0676, available online at http://www.idealibrary.com on IDEAL®

Source analysis of polyspike and wave complexes in juvenile myoclonic epilepsy

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We applied dipole modeling and brain distributed source analysis to find current sources comprising spikes and slow waves of polyspike and wave complexes (PSWC) in patients with juvenile myoclonic epilepsy (JME). The dipoles were localized in frontal, parietal and temporal lobes. The frontal dipoles were clustered in the frontal medial gyrus and fronto-orbital region. A midsagittal frontal current source was observed using brain distributed source analysis in all patients. When the slow wave was analyzed, multiple sources in different cortical regions were detected using dipole modeling and brain distributed analysis. These results show pre-frontal medial current sources corresponding to spikes and many diffuse sources in cortical regions corresponding to wave components of PSWC in patients with JME.

Key words: juvenile myoclonic epilepsy; polyspike and wave complexes; dipole modeling; source analysis.

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is a syndrome, beginning in puberty, characterized by myoclonic jerks in the morning, tonic–clonic seizures (TCS), and, less frequently, absence seizures. Nowadays, it has been recognized that JME is frequently an age dependent syndrome, corresponding to 5%–10 % of all epilepsies in adolescent and adult groups[1]. Childhood absences, juvenile absences, grand mal on awakening and JME are subtypes of idiopathic generalized epilepsy (IGE) that have been recognized as a broad neurobiological continuum with similar genetic ground, onset age, and electroencephalographic characteristics[2]. Generalized spike–wave (SWC)[5] and polyspike–wave complexes (PSWC), with fronto-central accentuation are the typical EEG pattern shown in JME[1].

Jasper[3] described frontal and parieto-occipital phase reversals of SWC, and bilateral propagation was achieved in 20 milliseconds, proposing the centro-encephalic hypothesis of generalized epilepsies. Years later, EEG studies of the spatial distribution of SWC and PSWC in childhood absences and other IGE syndromes, detected a frontal distributed paroxysmal activity in IGE[4–6]. In recent years, brain topographic maps and source analysis with dipole modeling have been used[7–9]. These methods provide the means of finding sources in frontal, fronto-polar and orbito-frontal regions. On the other hand, in patients with JME, anatomophatological examinations[10], functional evaluation of visual working memory tasks with PET[11], MRI voxel-based morphometric analysis[12] and magnetic resonance spectroscopy (MRS)[13] studies have detected frontal alterations.

In the last decade, some procedures analyzing current sources have been developed. Dipole modeling has proved to be useful for the punctual localization of sources of interictal activity in patients with different types of epilepsy[14]. With brain distributed source analysis, it is possible to obtain a three-dimensional (3D) model, where the solution is not a single point, but a volume with distributed sources. Variable

resolution electromagnetic tomography (VARETA)[15] is one of these methods, and has been used in the localization of EEG sources of evoked potentials, brain lesions and different cognitive tasks.

In opposition to partial epilepsies, where focal ictal and interictal activities are detected, and where intracranial and intracerebral monitoring is used in surgical cases, invasive monitoring in IGE is rarely indicated. Therefore, methods of current source analysis such as dipole modeling and brain distributed source analysis are the keystone for studying epileptogenic activity in patients with IGE. Although some studies of source analysis of IGE have been carried out, at this moment no studies have been performed with PSWC in patients with JME. Therefore, the aim of this paper was to use both methods for determining current sources of PSWC in patients with JME.

MATERIALS AND METHODS

Five patients with JME were studied. Mean age was 23 ± 11 years, with an age range between 13 and 41 years. Four patients were female and one male. After giving their informed consent, all patients underwent clinical neurological examinations. The patients were selected from the General Hospital of Querétaro City, Mexico.

The onset of epilepsy had a mean age of 13 years with myoclonic jerks in three patients, one with absences and the other with TCS. All patients had myoclonic and TCS. Both types of seizures were always present in the first hour after awakening. All patients had normal neurological examinations and characteristic paroxysmal generalized activity with PSWC in EEG recordings, with a standard antiepileptic drug treatment.

