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Case Report

A Case of Idiopathic Scoliosis with Intraoperative Neurophysiological Monitoring Abnormalities Leading to the Diagnosis of Charcot-Marie-Tooth Disease 1B

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Summary

The current case report describes the clinical and genetic characteristics of a 16-year-old female proband. She did not have any subjective neurological symptoms preoperatively and who was incidentally diagnosed due to abnormal intraoperative neurophysiological monitoring (IONM) using transcranial electrical stimulation motor evoked potentials (TES-MEP) and somatosensory evoked potentials (SEP) for idiopathic scoliosis, leading to the diagnosis of Charcot-Marie-Tooth disease (CMT) 1B. There was no similar disease in her family history. Nerve conduction velocity testing revealed decreased conduction velocity of the median nerve, and genetic testing indicated myelin protein zero (*MPZ*) mutation (c242A > G), leading to the diagnosis of demyelinating type CMT1B. The parents had no genetic mutation, and this was a case of de novo mutation. CMT1B is an important differential diagnosis because, similar to our case, there may not be any clinical symptoms. The disease was discovered during a careful evaluation of the patient's scoliosis and other complications. TES-MEP was more useful than SEP for IONM of scoliosis with CMT1B.

Key Words: Charcot-Marie-Tooth disease (CMT) 1B, myelin protein zero (*MPZ*) mutation, intraoperative neurophysiological monitoring (IONM), scoliosis

Introduction

Charcot-Marie-Tooth disease (CMT) is characterized by an inherited neuropathy of the motor and sensory nerves, foot deformity, and altered tendon reflexes. It has a bimodal distribution of age of onset, with onset most commonly at age < 20 years or > 60 years. The disease is characterized by orthopedic problems, which

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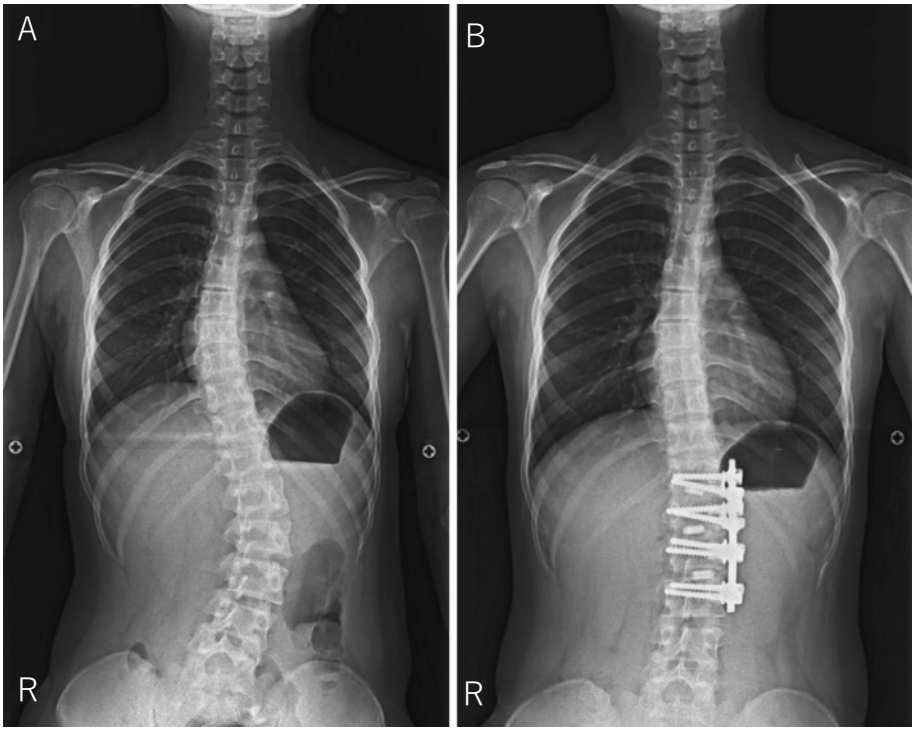

Figure 1 Preoperative **(A)** and postoperative **(B)** spinal X-rays of scoliosis.

include muscle atrophy of the lower extremities (called "champagne bottle-like"), pes caves, glove-sock type sensory disturbance, autonomic neuropathy, and tremor. More than 80 genes have been identified that cause CMT. CMT has been classified as demyelinating, axonal, or intermediate according to the nerve conduction velocity (NCV). However, in 2018, Magy et al. proposed a new classification based on the inheritance type, neuropathy type, and genes[1,2].

