Ogniskowy początek wyładowań w napadach nieświadomości w obrazowaniu czasowo-przestrzennym MEG

Focal onset in absence seizures: evidence from MEG spatio-temporal dynamics

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STRESZCZENIE

Napady nieświadomości w przyjętej nomenklaturze określane są jako pierwotnie uogólnione z obustronnym, synchronicznym początkiem wyładowań. Jednak w literaturze naukowej pojawiają się doniesienia o ogniskowym początku napadów nieświadomości z nagłym uogólnieniem w postaci zespołów iglica-fala wolna. Większość z tych publikacji dotyczy badań z użyciem EEG, z nielicznym użyciem obrazowania funkcjonalnego. Jako pierwsi przedstawiamy w poniższej pracy przypadek pacjenta (wiek 9 lat) z typowymi napadami świadomości z ogniskowym początkiem wyładowań w badaniu MEG. Monitorowanie video-EEG potwierdziło diagnozę typowych napadów nieświadomości z licznymi epizodami obustronnych, synchronicznych uogólnionych wyładowań w postaci zespołów iglica fala wolna 3–3,5 Hz. Badania MEG zostały wykonane z jednoczesnym monitorowaniem zapisu EEG. Analiza czasowo-przestrzenna wyładowań napadowych wykazała ogniskowy początek wyładowań z okolicy czołowej lewej półkuli z następującym objęciem wyładowaniem wzgórze, niewidoczne w zapisie EEG, sugerujące ognisko czołowe lewej półkuli z nagłą propagacją poprzez drogę korowo-wzgórzową. W przypadkach z częstymi napadami świadomości ogniskowy charakter wyładowań może zostać określony z użyciem nieinwazyjnej techniki obrazowania MEG.

Słowa kluczowe: padaczka, napady nieświadomości, magnetoencefalografia

ABSTRACT

Absence seizures are commonly described as primarily generalized seizures with a bilateral onset. Seldom, but ceaseless, publications have reported a focal origin in absence seizures with rapid generalization of spike-wave discharges. Most of these reports are EEG studies; few functional neuroimaging techniques have addressed the matter. We report a patient (aged 9) with typical absence seizures demonstrated to be of focal origin by Magnetoencephalography (MEG). Video-EEG monitoring confirmed diagnosis from numerous episodes of typical absence seizures associated with generalized synchronous 3 to 3.5 Hz spike-and-wave discharges. MEG was performed with simultaneous scalp EEG recording. Spatiotemporal analysis of ictal MEG spike-wave discharges demonstrated focal left frontal seizure onset and anterior thalamic involvement, not seen in EEG, suggesting a left frontal seizure origin, with generalization through rapid thalamocortical propagation. In patients with frequent absence seizure episodes the origin of seizures may be demonstrated and differentiated noninvasively with functional imaging using MEG.

Key words: epilepsy, absence seizure, magnetoencephalography

INTRODUCTION

Magnetoencephalography (MEG) is a non-invasive procedure which directly record neurophysiological processes in the brain. MEG detects the magnetic fields generated by spontaneous or evoked brain activity. Its high temporal resolution permits assessment of fractions of milliseconds. Since the influence of skull, scalp, cerebrospinal fluid and brain tissue on magnetic fields is weak, MEG enables an almost undistorted view of the brain activity. Therefore, MEG source analysis after being overlaid onto patient's individual MRI yields a realistic image of the location of underlying tissue causing neurophysiological activity. MEG has become recently an indispensable diagnostic technology and aids in treatment decisions of epileptic patients. In this context, absence seizures are commonly described as primarily generalized seizures, featuring a sudden bilateral

synchronous spike and wave burst on the electroencephalography (EEG). Some studies have reported a focal origin for absence seizures giving evidence that although spike-wave discharges develop rapidly they may not be diffuse [1–6]. In these instances generalization may be due to rapid spread and secondary bilateral synchrony. An open question is whether specific, rather than diffuse, regions of cerebral cortex are activated at the onset and during the propagation of absence seizure. Clear documentation of the focal origin has depended on invasive cortical and thalamic recordings in humans. The understanding of brain processes during human absence seizures requires detailed information on activation timing within and between different brain sites. Such data can be obtained by magnetoencephalography (MEG) that tracks activation sequences with a millisecond

temporal accuracy. We report one patient with typical clinical absence seizures demonstrated to be of focal origin by MEG.