Twenty minutes of EEG recordings were obtained in a quiet room using the Medicid-03M system. The amplifier's characteristics were: 10 000 dB of gain, low cut filters at 0.05 Hz and high filters at 70 Hz. Nineteen referential leads of the International 10/20 system were recorded using linked earlobes as reference. The impedance was under 5 kΩ in all electrodes. The sampling frequency was 200 Hz. During experimentation, average, current source density (CSD) reference and transversal and longitudinal bipolar montages were used.

All EEG phenomena identified as paroxysmal activity were selected for analysis. The recordings were reviewed by two neurophysiologists (TH and ES-R) and only those EEG segments on which agreement was reached were used for analysis.

Dipole modeling was carried out by means of brain electric source analysis (BESA) software[16]. The dipole location, orientation and amplitude were estimated. A three shell spherical model of the head was used. Goodness of fit was estimated by residual variance (RV), defined as the percentage of the spike variance that could not be explained by the proposed model. The RV was calculated over the peak of the spike. We used the single instantaneous approach in dipole modeling.

VARETA[15] was used for obtaining current sources of paroxysmal activity. This method is a discrete spline distributed solution that imposes different amounts of spatial smoothness for different types of generators selected by a data driven search procedure. The Probabilistic Brain Atlases used in this study were developed at the Montreal Neurological Institute[17]. In order to be able to compare the images of each time point, fixed maximum and minimum values were used. The same segments of EEG used in dipole models were used in VARETA. We calculated solutions every 5 milliseconds in a period of 300 milliseconds which included the entire PSWC. However, the comparison of the source topography provided by BESA and VARETA was made with the solution corresponding to the peak of the spikes.

RESULTS

In all EEG records, a generalized paroxysmal activity of PSWC was identified, with a duration of 2–6 seconds. The frequency of the PSWC was of 3.5–4 Hz. At the beginning of the paroxysmal activity the complexes were best observed in F3 or F4, and in the interhemispheric part, in the Fz electrode. All maps showed maximum electronegativity in the frontal region. An asymmetrical beginning of paroxysmal activity was detected in all five patients for all montages (Fig. 1).

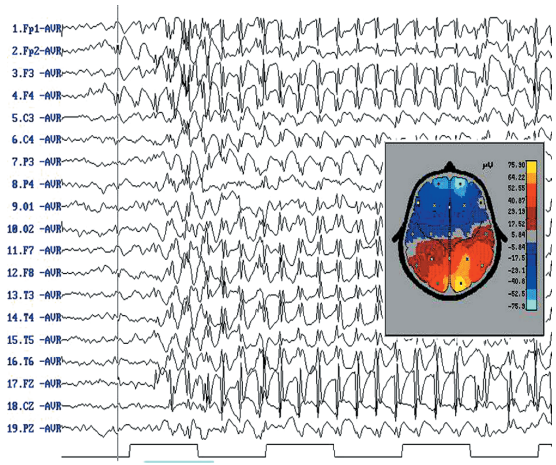

Fig. 1: EEG of a patient with JME showing paroxysmal activity of PSWC. A maximum electronegative region is observed in frontal electrodes. In the EEG recording it is possible to observe an asymmetrical beginning.

A model with two dipoles was necessary for all five patients, the mean RV was of 3.55 ± 0.75 with a range of 2.71–4.28. In all patients, frontal, parietal and temporal lobe dipole localization was found. Frontal dipoles were always those that could best explain the model variance in each patient. The parietal and temporal dipole localization always corresponded to secondary dipoles. When the 10 dipoles of five patients were superimposed, seven dipoles were localized in the frontal lobe, two in parietal and one in temporal lobe. Frontal dipoles were clustered in two sites; three in the frontal medial gyrus and four in the fronto-orbital region, very close to the midline in all cases (Fig. 2). The vertical orientation was present in five out of seven frontal dipoles. The parietal and temporal dipoles had low magnitudes and were localized far away from the midline.

