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Decreased cortical excitability in Unverricht–Lundborg disease in the long-term follow-up: A consecutive SEP study

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HIGHLIGHTS

- Unverricht-Lundborg disease (ULD) patients show self-limited clinical course.
- Giant somatosensory evoked potentials showed disappeared N40 in two ULD patients.
- We showed the clinico-electrophysiological correlates in self-limited ULD patients.

ABSTRACT

Objective: To delineate long-term change of cortical excitability by measuring somatosensory evoked potentials (SEPs) in patients with Unverricht–Lundborg disease (ULD).
Methods: SEPs to median nerve stimulation were repeatedly examined in two genetically proven ULD patients manifesting stable condition over 16 years, namely disabling but non-progressive myoclonus and cessation of generalised tonic–clonic seizures.
Results: In both patients, five sets of early cortical components were identified 16 years ago: two tangential components of N20–P20 and P30–N30 and three radial components of P25, N35 and N40. Cortical SEPs were regarded as abnormally enhanced 'giant' based on the N35 amplitude (>mean + 3 SD of normal controls). The bimodal negative peaks of N35 and N40 showed different spatial distribution: N35 maximum in the central area and N40 in the centro-parietal area. At present, N35 remained giant while N40 disappeared in both patients.
Conclusions: It is possible that currently preserved giant SEPs at least at N35 reflect disabling cortical myoclonus and that disappearance of N40 might reflect a lesser degree of increased cortico-cortical connectivity and/or decreased cortical hyperexcitability in the association cortices. It might possibly have resulted in the disappearance of GTCSs.
Significance: We delineated long-term change of giant SEP in ULD.

1. Introduction

Unverricht–Lundborg disease (ULD) is the most common type of progressive myoclonus epilepsy (PME) that is characterised by myoclonus, epileptic seizures and cerebellar ataxia, and is nowadays called progressive myoclonus epilepsy type 1 (EPM1) (Kälviäinen et al., 2008). As in other diseases among PMEs, the somatosensory evoked potentials (SEPs) usually show selected enhancement of cortical components called giant SEPs. It could represent hyperexcitability of the primary sensorimotor cortices (Shibasaki et al., 1985).

Although it is termed as 'progressive', Magaudda et al. recently reported 20 patients of ULD with lesser degree of progression or rather self-limited process in the later life. In their long-term follow-up over 20 years, patients initially showed progression of myoclonus in the first 5 years of disease. Worsening of myoclonus, however, then ceased and epileptic seizures became much less after 10 years of evolution. Its pathomechanism is uncertain, and to date, no neurophysiological correlates of this interesting clinical

Abbreviations: PME, progressive myoclonus epilepsy; EPM1, progressive myoclonus epilepsy type 1; ULD, Unverricht–Lundborg disease; SEP, somatosensory evoked potential.

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observation have been investigated from the viewpoint of giant SEP that could represent cortical excitability.

By means of a consecutive SEP investigation, we delineated the clinico-electrophysiological correlates in two ULD patients showing apparently self-limited, long, clinical course.

2. Methods

2.1. Patients

We employed two patients with genetically diagnosed ULD. Gene analysis showed expansion of a dodecamer repeat in the cystatin B gene promoter region. Both patients have been followed by a board-certified neurologist (AI) throughout for 16 years. Thorough clinical and electrophysiological examinations were performed 16 years ago and in the present investigation.

Patient 1 was a 58-year-old man. The generalised tonic–clonic seizures (GTCSs) started at the age of 14 years, and the patient has been on the antiepileptic drugs. Then, myoclonus and cerebellar ataxia appeared around the age of 20 years. While the GTCSs disappeared by the age of 25 years, myoclonus and cerebellar ataxia progressed until the age of 30 years and became stable since then. The patient also developed a mild dementia with behavioural and character changes in his 20 s that had not progressed until now. At the time of the present investigation at age 58 years, he was wheelchair bound because of moderately disabling postural and action myoclonus. In addition, neurological examination revealed moderate to severe cerebellar ataxia and scanning speech. A brain magnetic resonance imaging (MRI) showed mild diffuse atrophy of the cerebrum and cerebellum. Electroencephalography (EEG) demonstrated normal (8–9 Hz) posterior background activity without epileptiform discharges. As compared with those taken 16 years ago, no apparent interval changes were noted in both brain MRI and EEG findings.

