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Magnetoencephalographic Abnormalities in Creutzfeldt-Jakob Disease: A Case Report

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Key Words

Creutzfeldt-Jakob disease · Prion disease · Transmissible spongiform encephalopathy · Magnetoencephalography

Abstract

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease with no effective therapy available. We recorded spontaneous magnetoencephalography and auditory evoked fields (AEFs) from a male patient with a rapidly progressive memory disorder, ataxia and myoclonus. Post-mortem examination confirmed sporadic CJD. Sources of the abnormal slow wave activity were localized with a beamformer software. Sources of sharp transients and AEFs were modeled with equivalent current dipoles. The estimated sources of spontaneous activity abnormalities were more dominant in the left hemisphere, in line with left-dominant abnormalities in diffusion-weighted MRI. Sources of AEFs were found in both temporal lobes. Magnetoencephalography measurements on CJD patients are feasible, and provide efficient means for localizing abnormal cortical activity in CJD.

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare progressive neurodegenerative disease affecting one person per million per year. CJD belongs to the group of transmissible spongiform encephalopathies also known as prion diseases. Prion diseases are caused by abnormal metabolism and conformation of the cellular prion protein, the primary function of which is ambiguous. CJD is characterized by rapidly progressive dementia, ataxia, myoclonus and by pyramidal and extrapyramidal motor symptoms. The disease is fatal and no effective treatment exists [1].

Definite diagnosis of CJD requires histopathological examination of the brain tissue usually obtained post-mortem. However, clinical symptoms, typical EEG-findings,

detection of 14-3-3 protein in the cerebrospinal fluid (CSF) and abnormal cortical and subcortical signal in diffusion-weighted MRI allow clinical diagnosis of CJD [1].

Typical EEG in CJD displays frontal intermittent rhythmical delta activity (FIRDA) and periodic sharp wave complexes (PSWC). FIRDA is usually detected already in the early stages of the disease whereas PSWCs suggest a more progressed disease [2]. The appearance of motor symptoms, particularly myoclonus, usually correlates with the appearance of PSWCs in EEG [3, 4]. In two CJD patients, the source locations of PSWCs correlated with the extent of visible lesions in diffusion-weighted MRI [5]. Cortical, but not striatal MRI lesions are associated with the PSWCs [6].

No previous reports exist on magnetoencephalography (MEG) in CJD. Here we describe the MEG findings of a patient with histopathologically confirmed sporadic CJD.

Methods

Patient

A 33-year-old man developed a progressive memory dysfunction and impaired fine motor skills during a one-year period. Regular use of alcohol was reported, but otherwise the patient had had no major health problems.

In the initial clinical examination, the patient had significant amnesia and ataxia. Head MRI was considered to be normal. Electromyography showed signs of peripheral neuropathy. The symptoms were considered to be alcohol-related, thiamine substitution was started and the patient was referred to the district hospital for rehabilitation.

Due to progressive cognitive decline, ataxia, vertical gaze palsy and gait abnormality, the patient was again referred to the University Hospital. Abnormal diffusion-weighted signals in the basal ganglia, thalami and frontotemporal cortex, more prominent in the left hemisphere, were detected in the control MRI (fig. 1). In retrospective analysis, the initial MRI also showed bilateral signal abnormalities in the basal ganglia in T2-weighted and FLAIR sequences. Increased tau protein and 14-3-3 protein in CSF supported the diagnosis of CJD. In an EEG recorded on the same day, but not simultaneously with MEG, slow wave activity was more pronounced in the left hemisphere, but no sharp wave complexes were detected. Occasional myoclonus, triggered by sudden loud noises, was observed one week before the MEG recording. Spontaneous myoclonus of the limbs developed after the MEG.

The patient died from a probable pulmonary embolism six days after the MEG recording, before planned follow-up MEG. Neuropathological examination confirmed sporadic CJD.

