SHORT REPORT

Improvement of central motor conduction after bone marrow transplantation in adrenoleukodystrophy

T Hitomi, T Mezaki, T Tsujii, M Kinoshita, H Tomimoto, A Ikeda, S Shimohama, T Okazaki, T Uchiyama, H Shibasaki

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The case is described of a 20 year old man with adrenoleukodystrophy who showed right spastic hemiparesis and gait disturbance. Brain magnetic resonance imaging disclosed predominant involvement of the left corticospinal pathway. The clinical symptoms improved after bone marrow transplantation. Transcranial magnetic stimulation disclosed significant improvement in various parameters of central motor conduction.

Adrenoleukodystrophy (ALD) is an X linked recessive disorder characterised by the increased serum very long chain fatty acid (VLCFA) and a mutation of the ALD protein gene. Recently bone marrow transplantation (BMT) has been reported to improve neurological and neuropsychological symptoms associated with the improvement of MRI findings and the reduction of serum VLCFA levels if applied in the early phase of the disease.^{1–5} However, electrophysiological studies such as short latency somatosensory evoked potential (SSEP), brain stem auditory evoked potential (BAEP), and visual evoked potential (VEP) have not consistently reflected clinical changes after BMT;^{2,4} and, to our knowledge, transcranial magnetic stimulation (TMS) has never been applied for this purpose.

We report a patient with ALD in whom BMT was effective to alleviate his symptoms. In this patient, TMS was helpful to demonstrate the improvement of motor function.

CASE REPORT

A 20 year old man had been healthy until he presented with progressive right motor hemiparesis and gait disturbance three months before visiting our hospital. Clinical examination upon admission revealed mild cognitive impairment (Wechsler Adult Intelligence Scale Revised (WAIS-R): Total IQ (TIQ):76, Verbal IQ (VIQ):74, Performance IQ (PIQ):88), right motor hemiparesis including facial muscles with exaggerated deep tendon reflexes, and mild sensory disturbance on the right limbs. Abdominal reflexes were absent bilaterally. T2 weighted MR scan disclosed high signal intensities in the white matter extending from the left corona radiata to the left medullary pyramis, the splenium of the corpus callosum, and the bilateral regions around the posterior horn of the lateral ventricle. A part of those regions showed gadolinium enhancement. Because of increased serum VLCFA values (C24/C22:1.554 (normal: 0.628–0.977), C25/C22:0.077 (normal: 0.012–0.023), C26/C22:0.035 (normal: 0.003–0.006)) and point mutation (TCG→TTG) of 606 codon of ALD protein gene, he was diagnosed as having ALD. There was no consanguinity in his family, and no other relatives had neurological symptoms.

Lorenzo's oil was started five months after the clinical onset, but no clinical improvement was seen at least for the following three months. With informed consent, BMT was performed eight months after the clinical onset. Immunosuppressants (busulfan, cyclophosphamide, methotrexate, tac-

rolimus hydrate, and corticosteroids) were administered together with BMT. One month after BMT, his motor symptoms began to improve gradually. Two months after BMT, muscle strength was 5 (Medical Research Council scale on manual muscle testing) in the right upper limb (before BMT:4), and 4+ to 5 in the right lower limb (before BMT:4). There was moderate improvement in the gait, sensory functions on the right limbs, and cognitive function (WAIS-R: TIQ:91, VIQ:87, PIQ:100). Serum VLCFA was reduced (C24/C22:1.308, C25/C22:0.063, C26/C22:0.033), but was still abnormal. In MRI study, there was a modest reduction in the area enhanced by gadolinium, although fluid attenuated inversion recovery or T₂ weighted images did not disclose any significant change. Follow up MRI performed four months after BMT showed similar findings.

Electrophysiological assessment

Before BMT, nerve conduction study disclosed no evidence of peripheral abnormality. As for SSEP, cortical responses to the posterior tibial nerve stimulation were normal in latencies, but asymmetric for N₃₂-P₄₀ peak to peak amplitudes; 2.2 µV for the left and 0.9 µV for the right stimulation. VEP showed prolonged P₁₀₀ latencies both on the left (135 ms) and right (136 ms) hemifield stimulation, indicating involvement of bilateral optic radiations. BAEP showed prolonged latencies of wave III (4.7 ms) and V (7.0 ms), and inter-peak latencies were also prolonged; I-III (3.1 ms) and I-V (5.4 ms). These findings did not significantly change after BMT.

Motor evoked potential (MEP) was elicited by TMS with a magnetic stimulator (Magstim Model 200, Magstim, UK) and a circular coil with a diameter of 120 mm. Stimuli were delivered at the vertex, and MEPs were recorded from the surface electrodes placed on the first dorsal interosseous (FDI) muscle of the hand. Threshold intensity was determined according to the standard method.^{6,7} Test stimulus was given with intensity of 20% above the motor threshold. If the threshold was over 80% of the maximum intensity of the stimulator, the latter was given as the test stimulus. Central motor conduction time (CMCT) was calculated according to the following equation; CMCT (ms)=total conduction time (TCT)–(distal latency+F wave latency–1)/2. TCT represents the MEP latency after the cortical stimulation, and distal or F wave latency is the latency of the compound muscle action potential or F waves, respectively, elicited by electric stimulation of the ulnar nerve at wrist.