We describe an asymptomatic case of CMT1B, who was incidentally diagnosed based on abnormal intraoperative neurophysiological monitoring (IONM) during surgery for idiopathic scoliosis. IONM is not usually used as a diagnostic tool, but our unique monitoring experience showed that IONM, along with clinical and laboratory investigations, is useful for the postoperative diagnosis of underlying neuromuscular diseases.

Clinical Summary

A 16-year-old female with idiopathic scoliosis underwent anterior lumbar spinal fusion surgery at our orthopedic surgery center (Fig. 1). IONM was performed using transcranial electrical stimulation motor evoked potentials (TES-MEP) and somatosensory evoked potentials (SEP), which revealed poor guidance of the left and right short abductor pollicis brevis and adductor hallucis, and delayed latency or poor guidance of the lower extremities during TES-MEP (Fig. 2) and SEP (Fig. 3). The postoperative nerve conduction velocity test also revealed abnormal findings (Table 1), and the patient was referred to our department. There were no notable findings in her medical or developmental history. The patient's maternal grandfather had a similar disorder, but he was not seen by a medical institution, so the details were unknown. Her mother, father, and sister did not have any abnormalities.

Physical examination revealed a height of 150.1 cm, weight of 45.5 kg, and body mass index of 20.2 kg/m^2. Neurological examination revealed clear consciousness and no special findings in the cranial nerve examination. Manual muscle testing revealed a power of 5/5 for deltoid, biceps, triceps, wrist extension and flexion, flexor digitorum superficialis and profundus, and opponens, a power of 5-/5- for abductor pollicis brevis, first dorsal interosseous, and abductor digiti minimi, a power of 5-/-5- for extensor digitorum and iliopsoas, and a power of 5/5- for quadriceps femoris, hamstrings, tibialis anterior, gastrocnemius, and soleus. Tendon reflexes were absent in bilateral upper and lower extremities. The sensory system was mildly af-

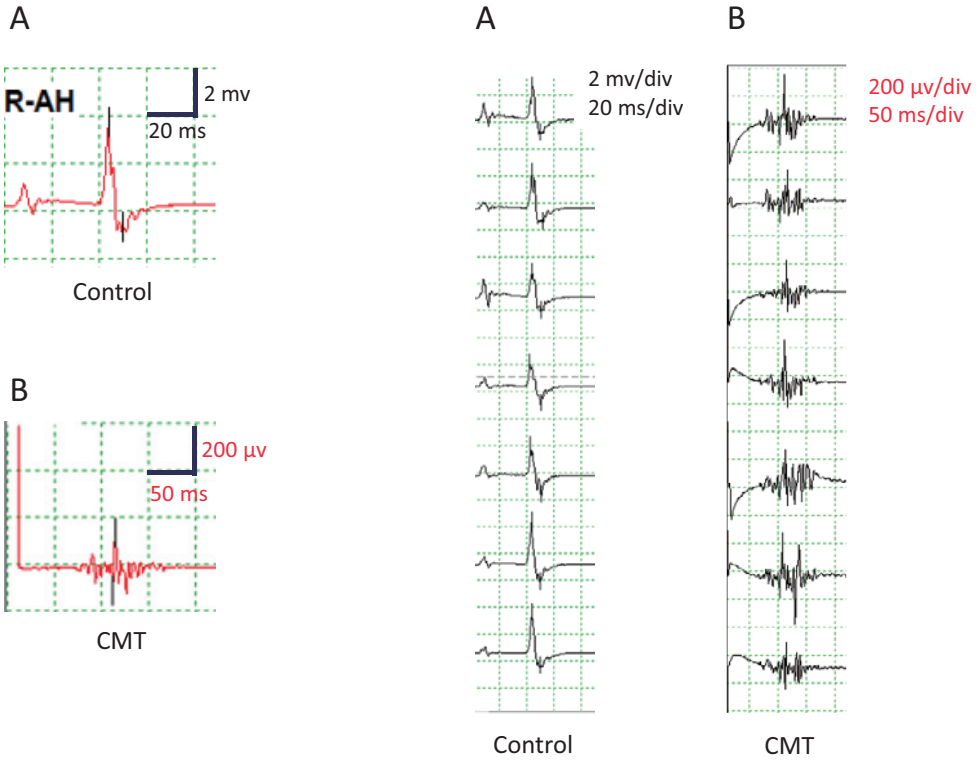

Figure 2 Transcranial MEP waveforms of control **(A)** and CMT1B **(B)** during intraoperative neuromonitoring. MEP latency is prolonged and amplitude is lower in CMT1B compared to control. MEP, motor evoked potentials; CMT, Charcot-Marie-Tooth disease.