CASE REPORT

We describe the case of a 7-year-old, right-handed girl with typical absence generalized seizures starting at 6 years of age. The patient's first seizure, while watching T.V, was characterized by bilateral eyelids flickering and lip smacking with duration of 2 minutes. This first clonic seizure was later followed by "absence seizures".

Initial diagnosis of typical childhood absence epilepsy was based on the International League Against Epilepsy (ILAE) standards [7]. The patient was admitted into the epilepsy unit for long-term video-EEG monitoring. During her 2-day stay she had more than 15 seizures characterized by sudden, subtle change of facial expression, interruption of ongoing activities and impairment of consciousness followed by sudden eye opening and eyelid flickers. Total duration of these episodes was between 15 and 30 seconds.

The 19 channels EEG recording based on 10-20 system with averaged reference showed generalized, high voltage synchronous and symmetric regular 3 Hz spike-and wave discharges lasting 15–20 s (Figure 1) with abrupt onset and offset. Normal background activity was resumed in seconds. Episodes were highly reproducible under hyperventilation conditions.

These absence seizures were occurring several times per day. Past medical history was negative except for family history of night-time urinary incontinence. Intellectual development, neurological examination, and structural imaging findings were all normal. Patient was put on Valproate (VPA) and has been seizure free for 6 months so far.

MEG CONTRIBUTION

Multichannel magnetoencephalography recording and source localization was obtained with concomitant EEG. A whole-head biomagnetometer (4D Neuroimaging Magnes 2500 WH, San Diego, CA) was used for MEG recordings. EEG was simultaneously obtained by employing scalp electrodes according to the international 10-20 system. The sampling rate was 678 Hz, MEG data were digitally filtered at a band pass width of 1 to 70 Hz in data analysis. Two 10-minute MEG recording sessions were carried out. The data were visually examined and segments of interest containing epileptiform activity were selected for dipole source localization. Using the single Equivalent Current Dipole (ECD) model and the 4D Neuroimaging software for MEG source calculations dipole localizations were obtained. Best fit dipoles according to a correlation coefficient of .90 or greater and a confidence volume under 5 cm³ were selected. Further dipole selection criteria threshold pinpointed dipoles to .97 correlation coefficient or above and 1 cm³ confidence volume or under for 90% of the dipoles. MEG locations were obtained and fused onto the individual magnetic resonance images (MRI) based on 3 fiducial points (left and right tragus and nasion) and the patient's scalp digitization. Digitization was accomplished prior to MEG acquisition using a

Polhemus Colchester, VT wand. 4D software was used for the transformation and overlaying of the MEG dipoles onto the MRI.

Four spontaneous spike and wave generalization episodes with simultaneous absence-like clinical manifestations, with the duration range between 9 and 25 seconds, were registered over a total period of 20 minutes MEG-EEG combined recording.

The generalization episodes consisted of synchronous bilateral 3 Hz spike and wave epileptiform activity registered by MEG channels with no clear morphological correlation on the simultaneous EEG tracing (Figure 2). First spike and wave bursts were particularly recorded by left and anterior MEG channels. Onset of seizures as determined by ECD calculations and MEG localizations was pinpointed to the left frontal inferior region (Figures 2 and 3A). Dipoles localized thus focally were calculated from the first consecutive spike and wave events, seen mainly on the left MEG channels (Figures 2 and 3B). Within 128 ms, left thalamus was engaged (Figures 2 and 3C), coinciding with the slope of the slow wave of the second spike-wave event registered by MEG. From then on, left frontal orbicular cortex and thalamus were drawn in cycles (Figures 2, 3D and 3E). Only 424 ms after seizure onset was the contralateral frontal orbicular cortex involved, coinciding with the clear onset of EEG bilateral synchronized spike-wave discharges and with the clear loss of focality in the MEG (Figures 2 and 3F).