Abbreviations: ALD, adrenoleukodystrophy; BAEP, brain stem auditory evoked potential; BMT, bone marrow transplantation; CMCT, central motor conduction time; FDI, first dorsal interosseous; MEP, motor evoked potential; SSEP, short latency somatosensory evoked potential; TCT, total conduction time; TMS, transcranial magnetic stimulation; VEP, visual evoked potential; VLCFA, very long chain fatty acid; WAIS-R, Wechsler Adult Intelligence Scale Revised

Figure 1 Motor evoked potentials (MEPs) before and after the bone marrow transplantation (BMT). MEPs were recorded from the first dorsal interosseous (FDI) muscle of the hand. On the right side (Rt FDI), MEPs were delayed and dispersed, and their amplitudes were much lower than those on the unaffected side (Lt FDI) (A–D). After BMT, MEP amplitude increased fourfold on the right side, although still much smaller compared with that on the left side (E, F). Note the difference of the amplitude scale between A, C, E and B, D, F.

The TMS study recorded on the right FDI muscle five months before BMT showed increased threshold (84%), prolonged TCT (33.5 ms), CMCT (19.3 ms), and decreased MEP amplitude (0.1 mV) with dispersed waveform (fig 1A). For the left FDI muscle, these parameters were normal (threshold intensity 49%, TCT 22 ms, MEP amplitude 3.0 mV) (fig 1B). Shortly before BMT, all the parameters on the right side were similar or even worse (threshold intensity (70%), TCT (36 ms), MEP amplitude (0.1 mV)) (fig 1C). The left side was again normal (fig 1D). Two months after BMT, threshold intensity on the right side decreased to 52%, and TCT and CMCT shortened to 30.7 ms and 16.0 ms, respectively. MEP amplitude increased to 0.4 mV, and the waveform also improved (fig 1E). There was no apparent change on the left side (threshold intensity 42%, TCT 22 ms, CMCT 8.0 ms, MEP amplitude 2.8 mV) (fig 1F). Follow up TMS studies, performed four and seven months after BMT, did not show further significant changes.

DISCUSSION

In this patient, the diagnosis of ALD was confirmed based on the increased serum VLCFA values and point mutation of ALD protein gene, although the clinical symptoms were rather atypical in that the affected systems were mostly unilateral. As the result of early diagnosis, he was successfully treated with BMT nine months after the onset of symptoms. Because the clinical severity was stable for at least five months before BMT, we attribute the post-transplantational improvement to BMT itself. Some additional benefit of immunosuppressants will be unlikely, because they have not been successful for treating ALD so far.⁸ After BMT, the increased MRI area modestly decreased, and TMS was useful to detect the functional improvement of the motor pathway, although parameters of SSEP, VEP, and BAEP did not change. The diminishing enhancement of MRI after BMT in ALD patients has been reported.⁹

In 1984 Moser *et al* first applied BMT to a 13 year old patient with ALD.¹⁰ After BMT, his neurological symptoms persisted although the VLCFA value was normalised. Subsequently, several reports have demonstrated that BMT is effective if applied

at an early stage of ALD. Shapiro *et al* followed up 12 patients with ALD of childhood onset for 5–10 years after BMT and reported a long term beneficial effect in the cases treated early in the clinical course.⁴ Suzuki *et al* reported that two out of their four patients had favourable outcomes and the other two had no improvement after BMT.⁵

TMS is the only way currently available to evaluate the function of central motor pathway non-invasively. In multiple sclerosis, TMS is reported to be useful for detecting and evaluating the abnormality of corticospinal tract function before and after the corticosteroid therapy.^{11–14} Besides, TMS is reported its usefulness for evaluating of the corticospinal tract function in ALD.^{15–17} Kano *et al* successfully used CMCT as an index of central motor conduction during corticosteroid therapy in ALD.¹⁷ To our knowledge, TMS has never been applied to evaluate the effect of BMT in ALD. This is the first report to indicate that TMS can quantitatively demonstrate the improvement of central motor conduction after BMT in ALD.

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Authors' affiliations

T Hitomi, T Mezaki, T Tsujii, M Kinoshita, H Tomimoto, A Ikeda, S Shimohama, H Shibasaki, Department of Neurology, Kyoto University Hospital, Japan
T Okazaki, T Uchiyama, Department of Haematology and Oncology, Kyoto University Hospital

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Correspondence to: Dr T Hitomi, Department of Neurology, Kyoto University Hospital, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan; hitomi46@kuhp.kyoto-u.ac.jp

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