Case Report

Serial Somatosensory Evoked Potentials in a Patient with Familial Hypobetalipoproteinemia, and Vitamin E Deficiency

Sadatoshi TSUJI, Takenori UOZUMI, Yoichi ITO, Akio OHNISHI and Yoshiyuki MURAI

Serial somatosensory evoked potentials (SEPs) to median and posterior tibial nerve stimulation in a case with familial heterozygous hypobetalipoproteinemia and vitamin E deficiency were investigated over a period of 4 years. In serial SEPs to posterior tibial nerve stimulation, interpeak latencies between N20 and P2 were delayed even in the early clinical stage, although the peak latency of N20 was normal. N20 latency was delayed when the patient noted paresthesia of the lower extremities. Interpeak latencies between N20 and P2 were progressively prolonged, and finally both peaks disappeared. Progressive dysfunctions of spinal posterior columns and peripheral somatosensory pathways were discovered by serial SEP studies.

Key words: Posterior tibial nerve stimulation, Median nerve stimulation

It is well known that β-lipoprotein and vitamin E play important roles in the maintenance of neurological structure and function in humans. Various neurological complications have been reported in cases with abetalipoproteinemia and/or vitamin E deficiency (1). Cerebellar ataxia, loss of posterior column function, pyramidal signs and peripheral neuropathy are rarely noted in cases with heterozygous hypobetalipoproteinemia (2-8). Neurophysiological investigations have shown normal cerebral evoked potentials in 4 cases with hypobetalipoproteinemia (3). However, no serial study of somatosensory evoked potentials (SEPs) in cases with hypobetalipoproteinemia and vitamin E deficiency has been reported.

CASE REPORT

A 61-year-old Japanese male, at the age of 55 years, noted an unsteady gait which became progressively worse forcing him to use a walker at age 58, and at age 59, he was unable to stand without being supported. Paresthesia developed on the feet and legs at age 59, which ascended to the groins at 60 years of age. Slurred speech also developed at 59 years of age. From age 57 he had been treated with large doses of vitamin E, 600-1,200 mg/day orally, which were not effective for the neurological symptoms or signs. There was no consanguinity in the family.

Neurological examination at age 61 showed normal mental function, normal optic fundi, horizontal nystagmus at lateral gazes and vertigo, severe scanning speech, and moderate ataxia of the upper extremities and marked ataxia of the lower extremities. He was unable to stand because of a severe truncal ataxia. There were mild sensory disturbances in all the modalities on the finger tips of both hands and moderate sensory disturbances below the Th10 level with a distal dominancy. Deep tendon reflexes were hypoactive in the upper extremities and absent in the lower extremities. Babinski sign was elicited bilaterally. There was mild to moderate muscle weakness of both lower extremities. There were no extrapyramidal signs,

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orthostatic hypotension, sphincter disturbance nor impotence.

Laboratory study

The following studies showed normal or negative results: serological studies, liver function test, total protein and serum protein electrophoresis, roentgenograms of spine. Examination of the upper gastrointestinal tract showed no abnormalities. No acanthocytosis of the red blood cells was seen in wet or dry preparations.

Serum total cholesterol (52–77 mg/dl), low density lipoproteins (LDL) + very low density lipoproteins (VLDL) cholesterol (0–11 mg/dl), and β-lipoprotein (46–80 mg/dl) were significantly lower than the control (Table 1). High density lipoproteins (HDL) cholesterol (35–135 mg/dl, normal range: 29–70) was within normal limits or slightly increased. Electrophoretic studies of lipoprotein revealed decreased β-lipoprotein (20%, normal range: 44.1 ± 5.8) and slightly increased α-lipoprotein (58%, normal range: 36.1 ± 6.2). Pre-β-lipoprotein was normal (22%, normal range: 18.8 ± 1.9). The value of serum apolipoprotein B (9–33 mg/dl) was decreased (normal range: 35–155), however, that of serum apolipoprotein A was normal (180–202 mg/dl, normal range: 150–300). Chromatographic studies of serum phospholipids and red blood cells including sphingomyelin, lecithin and lyssolecithin were within normal limits. Serum triglycerides were normal (38–76 mg/dl, Table 1).

The plasma vitamin E level was decreased (0.56 mg/dl, normal range: 0.75–1.41) (Table 1), although plasma vitamin A (17.5–33.6 μg/dl, normal range: 10–70) and carotene (78.1 μg/ml, normal range: 50–400) were both normal.

