Multimodal Imaging Finding In Unverricht-Lundborg Disease

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Citation

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Abstract

Purpose: To investigate the pathophysiology of Unverricht-Lundborg disease (ULD) is using magnetoencephalography (MEG) and positron emission tomography using 18-fluoro-2-deoxyglucose (FDG-PET) in a ULD patient.

Methods: MEG was recorded using a 204-channel whole-head MEG system, and the cortical activities preceding myoclonus of the patient were averaged. Equivalent current dipoles (ECDs) were calculated for the averaged spike. FDG-PET was performed in the interictal state.

Results: The result of MEG demonstrated an electromagnetic cortical activity in the left centroparietal area, and the peak of this activity preceded the onset of myoclonic discharge on the electromyogram by 16.0 ms. ECD calculated at the peak was located in the left post central area. FDG-PET images showed regional hypometabolism in the left part of the pons.

Conclusions: Functional abnormalities in the sensorimotor cortex and the brainstem coexist in this patient with ULD. Both dysfunctions were considered to be related to the pathogenesis of ULD.

INTRODUCTION

Unverricht-Lundborg disease (ULD) is a subtype of progressive myoclonus epilepsy (PME), caused by mutations in the cystatin B gene [1]. Typical clinical symptoms seen in patients with ULD are myoclonus, tonic-clonic epileptic seizures, and progressive neurologic deterioration [2]. A reduced level of the cystatin B gene product seems to be the primary mechanism in this disease pathology; however, any more detailed pathogenetic mechanisms are as yet unknown. In the present study, we performed magnetoencephalography (MEG) and positron emission tomography with 18-fluoro-2-deoxyglucose (FDG-PET) in a patient with ULD and investigated the dysfunction in specific parts of the brain.

CASE REPORT

The patient was 37-year-old male. He was born after an uncomplicated pregnancy, and his psychomotor development during early childhood was normal. There was no family history of epilepsy. At the age of 13 years, he experienced occasional, unexpected, sudden myoclonic jerks. These myoclonic seizures occurred daily, and generalized tonic-clonic seizures also occurred once or twice per month. He was treated with carbamazepine, phenobarbital, clonazepam and phenytoin, but his seizures were only partially controlled. He entered high school at the age of 15 years, but he experienced learning difficulties at this time.

Neurological examination showed that his gait was slightly ataxic. On the Wechsler Adult Intelligence Scale-Revised (WAIS-R), he scored an IQ of 67 (verbal IQ 73; performance IQ 68). On the interictal EEG, slow background activity was observed. Brain MRI scans of the patient showed mild cerebral atrophy, but no structural lesions were observed. Genetic testing of the patient showed an expansion of the dodecamer repeat in the promoter region of the cystatin B gene. The administration of valproate reduced the frequency of his seizures to a weekly occurrence.

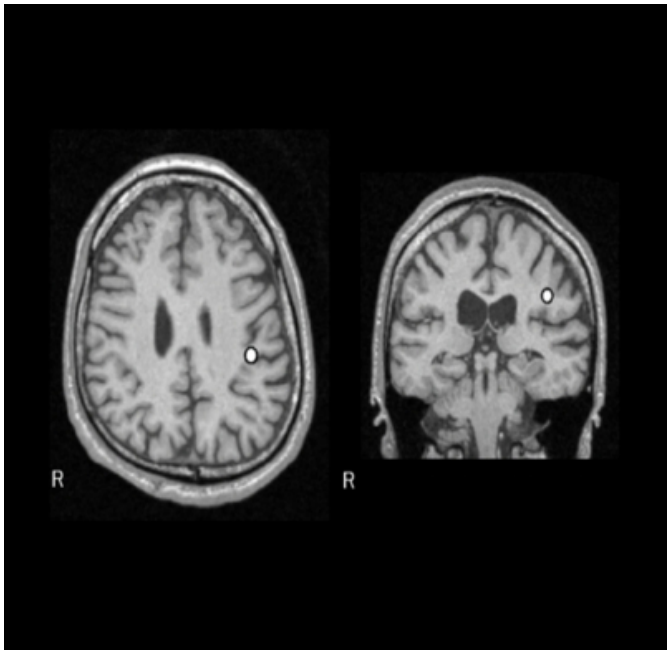
MEG was recorded with a 204-channel whole-head MEG system (Neuromag, Helsinki, Finland) in a magnetically shielded chamber. The sampling rate was 600Hz and MEG data were filtered digitally at a bandpass width of 0.5 to 30 Hz in data analysis. Surface electromyographic (EMG) records of the right forearm flexor muscles, in which

myoclonic jerks occurred most frequently, were also simultaneously obtained. Jerk-locked back-averaging (JLA) was performed, using EMG signals as a trigger. The MEG signals were averaged with respect to the onset of the EMG discharge caused by the myoclonus, which was determined visually. The analysis time window was 300 msec, covering 200 msec before myoclonus and 100 msec after. In the recording session, 27 responses were obtained for the JLA. Equivalent current dipoles (ECDs) were calculated for the averaged spike preceding the trigger according to a single dipole model. ECDs with a goodness-of-fit value greater than 60 % were considered adequate sources.