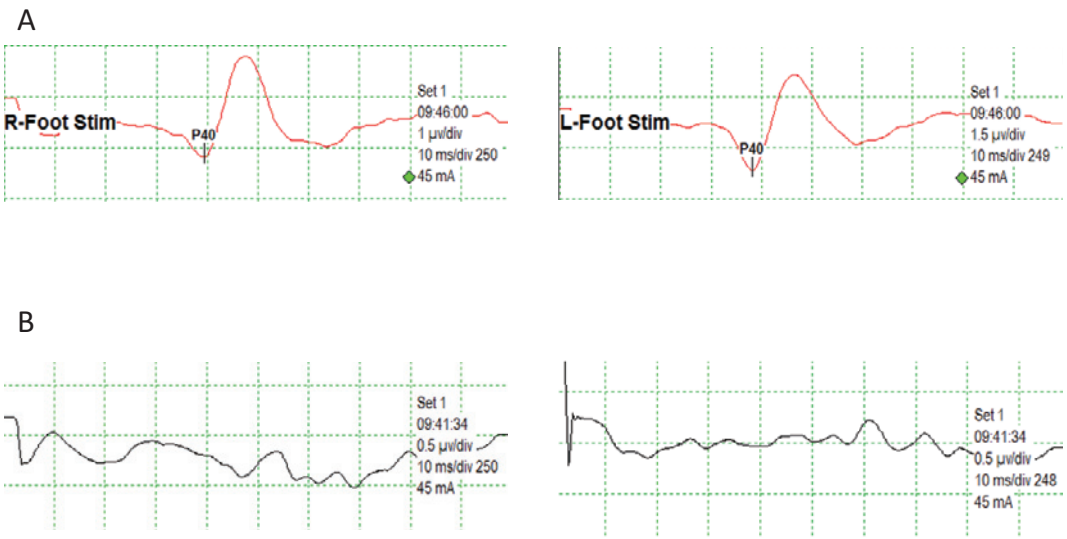

Figure 3 SEP waveform during intraoperative neuromonitoring of control **(A)** and CMT1B **(B)**. P40 of SEP was not induced in CMT1B compared to control. SEP, somatosensory evoked potentials; CTM, Charcot-Marie-Tooth disease.

fected in the peripheral extremities, but there were no abnormal sensations or left-right differences, and there was no obvious numbness or decreased warmth or pain sensation. Vibratory sensation was decreased to 12 s/12 s at the radial head and 8 s/8 s at the medial malleolus. There was no muscle atrophy in the extremities. However, there was slight pes caves and no limb joint deformity except for the spine.

Table 1 Nerve conduction study results

Nerve unit	DL (ms)	CMAP amplitude (mV)	MCV (m/s)	CB	DL (ms)	SCV (m/s)	SNAP amplitude (μV)
Right median	**8.2**	**1.98**	**17.0**	-	**4.7**	**27.6**	**0.57**
Right ulnar	**6.9**	**1.40**	**12.6**	-	**6.3**	**15.9**	**0.57**
Right peroneal	No response	No response	No response	-	No response	No response	No response
Right sural	No response	No response	No response	-	No response	No response	No response

CB, conduction block; CMAP, compound muscle action potential; DL, distal latency; MCV, Motor conduction velocity; SNAP, sensory nerve active potential; SCV, sensory conduction velocity. Note: Abnormal values are marked with bold characters.

Blood counts and biochemistry showed no obvious abnormal findings. Autoantibodies for collagen disease and vasculitis were negative, and vitamin B1 level was low at 17 ng/mL (reference value: 24-66 ng/mL). Nerve conduction study (right side) showed skin temperature of 36.2°C in the upper extremity and 36.2°C in the lower extremity. The motor and sensory nerve conduction velocities of the right median nerve were markedly decreased to 17 m/s and 27.6 m/s, respectively, with prolonged distal latency and decreased amplitude (Table 1).

Genetic testing for suspected CMT revealed no duplication of peripheral myelin protein 22 (*PMP 22*), but identified a myelin protein zero (*MPZ*) mutation (*MPZ* c242A > G, p.H81R heterozygous), leading to the diagnosis of CMT 1B. Genetic testing of the parents was also performed, but there was no *MPZ* mutation. Therefore, our patient had a de novo mutation. We informed the patient that she had no symptoms that would interfere with her daily life at this point, but that clinical symptoms might gradually appear in the future. We decided to keep the patient on follow-up. We also suggested genetic counseling because of the possibility of inheritance to the next generation.

