Improvement of central motor conduction after bone marrow transplantation in adrenoleukodystrophy

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The case is described of a 20 year old man with adreno-leukodystrophy 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. However, electrophysiological studies such as short latency somatosensory evoked potential (SEP), brain stem auditory evoked potential (BAEP), and visual evoked potential (VEP) have not consistently reflected clinical changes after BMT, 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 of the hand. Threshold intensity was determined according to the standard method. If the threshold was over 80% above the motor threshold, 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.

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. 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.

Electrophysiological assessment
Before BMT, nerve conduction study disclosed no evidence of peripheral abnormality. As for SEP, cortical responses to the posterior tibial nerve stimulation were normal in latencies, but asymmetric for N13-P15 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.

Abbreviations: ALD, adrenoleukodystrophy; 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

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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, all the parameters on the right side were similar or even worse (threshold intensity (70%), TCT (36 ms), MEP amplitude (0.1 mV)) (fig 1E). The left side was again normal (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. 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.

In 1984 Moser et al first applied BMT to a 13 year old patient with 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. Suzuki et al reported that two out of their four patients had favourable outcomes and the other two had no improvement after BMT.

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. Besides, TMS is reported its usefulness for evaluating of the corticospinal tract function in ALD. Kano et al successfully used CMCT as an index of central motor conduction during corticosteroid therapy in ALD. 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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