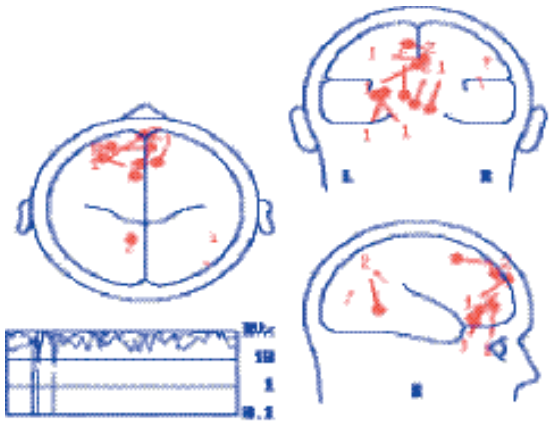

Fig. 2: Results of dipole modeling of five patients, with two dipoles each one. Frontal, parietal and temporal lobe dipole localization is shown. Frontal lobe clustering was observed in two regions: frontal medial gyrus and fronto-orbital region. All dipoles outside the frontal lobe were secondary dipoles.

A bilateral current source in the medial frontal gyrus was observed in all patients when the spikes were analyzed with brain distributed analysis. Only in one patient was a parietal source found in addition to the frontal localization, similarly as with dipole modeling. Symmetrical and bilateral distribution was observed in spite of lateralized EEG recordings. In four patients, the sources were in the anterior part of the medial frontal gyrus, and in the remaining one, the sources were located in the posterior part of the same gyrus (Fig. 3).

When the slow wave of PSWC was analyzed, multiple sources in different parts of the cortical brain were detected (Fig. 4). Sources in a large zone of the medial frontal gyrus, para-central lobule, orbital gyrus and far regions, including the temporal lobe were observed in all patients.

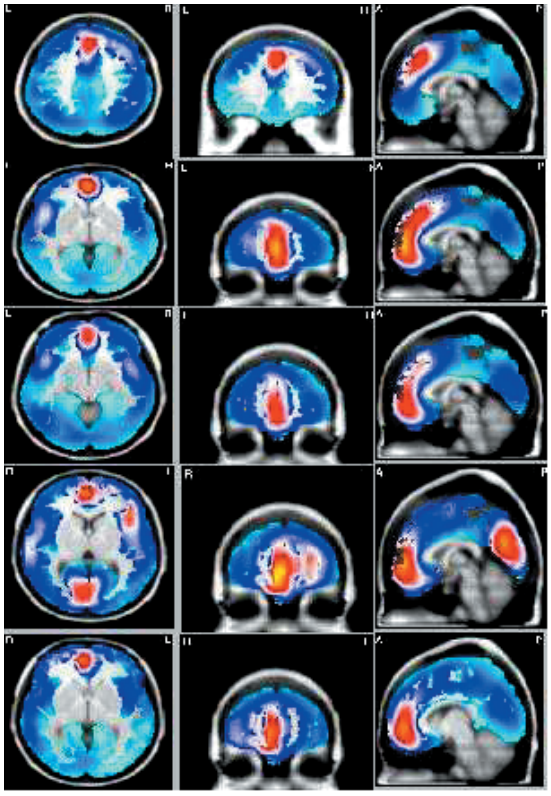

Fig. 3: Polyspike component of PSWC analyzed with the brain distributed source method (VARETA). Axial, coronal and sagital slices of the five patients are shown. A current source in the pre-frontal region was observed in all patients, specifically in the frontal medial gyrus.

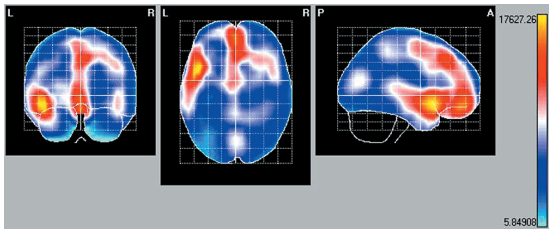

Fig. 4: Brain distributed source analysis with VARETA of the slow component of PSWC is shown. Axial, coronal and sagittal slices in maximum-intensity projections were used. The sources of slow wave were localized in different regions of the cortical brain. These included medial frontal gyrus, para-central lobule, orbital gyrus and temporal regions.