In the study of serial changes of serum lipids after butter tolerance tests (butter 1 g per weight 1 kg, orally), the serum β-lipoproteins were significantly lower than those of normal control before and after the tolerance test (patient: before: 127, after 1 h: 127, 2 h: 164, 6 h: 108 mg/dl, control: before: 260, after 1 h: 288, 2 h: 344, 6 h: 248 mg/dl). Regarding serum triglycerides and chylomicrons (turbidimetry),

<table>
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<tr>
<th>Table 1. Serial SEPs and serum lipid studies.</th>
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<tbody>
<tr>
<td>Date</td>
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<tr>
<td></td>
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<tr>
<td>Sep. 1983 (57y)</td>
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<td>Sep. 1984 (58y)</td>
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<td>Apr. 1985 (58y)</td>
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<td>Aug. 1985 (59y)</td>
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<tr>
<td>July 1986 (60y)</td>
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<td>Oct. 1987 (61y)</td>
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<td>Normal**</td>
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<table>
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<tr>
<th>Date</th>
<th>Left MN stimulation (ms)</th>
<th>Serum lipid (mg/dl)</th>
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<tbody>
<tr>
<td></td>
<td>N9</td>
<td>N13</td>
</tr>
<tr>
<td></td>
<td>160–3,000 Hz</td>
<td>32–300 Hz</td>
</tr>
<tr>
<td>Sep. 1983 (57y)</td>
<td>8.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Sep. 1984 (58y)</td>
<td>9.2</td>
<td>13.4</td>
</tr>
<tr>
<td>Sep. 1985 (58y)</td>
<td>9.1</td>
<td>13.6</td>
</tr>
<tr>
<td>July 1986 (60y)</td>
<td>9.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Oct. 1987 (61y)</td>
<td>9.1</td>
<td>14.3</td>
</tr>
<tr>
<td>Normal**</td>
<td>9.1±0.8(21)</td>
<td>12.5±0.9(21)</td>
</tr>
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*Vit.E 600–1,200 mg/day P.O.; **Mean±S.D. (No.)

SEPs, somatosensory evoked potentials; PTN, posterior tibial nerve; MN, median nerve; TG, triglyceride; T.chol, total cholesterol; β-lipo, β-lipoprotein; Vit.E, vitamin E
however, there were no significant changes between
the patient and the normal control after the test.
Computerized tomography of the head showed
that cerebellar atrophy had been prominent on the
vermis since age 59. Electroencephalography showed
no abnormalities during the same period. Needle
electromyography showed giant spikes and de-
creased motor unit potentials in the right vastus
medial, tibialis anterior and gastrocnemius muscles.
Nerve conduction studies showed normal motor con-
duction velocity (MCV: 56.0 m/s) and sensory con-
duction velocity (SCV: 50.0 m/s) in the right median
ers, and slow MCV (34.6 m/s) in the right
peroneal nerve. The right sural nerve showed normal
SCV (46.7 m/s), but decreased amplitude of the
sensory potentials (4 μV) at age 60. A biopsy of the
right sural nerve and the right short peroneal muscle
was done at age 59. There was a mild loss of large
and small myelinated fibers in the sural nerve.
Moderate to severe neurogenic muscular changes
with reinnervation were noted in the short peroneal
muscle.

Familial study

No neurological abnormalities were found in the
patient’s wife or four children. The values of serum
total cholesterol (83–109 mg/dl), LDL + VLDL
cholesterol (33–43 mg/dl) and β-lipoprotein
(44–120 mg/dl) were lower than control in three of
four children. His wife and second daughter,
however, showed normal values in the serum lipids.
HDL cholesterol was normal (37–58 mg/dl) in all
subjects. His third daughter (23 years) showed a
normal level of vitamin E (1.25 mg/dl).

Evoked potentials study

Serial SEPs following median nerve (MN) and
posterior tibial nerve (PTN) stimulation were studied
during the 4 years prior to the patient’s death.
Brainstem auditory evoked potentials (BAEPs) and
pattern reversal visual evoked potentials (PVEPs)
were also studied. The methods and terminologies
of SEPs to MN and PTN stimulation have been
described elsewhere (9, 10).

The criteria for abnormal evoked potentials in
this article include the following: absence of evoked
potentials, and abnormal prolongation of peak and
interpeak latencies, greater than 3 standard devia-
tions (S.D.) from the mean.