DISCUSSION

The case presented here is the first to illustrate a focal frontal onset for Childhood Absence Seizures with secondarily bilateral synchronization, in which the thalamus is actively involved as seen by a non-invasive electromagnetic functional neuroimaging technique.

Focal onset

The girl we present fulfils the criteria for a childhood absence epilepsy diagnosis according to semeiological and neurophysiological criteria proposed by the ILAE [7] i.e. several daily clinical absences at 6–7 years of age combined with symmetric, bilateral, widespread spike-wave complexes at 3 Hz in the EEG. More so, her response to valproic acid is satisfactory, which argues for a typical case of absence seizure. However abrupt and synchronized the onsets of her seizures appear to be on the EEG, the MEG left channels consistently show epileptiform activity before the rest of the whole-head MEG channels and before the EEG tracings. Moreover, MEG allows the tracking of the neural generators responsible for each section of the spike or spike-wave event (Figure 3). Thus, despite the typical clinical scenario of childhood absence seizures, MEG very clearly shows a left frontal onset of the seizures with a quick secondary generalization probably triggered by the thalamic counterpart involved in the alternate frontal-thalamic lead found in the first 150 ms of the seizure.

The "generalized" nature of absence seizures appears to be more a convention of interpretation rather than a description of the EEG evidence. The possibility that

Fig. 1. Spontaneous 3 Hz spike and wave discharge showing bilateral features during long term monitorization. Seizure resolves just about 24 s after onset. *Uogólnione wyładowania w postaci zespołów iglica-fala wolna o częstotliwości 3Hz podczas długotrwałego monitorowania EEG. Wyładowania napadowe ustępują po 24 sekundach.*

Fig. 2. Simultaneous MEG and scalp EEG tracings during an ictal 3 Hz discharge. Only left, anterior and right MEG channels are represented. Labels A to F correspond to the MEG events for which localizations and contour maps are depicted in Figure 3. *Jednoczesny zapis MEG i EEG z rejestracją wyładowań w postaci zespołów iglica-fala wolna o częstotliwości 3Hz. Prezentowane są kanały MEG z obszarów przednich lewej i prawej półkuli. Mapy rozkładu pola magnetycznego oraz lokalizacje propagacji wyładowań dla momentów czasowych oznaczonych od A do F zostały przedstawione na Rycinie 3. Początek wyładowań widoczny w odprowadzeniach MEG przednich czołowych lewej półkuli, bez wyraźnego odniesienia w kanałach EEG. Spike and wave events are first detected by left frontal MEG channels with no clear correspondence on the simultaneous EEG*

Fig. 3. MEG localizations and corresponding isocontour maps for the events labelled A to F in Figure 2. Only representative dipoles that illustrate initial left frontal onset have been depicted, thalamus involvement and final right frontal activation before generalization. *Lokalizacje MEG oraz odpowiadające mapy rozkładu pola magnetycznego dla wyładowań oznaczonych od A do F na Rycinie 2. Przedstawiono reprezentacyjne dipole ukazujące początek wyładowań w regionie czołowym lewej półkuli, propagację czynności napadowej do wzgórza, obszaru czołowego prawej półkuli i uogólnienie wyładowań.*

absence seizures may be of frontal origin was already suggested by Kubota et al. (1997) [1] in a study of frontal lobe epilepsy with secondarily generalized 3 Hz spike-waves. The involvement of the neocortex in the initiation and synchronization of the generalized spike and wave discharges is supported by the finding that, after thalamectomy, the initiation of spike-wave complexes persists, although the thalamus seems to be required for rhythm maintenance [8]. Absence seizures were also reported to resolve in association with the resection of a frontal structural lesion [9]. Some absence seizures have been documented to originate in the frontal lobe, particularly in the mesial frontal region [2]. Detailed examination of conventional 10-20 EEG and even high-density array EEG patterns in spike-wave discharges has shown that, although they develop rapidly and may be difficult to lateralize, the spike-wave patterns are not diffuse but involve selective cortical networks predominant over the frontal cortex [4, 5, 10, 11].