Magnetoencephalography

The MEG was recorded in a magnetically shielded room with a 306-sensor Elekta whole-head MEG system (Elekta Oy, Helsinki, Finland). The patient was in a supine position. MEG signals were sampled at 600 Hz and band-pass filtered at 0.1–200 Hz. Vertical and horizontal electrooculography (EOG) were recorded. Head position was registered continuously during the whole measurement by using four HPI coils. Spontaneous brain activity was registered for 16 min. Auditory evoked fields (AEFs) were elicited by 1-kHz, 50-ms tones (1.5–2.5 s random ISI), delivered via a panel loudspeaker attached to the wall of the shielded room. The signals were post-processed with the tSSS (Elekta MaxFilter™; Elekta Oy) artifact rejection software [7].

The spontaneous MEG data were inspected visually and sharp transients were selected for equivalent current dipole (ECD) analysis. Sources of slow oscillations (0.1–8 Hz) were localized using an experimental beamformer package (Elekta Oy). The beamformer analysis was done on the original data. The noise power, required for covariance statistics, was calculated from high-pass filtered data thus

labeling oscillations that had frequency greater than 8 Hz as noise. A ten-second segment with the clearest FIRDA-like activity was selected for the analysis.

The AEFs were analyzed with ECDs. Epochs contaminated by eye movements and blinks in EOG were discarded from the averages; 150 epochs were included in the averaged AEFs. A 600-ms analysis time included a 100-ms prestimulus baseline. A low-pass filter at 40 Hz was applied to averaged responses. All source localization was done using an individual single-layer boundary element method model obtained using the FreeSurfer and the MNE-suite software (Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Mass., USA).

Results

MEG showed abnormal delta and low theta band activity in both hemispheres. FIRDA-like intermittent runs of high amplitude slow wave activity were observed as well. No clear PSWCs were present. However, frequent sharp transients were observed. All of these signals were most pronounced in the left hemisphere ([fig. 2a](#)).

The sources of low frequency oscillations were scattered over a relatively large area, but the maximum activity in the beamformer results occurred in the left frontotemporal area, in line with the visual impression of the MEG signals ([fig. 2b](#)).

Sharp transient activity produced dipolar field patterns that could readily be localized with ECDs. The sources varied and were spread around the whole brain. However, the clearest cluster of ECD sources was found in the left frontotemporal region ([fig. 2c](#)).

Auditory stimulation produced clearly identifiable P50m, N100m and P200m deflections in both hemispheres. The P50m and P200m had a somewhat larger amplitude in the left than in the right hemisphere. ECD sources were approximately in the normal anatomical locations in close vicinity of the Sylvian fissure ([fig. 3](#)). The ratio of the P200m/N100m source amplitudes was 1.7 in the left and 0.6 in the right hemisphere.

Discussion

This is the first MEG recording in a patient with neuropathologically verified sporadic CJD. Our patient was quite young and had thalamic hyperintensity in MRI raising suspicion of variant CJD. However, neuropathological examination verified sporadic CJD. In addition, the patient had no signs of depression and apathy at the onset of symptoms that are typical for variant CJD.

The clinical diagnosis of CJD is challenging as the symptoms, the results from imaging studies and the CSF findings are somewhat nonspecific. The typical PSWCs in EEG are only present in some patients and usually signify the terminal state of CJD [2]. Further, in some cases, the typical EEG findings disappear with disease progression. The PSWC were not observed in the EEG of our patient.

MEG revealed abnormal slow wave activity that was more prominent in the more damaged left hemisphere, as shown by MRI. The sharp transients were clearly multifocal, but their sources were also concentrated in the left hemisphere. Thus, two different source localization methods (ECDs and beamformer) produced results that were consistent with the left-dominant cortical and subcortical abnormalities in the diffusion-weighted MRI.

Previous EEG studies have shown either normal [9] or deteriorated [10] brainstem auditory evoked potentials in CJD. Clear cortical AEFs were evident in our patient. The sources of AEF P50m and P200m deflections were stronger in the left, more damaged hemisphere. In healthy subjects, the ratio of P200m/N100m deflections is about 0.3 [8]. In our patient, the ratio of P200m/N100m source strengths was 1.7 in the left and 0.6 in the right hemisphere, suggesting abnormally dominant P200m deflections particularly in the more affected left hemisphere. Thus, our results suggest that cortical auditory processing is not diminished in CJD. In contrast, there appears to be excitation or disinhibition of the P50m and P200m generators.