Discussion

The neurological findings in this case showed loss of limb tendon reflexes and decreased vibratory sensation predominantly in the lower extremities. However, there was no obvious sensory disturbance or muscle weakness that was apparent enough to be noticed. There was only a mild pes caves, which did not interfere with daily activities. CMT is diagnosed on nerve findings, NCV study, and genetic analysis[1,2]. The NCV study shows a decrease in NCV of the median nerve to < 38 m/s, which is consistent with demyelination, a decrease in compound muscle action potential (CMAP), and abnormalities in the motor or sensory nerves of the median, ulnar, peroneal, and sural nerves. The majority of patients with early-onset CMT1B will have delayed walking and very slow motor NCV (< 15 m/s). Those with late onset CMT1B will walk at a normal age and usually have intermediate or normal motor NCV (> 35 m/s). The motor NCV was similar to the intermediate type in the present case.

CMT is a genetically heterogeneous group of peripheral neuropathies, of which most are associated with mutations in four genes, including *PMP22*, *MPZ*, gap junction protein beta1 (*GJB1*), and mitofusin2 (*MFN2*). CMT can be divided into several phenotypes as follows: i) CMT1, CMT2, and autosomal dominant intermediate CMT are typically inherited in an autosomal dominant manner; ii) CMT1B with early/late onset and reduced nerve conduction velocity (NCV) (demyelinating type); iii) CMT2I with a manifestation in adulthood and normal NCV (axonal type); iv) CMT4 has autosomal recessive inheritance and CMTX has X-linked inheritance; and V) Dejerine-Sottas syndrome with infant-onset disease and reduced NCV[2].

In this case, the diagnosis of CMT1B was made based on the finding of *MPZ* mutation in the genetic test. *MPZ* mutations have been reported in more than 95 different strains of CMT with various clinical forms, including demyelinating, axonal, and intermediate types[2,3]. It has been reported that de novo variants were found in 25% of cases with *MPZ* mutations[4], and there are many cases of de novo mutations as well as familial occurrences.

Scoliosis is found in one-third of CMT patients. Among various phenotypes, *MPZ* mutations are reported to be associated with a high rate of scoliosis[5]. This case was discovered incidentally during IONM for surgery for a complication of scoliosis. A similar cases of Freidreich's ataxia, giant axonal neuropathy, and ataxia telangiectasia was previously diagnosed on IONM[6,7]. IONM of TES-MEP and SEP is a reliable method to provide information regarding spinal cord and peripheral nerve integrity during spinal deformity surgery. In the present case, the TES-MEP showed prolonged waveform latency and reduced amplitude, suggesting preoperative abnormalities in the conduction pathways that stimulate the cerebral motor cortex and reach the muscles via the spinal cord and peripheral nerves. The SEP of the conduction pathway from peripheral nerve stimulation through the posterior spinal cord and thalamus to the cerebral sensory cortex was similarly poorly delineated, suggesting that the lesion was mainly in the peripheral nerves. An NCV was performed to assess peripheral neuropathy, leading to the diagnosis of CMT, which is difficult to diagnose in cases with minor clinical symptoms. Correction of spinal deformity is, in fact, considered the most dangerous stage of scoliosis surgery. However, minor drops in blood pressure in conjunction with surgical manipulation may lead to spinal cord damage at any stage of the operation. Lesions of the motor pathways with sparing of the dorsal column function due to selective ischemia in the anterior spinal artery territory may occur. For this reason, a multimodal approach with SEP and TES-MEP under total intravenous anesthesia is mandatory to obtain comprehensive information about spinal cord integrity, including both the descending motor and ascending sensory pathways, and to minimize the rate of false positive and false negative results[7]. Combined SEP and TES-MEP provide a safe, reliable, and sensitive method for monitoring the spinal cord function during orthopedic surgery. This method not only improves the sensitivity and predictive ability of monitoring, but also increases the number of patients for whom satisfactory monitoring of spinal function is possible and is better than a single modality for detecting an unconfirmed diagnosis[8]. This experience has led to the use of longer sweep lengths during monitoring surgery for scoliosis complicated by CMT, allowing baseline TES-MEP measurements, and allowing surgeons to proceed more safely with these complex patients[9].

In conclusion, in this case, TES-MEP was useful for IONM of idiopathic scoliosis and led to the diagnosis of CMT. Molecular genetic testing of the MPZ gene should be considered to confirm the diagnosis of CMT in patients with neurological disorders. Awareness of the common electrophysiologic findings and difficulties in monitoring patients with polyneuropathy can prepare the IONM team to be vigilant when monitoring a patient with presumed idiopathic scoliosis who has baseline neurophysiologic findings suggestive of a possible unrecognized CMT.

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