DISCUSSION

JME is a type of IGE. Frontal maximal activity in frontal surface electrodes has been shown in previous studies of patients with absence seizures and generalized SWC[4,6]. Only patients with JME and PSWC were included in our study, their EEG recordings showed a characteristic frontal maximum voltage localized in Fz, F3 and F4 electrodes, similar to the one found in patients with absence seizures.

This confirmed the concept that IGE is a group with similar EEG characteristics[18].

The main advantage of dipole modeling and brain distributed source analysis is their capacity for a 3D localization. With these methods, we were able to detect pre-frontal sources of spikes of PSWC in patients with JME. There is agreement in the localization of sources with both methods, especially when the main dipole is compared with the source within brain distributed source analysis. In patients with absences and SWC, pre-frontal, orbito-frontal, and fronto-polar sources have been detected with dipole modeling. Rodin[8] using a source analysis with dipole modeling, found a source wave in frontal, fronto-polar and orbito-frontal areas.

On the other side, in neuropathological, MRI, PET and neuropsychological studies in JME, alterations in pre-frontal regions have been detected, but there are no available studies with source localization methods. Our results show, especially the ones obtained with brain distributed source methods, that the sources of PSWC are located in pre-frontal areas and spare polar regions and cingulate gyrus. Structural cortical abnormalities have been demonstrated in pre-frontal cortical areas in patients with JME. In neuropathological studies, Meencke and Janz[10] found microdysgenesis and increased neuronal density in frontal cortex. However, neuropathological studies in this type of patient have been very rare. *In vivo* studies with different neuroimage approaches in this direction are promissory. Woermann[12] with voxel-based statistical parametric mapping analysis reported an increase in cortical gray matter in mesial frontal lobe of 20 patients with JME. Studies with MRS of patients with JME showed a decrease in N-acetyl aspartate (NAA) in the pre-frontal region[13]. NAA is especially located in neurons, and a reduction in the NAA signal has been interpreted as indicating loss or dysfunction of neurons. Therefore, the electrophysiological result could have an anatomical background.

There is enough evidence of pre-frontal alterations in JME; but what is the functional repercussion in these patients? It has been proposed that spikes of SWC and PSWC signal a short excitation period in neurons[19], and our results suggest that pre-frontal medial regions contain hyperexcitable neurons. This cortical hyperexcitability has been detected with evoked motor potentials by transcranial magnetic stimulation, where a decreased stimulation threshold has been found when the magnetic stimulation is synchronized with the spikes. In opposition, when the stimuli are delivered during the slow wave component, the stimulation threshold is increased, in agreement with the experimental results reporting a wave component corresponding to long periods of inhibition[20]. Our results show that slow wave current sources are sparse in many cortical regions reflecting a more diffuse inhibitory process.

Very interesting results have been reported in relation to the effects that SWC and PSWC have in normal neuronal network functioning, such as disruption of cognitive processes in the pre-frontal area, mainly affecting working memory (WM). Baddeley[21] defined WM as a system in charge of the temporary maintenance and manipulation of information necessary for the performance of complex cognitive activities. Previous studies have shown that pre-frontal cortex is involved in human working memory[22]. Patients with JME have shown a regional decrease in relative glucose uptake at rest in an 18FDG-PET study, and no increase in activity in dorso-lateral pre-frontal cortex during a visual working memory task[11]. Although, epileptic syndromes in IGE have some similarities, the affectation of working memory could be different. It has been proposed that absences are the suspension of WM, a function of frontal lobe, with immediate restoration of consciousness when absences finish[23]. In opposition, in JME the absences are less frequent and when patients have myoclonic jerks the consciousness is spared, although more accurate studies have reported an impairment of visual WM[24]. Otherwise, the presence of myoclonic jerks could be due to the propagation of ictal activity to pre-motor areas.

CONCLUSION

Our results show evidence of pre-frontal medial current sources corresponding to spike components of PSWC and many diffuse sources in cortical regions corresponding to wave components of PSWC in patients with JME. These results are in agreement with previous studies of anatomical and functional impairment in pre-frontal regions in this type of patient.

ACKNOWLEDGEMENTS

The project was partially supported by CONACyT grant 30931-M and PAPITT grant IN205100. We are grateful to Marcela Sánchez for her revision of English version.

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