Conclusion

Our study shows that it is possible to obtain good quality MEG recordings from a patient with CJD, and model the sources of the abnormal signals. The distribution of the sources of the abnormal waveforms suggest an extensive disorder of cortical function in CJD. Disinhibition or abnormal excitation, as suggested by the AEFs, may be a factor contributing to myoclonia triggered by sudden loud noises in CJD. Obviously, a single case study is inadequate to determine whether MEG source modeling offers any benefit over the standard EEG as a diagnostic tool. To answer this question, further studies with follow-up are needed.

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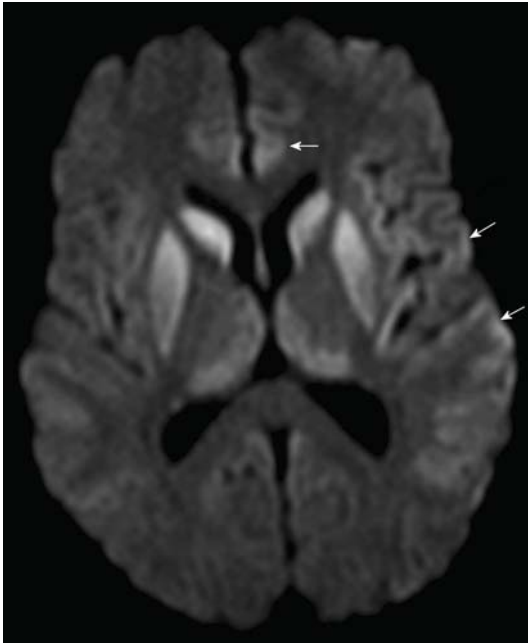


Fig. 1. Diffusion-weighted MRI revealed an abnormal hyperintensity in the thalami and striata bilaterally. Cortical involvement was mainly seen in the left frontotemporal and cingular cortex (arrows).



Fig. 2. **a** A ten-second segment of MEG signal from selected temporal sensors over both hemispheres. A FIRDA run starts during the last four seconds of the recording. A sharp transient is marked by the black rectangle. **b** Beamformer source estimation. The maximal activity is localized in the left frontotemporal area. **c** ECD locations of sharp transients are also most concentrated on the left frontotemporal area.

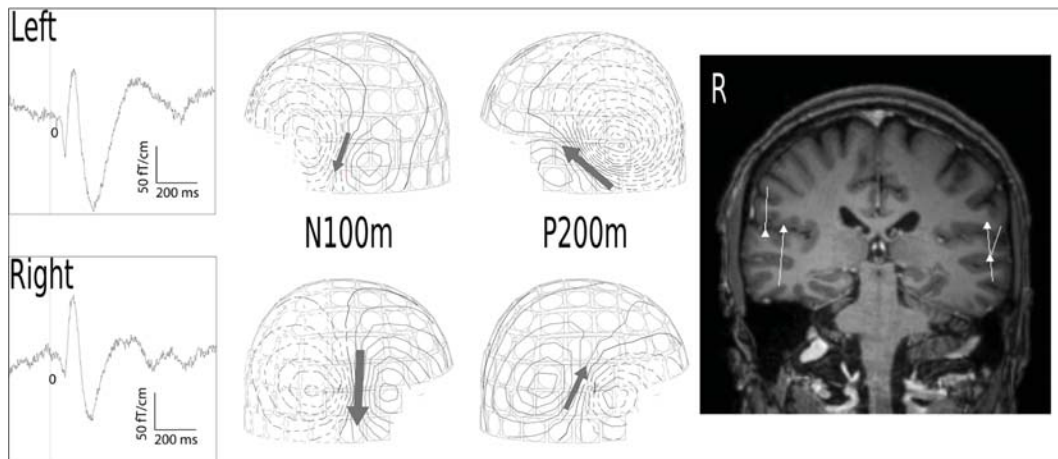


Fig. 3. AEFs from both hemispheres. Maximum responses (left); field patterns and ECDs (center); sources plotted on the head MRI (right).

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