In recent years, the advent of high-resolution structural and functional neuroimaging has disrupted the, until-then, harmonious cohabitation of the dichotic classification of epilepsies as “focal” or “generalized”. The new imaging techniques have revealed some focal brain abnormalities in patients with well documented idiopathic generalized epilepsy. These data have led to the hypothesis that, at

least, in some of the generalized epilepsies (i.e. absence) focal brain abnormalities may be involved in the seizure disorder. Millan et al. [3] reported an 8-year-old girl with a congenital left hemiparesis and atypical absence seizures associated with generalized synchronous and symmetrical 3 to 3.5 Hz spike-and-wave discharges by electroencephalography (EEG). Ictal positron emission tomography (PET) demonstrated focal right frontal hypermetabolism, suggesting a right frontal seizure origin. fMRI studies during absence seizures in human subjects showed major changes in thalamus (hyperactivation) and cortical areas with a complex set of hyperactivations in some parts of the frontal lobe and hypoactivations in other areas [12–16]. In addition, the fMRI findings in a marmoset model of absence-status epilepticus showed region-specific activation within the thalamus and cortex [17].

Cortico-thalamo-cortico circuit

In our patient MEG very clearly identifies a left frontal onset of the absence seizure with a quick secondary generalization, probably triggered by the thalamic counterpart involved in the alternate frontal-thalamic lead. It has been long demonstrated that the thalamocortical projections arising from the intralaminar nuclei project diffusely but particularly onto the frontal and parietal areas [18]. Further works on thalamocortical circuitry allowed Jasper and Droogleever

[19] to first reproduce bilateral 3Hz spike-wave discharges with arrest response in cats by stimulating the thalamic intralaminar nuclei. These very important investigations provided evidence of the existence of a subcortical (central) pacemaker. However, some years later evidence was obtained for a cortex leading role as has been addressed above. Supporters of this cortical theory believed in the thalamus as a secondary carrier and the frontal cortex area as the focal discharge area.

In the Meeren et al's works [20, 21] a bridge is tended between the focal (cortical) and thalamic (subcortical or generalized) seizures. Neither the thalamus alone nor the cortex alone suffices for a spike-wave discharge pattern to occur. In other words, it is mandatory that both a healthy reticular thalamic nucleus and a functionally intact cortex exist for the genesis of a spike-wave pattern. More so, it has been proved that bilateral thalamectomy does not stop the instigation of generalized spike-wave discharges, although the thalamus is required to sustain rhythmicity once the discharges are established [8, 22–24].

Our results describe a dynamical interaction between frontal cortex and thalamus of the left hemisphere for the first 424 ms, since when a clear bilateral pattern develops. Likewise, Meeren and colleagues [20] found a cortical focus as the leading structure in the constant bidirectional coupling with the thalamus during the first 500 ms of the

seizure, result that quite matches our findings. Recently, Stefan et al described seven patients with idiopathic generalized epilepsies using MEG and EEG. Source analysis showed most often involvement of frontal, perinsular and subcortical/thalamic areas. In all patients a unilateral frontal accentuation of activity could be observed. Patients with juvenile myoclonic and myoclonic absence epilepsy presented with localizations mainly in the central and premotor regions versus prefrontal accentuation in the other absence patients.

Still, the ECD is a low dimensional parametric model unable to represent multifocal sources. As the ECD dipole modelling method does not cover for simultaneous source generators we were not able to model a dipole on the right frontal region, as was more than once suggested by the contour maps within the first 400 ms from seizure onset. Nevertheless, the focal left frontal onset was quite obvious for the first 140 ms and ECD modelling was successful at pinpointing this origin.

The identification of a focal seizure origin plays important role in surgical treatment of intractable epilepsy. To our knowledge, our report is the first to use magnetoencephalography imaging to demonstrate a focal frontal onset for Childhood Absence Seizures with secondarily bilateral synchronization, in which the thalamus is actively involved.

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