Patient 2 was a 48-year-old man. GTCSs started at the age of 12 years, and he has been on the antiepileptic drugs. Myoclonus started almost at the same time, and cerebellar ataxia appeared around the age of 20 years. The patient developed a mild dementia with behavioural and character changes in his late teenage without any worsening until now. The patient has been seizure free since the age of 25 years, except for a few provoked seizures in his 30 s. Myoclonus and cerebellar ataxia, on the other hand, progressed until age 30 years, and had plateaued since then. In the present investigation, neurological examination showed similar findings to those of Patient 1: wheelchair bound due to moderately disabling postural and action myoclonus, moderate cerebellar ataxia and scanning speech. A brain MRI showed mild to moderate diffuse atrophy of the cerebrum and cerebellum. EEG demonstrated slow (7–8 Hz) posterior background activity and intermittent diffuse 3–4 Hz slow activity without epileptiform discharges. In comparison with previous findings, there were no apparent interval changes between over 16 years in both brain MRI and EEG findings.

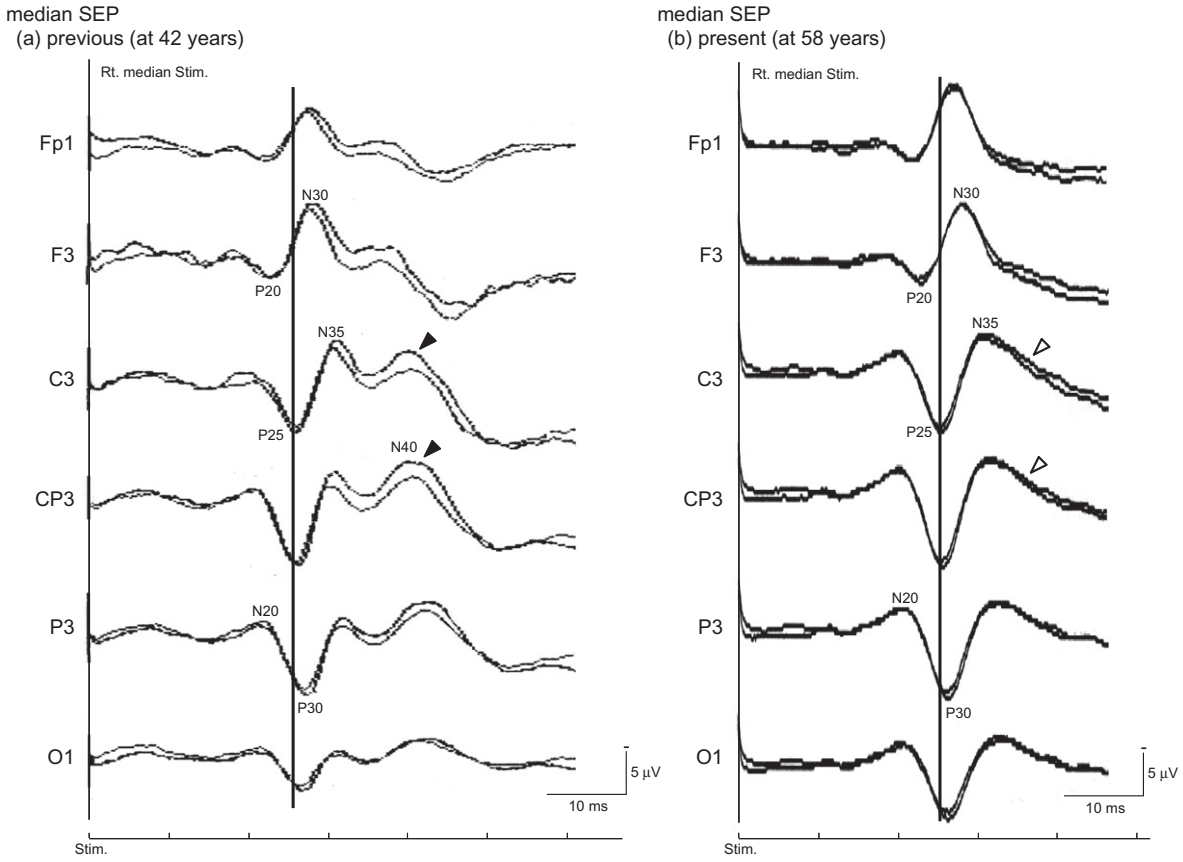

Fig. 1. Waveforms of SEPs to the median nerve stimulation in Patient 1. (a) In the previous study of 16 years ago, two tangential components (N20–P20 and P30–N30) and three radial components (P25, N35, and N40) were identified. A line drawn at 25.9 ms indicates a peak of P25 maximum at C3. A bimodal waveform was composed of N35 and N40 (black arrowhead). The amplitude of N35 at C3 was 10.1 μV measured from the preceding positive peak of P25, and fulfilled the criteria of giant SEP. The nomenclature of each cortical component was labelled at the electrode showing the highest amplitude. (b) In the present study, the bimodal waveform of N35 and N40 observed in the past study (a) changed into the unimodal N35 without N40 component (white arrowhead). The SEP remained giant according to the amplitude of N35 (11.1 μV). A line drawn at 25.4 ms indicates a peak of the central P25. Other conventions were the same as Fig. 1a.