The JLA results demonstrated an electromagnetic cortical activity preceding the myoclonus in the centroparietal area contralateral to the trigger muscle. The peak of the cortical activity on MEG preceded the onset of myoclonic discharge on EMG by 16.0 ms. ECD calculated at the peak was located in the left postcentral area of the brain (Fig. 1).

Figure 1

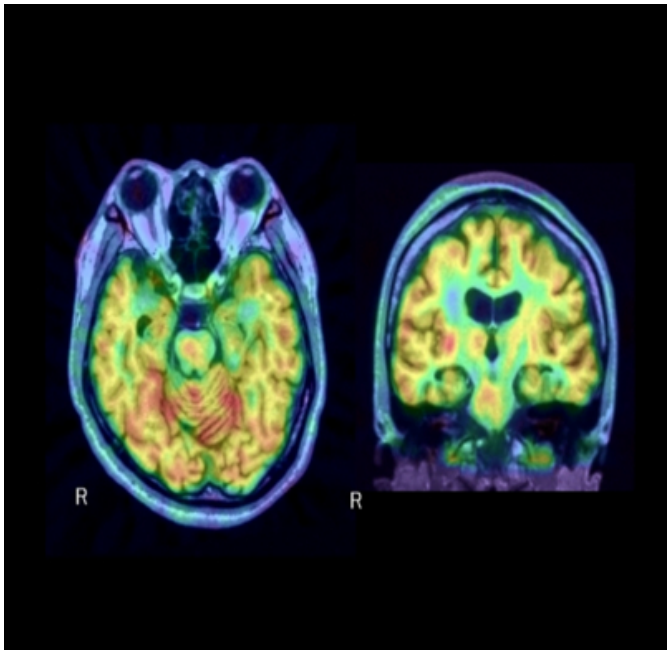
Figure 1: Equivalent current dipole (ECD) calculated for the peak of the averaged pre-myoclonus spike obtained by jerked-locked back-averaging. White circle represents the position of the ECD superimposed on the magnetic resonance images of the patient. The ECD was located in the left centroparietal area.



FDG-PET was performed in the interictal period using a whole-body scanner (ECAT EXACT HR+, Asahi-Siemens, Tokyo, Japan). The patient fasted for at least 5 hours. Images were acquired 60 minutes after injection of 400 MBq FDG using the three-dimensional method. These images were reconstructed by filtered back projection using a ramp filter without attenuation correction. FDG-PET images were co registered to the MRI data set of the patient, using a fully automatic multimodality image registration algorithm [3], and were visually interpreted by at least one experienced nuclear physician and one experienced epileptologist by consensus. The result of FDG-PET showed normal glucose metabolism in the brain cortex. Regional hypometabolism was detected in the left part of the pons (Fig. 2).

Figure 2

Figure 2: Superimposed images of FDG-PET and MRI. FDG-PET shows glucose hypometabolism in the left part of the pons.



DISCUSSION

In this case, there was a mutation in the cystatin B gene. The clinical features, including the age of onset, type of seizures, neurological findings, were typical of ULD. Dementia in the patient was mild, as reported by Lehesjoki and Koskiniemi [2]. Several researchers have reported that the administration of valproate is effective for PME [4], and the seizures of our patient also improved after valproate treatment.

Previous studies using JLA demonstrated that ECDs obtained from the averaged pre-myoclonic spikes were localized in the sensorimotor cortices of patients with PME [5,6,7]. Although the subjects in these studies comprised the patients with various PME subtypes, many of their etiologies were unknown, and they failed to include any ULD patients diagnosed with sufficient specific genetic and clinical features. Our MEG results indicated that sensorimotor

cortices played an important role in generating the ULD myoclonus, as well as in other types of PME.

FDG-PET images in the interictal state demonstrated a hypometabolic region in the pons. No spikes were seen on the interictal EEG of the patient; therefore, we considered that the glucose metabolism during the tracer injection was not affected by epileptic discharges. Mascalchi et al. revealed that atrophic changes in the brainstem, including pons, were detected using MRI in ULD patients [8]. Several researchers have reported that variable neuronal losses in the brainstem were found in patients with ULD who were examined pathologically [9], [10]. The brainstem of our patient was not specifically atrophic as seen by the MRI, although some mild cerebral atrophy was observed. Our FDG-PET results suggested that a functional deficit in the brainstem may have occurred before morphological changes could be observed using the MRI scan.

In PME patients, functional abnormalities in the cerebral cortex and the brainstem have been independently reported. The most interesting finding in our study was the coexistence of these abnormalities in the same patient. Our finding suggested that the decreased inhibitory activity in the sensorimotor cortex, which was suggested by several JLA studies [5],[6],[7], was related to a decreased control by the brainstem via the thalamocortical loop. On the other hand, we could not exclude the possibility of the coexistence of cortical reflex myoclonus and reticular reflex myoclonus, as suggested in a previous report [11].

In conclusion, multimodal imaging tools are highly valuable for investigating the pathophysiology in this case of ULD. Although MEG is useful for localizing the spike sources in the cortex, dysfunctions in deep regions still cannot be detected. The combined use of MEG and PET might allow a better characterization of the pathogenesis of ULD.

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