Serial studies of SEPs following the left PTN
stimulation are shown in Fig. 1. N20 component
recorded from Th12 – Ic2 derivation had a normal
peak latency and morphology until April 1985 and
slightly delayed latencies in August 1985 and July
1986 (Table 1). The peak latencies of P2 and N2
recorded from Ez – Fz derivation and the inter-

![Fig. 1. Serial SEPs following left posterior tibial nerve stimulation over a 4-year period. Th12, skin overlying spinous process of 12th thoracic vertebra; Ic2, skin overlying right iliac crest; Ez, midpoint between Cz and Pz; Fz, international 10–20 system. Number of stimuli, 1,024; Filter setting, 32–300 Hz (-3dB).](image-url)
peak latencies between N20 and P2 were progressively delayed from September 1983 (Table 1, Fig. 1). Finally, there were no spinal nor cortical SEPs following the PTN stimulation in October 1987.

Serial studies of SEPs following MN stimulation had been normal in the peak and interpeak latencies during his last 4 years (Table 1). BAEPs and PVEPs were normal in the peak latencies and morphologies in September 1983.

One of his daughters (23 years old) was examined for SEPs to median and posterior tibial nerve stimulation and for BAEPs which were within normal limits.

**DISCUSSION**

The propositus and his three children showed a heterozygous hypobetalipoproteinemia, although neurological abnormalities characterized by cerebellar ataxia, loss of posterior column sensory functions, pyramidal signs and sensorimotor peripheral neuropathy, and vitamin E deficiency were noted only in the propositus. These neurological signs were in good agreement with abetalipoproteinemia (8), however, β-lipoprotein was not absent in our patient. Neurological complications in heterozygous hypobetalipoproteinemia are still rare, although at least 15 cases (2–6, 11–13) have been reported.

Vitamin E deficiency is considered to play a possible role in the involvement of the central nervous system in abetalipoproteinemia and hypobetalipoproteinemia (1, 7, 8, 14, 15). The present patient showed reduced serum vitamin E levels at an early clinical stage. In spite of taking a large dose of vitamin E (600–1,200 mg/day), the serum levels of our patient were within the lower limits of normal range, and his neurological signs progressively worsened.

In serial SEP studies, the present patient showed delayed interpeak latencies between N20 and P2 (central conduction time between 5th lumbar cord and sensory cortex (9)) when the posterior tibial nerve was stimulated, and finally SEPs disappeared. In contrast, SEPs to median nerve stimulation, BAEPs and PVEPs had been normal in the peak and interpeak latencies, and also in the morphology. The results of serial SEP studies indicated a dysfunction of the somatosensory pathways at the posterior column between lumbar and cervical levels since the early clinical stage. As to N20, the peak latency was normal in the early clinical stage, and then began to be delayed in the later stage. These results correspond well to the animal experiments, in which the peripheral sensory pathways were not involved histologically at the early clinical stage of vitamin E deficiency in a rat (16, 17). When the N20 latency was delayed in the present patient, pathological examination of the sural nerve revealed a slight loss of large and small myelinated fibers.

The neurophysiological investigations in familial hypobetalipoproteinemia have been reported only by Andersen et al (1979) (3), who concluded that there were no signs of myelin dysfunction in the central nervous system because of normal peak latencies of VEPs and cortical SEPs in 4 patients. Thereafter, a few evoked potential studies in the cases with abetalipoproteinemia (18–21) or vitamin E deficiency (22–25) were reported. Delayed peak latencies or absent responses were noted in VEPs or SEPs to median or posterior tibial nerve stimulation in 7 cases of them.

Serum β-lipoprotein has been considered to play an important role as serum transport vehicle for substances essential for metabolism of myelin (26). In addition, Nelson et al (1981) (27) reported that animals with vitamin E deficiency had degeneration of axons in the gracile and cuneate nuclei of the brainstem, in the posterior columns of spinal cord and in the peripheral nerves with a selective loss of large myelinated fibers. Serial SEP studies in the present patient support these pathological data by the delayed interpeak latencies of N20 – P2 and peak latencies of N20 which are correlated to the dysfunction of posterior columns of the spinal cord and peripheral sensory fibers. Furthermore, neurophysiological studies in vitamin E deficiency of a rat (16, 17) showed delayed cortical SEPs and normal lumbar SEPs at the early stage of deficiency (after 40 weeks of deficiency), which are similar to our data.

Hypobetalipoproteinemia and vitamin E deficiency play an important role in the development of neurological abnormalities in animal studies. It can be suggested that the neurological deficits of the present patient were caused by both hypobetalipo-
proteinemia and vitamin E deficiency, because there were no neurological abnormalities in his children with hypobetalipoproteinemia and normal levels of vitamin E.

REFERENCES


