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Efficacy of Spinal Cord Stimulation Using Differential Target Multiplexed Stimulation for Intractable Pain of Hereditary Neuropathy with Liability to Pressure Palsies: A Case Report

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Abstract

Hereditary neuropathy with liability to pressure palsies is an extremely rare genetic disorder; it is an autosomal dominant disorder with a high incidence of neuropathic and/or musculoskeletal pain. A case of achieving pain relief by spinal cord stimulation using differential target multiplexed stimulation for a 44-year-old female patient with hereditary neuropathy with liability to pressure palsies who was experiencing severe pain in her back, face, and all four limbs is presented. In her early teens, the initial symptoms were numbness and weakness of a limb after movement, which improved spontaneously. Transient pain in her back followed by systemic and persistent muscle weakness and pain developed. Deletion of the gene for peripheral myelin protein 22 was detected by peripheral nerve biopsy. The diagnosis of hereditary neuropathy with liability to pressure palsies was made in her early thirties. A spinal cord stimulation trial was performed because her severe pain continued despite administering many medications. Therefore, two spinal cord stimulation systems were implanted at the C3-5 and Th8-9 levels by two procedures. Pain in her back, arms, and legs decreased from 8 to 1, 5 to 1, and 6 to 2 on the numerical rating scale, respectively. Furthermore, opioid usage was tapered. The pain of hereditary neuropathy with liability to pressure palsies has a complicated pathogenesis and is resistant to pharmacological treatment. Spinal cord stimulation using differential target multiplexed stimulation may be a viable treatment option.

Keywords: spinal cord stimulation, neuropathic pain, hereditary neuropathy with liability to pressure palsies, DTM

Introduction

Hereditary neuropathy with liability to pressure palsies (HNPP) is an extremely rare genetic disorder; it is an autosomal dominant disorder affecting peripheral nerves.[1,2] The prevalence of HNPP is estimated to be 2-16 per 100,000 population.[3] HNPP is difficult to diagnose because of its non-specific symptoms and lack of family history. A definitive diagnosis is made by genetic testing.[2] A gene deletion involving the peripheral myelin protein 22 (PMP22) gene on chromosome 17p11.2 is responsible.[4,5] HNPP used to be considered a pain-free disorder.[2,6] However, a high incidence of neuropathic and/or musculoskeletal pain has been recently reported in patients with HNPP, with neuropathic pain affecting 16.6%-75%.[7-9] The main pain symptom induced by HNPP was burning in the lower limbs.[7] The quality of life of patients with HNPP was significantly correlated with pain.[7]

Spinal cord stimulation (SCS) has been used for decades to treat chronic neuropathic pain.[10] The conventional paresthesia-based SCS uses tonic stimulation that induces a sense of paresthesia. Recently, new SCS stimulation methods without paresthesia have been developed. Differential target multiplexed (DTM) stimulation (Medtronic Inc., Minneapolis, MN, USA) is one of the latest new paresthesia-free stimulation methods, and it can be supe-

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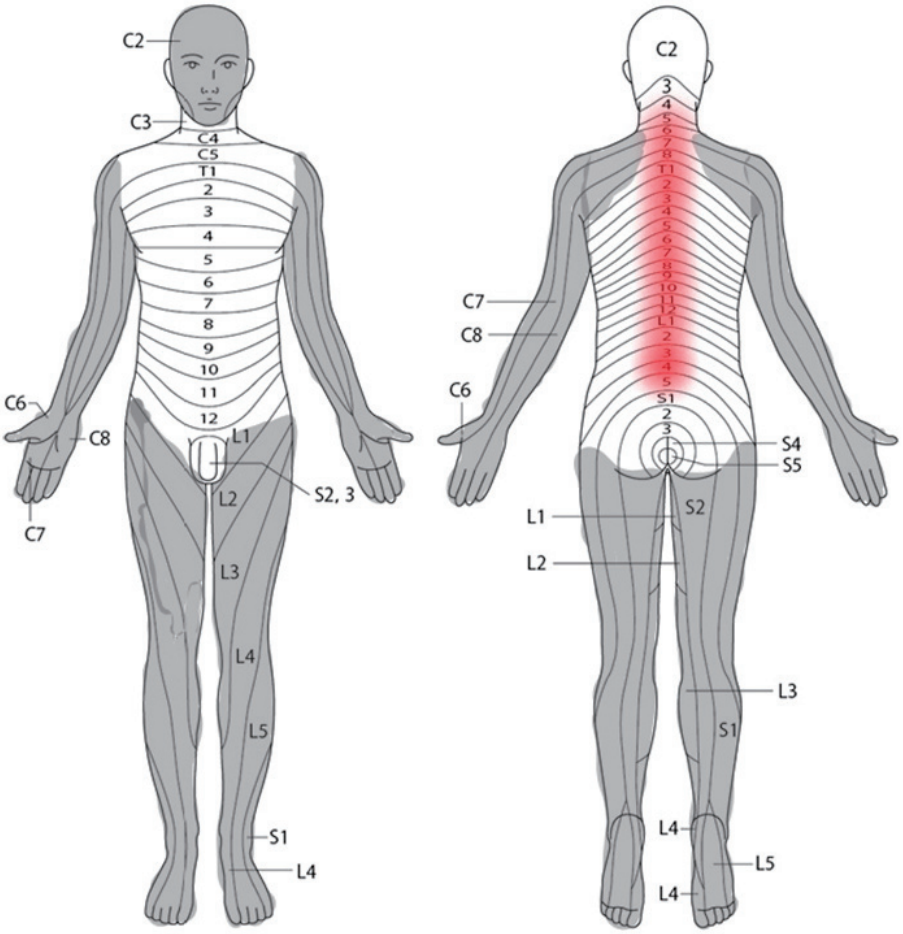

Fig. 1 The schematic diagram shows the pain locations, including her back, all four limbs, and face. The numerical rating scale scores for back pain are 8 (red color), and bilateral arms and legs are 5 and 6, respectively (gray color).

rior to conventional stimulation.[11,12] This is the first case report of the efficacy of SCS using DTM stimulation for the intractable pain of HNPP.

Case Report

A 44-year-old woman had severe pain in her back, all four limbs, and face (Fig. 1). Her clinical course was long and complicated. She had no relevant family or past history. In her early teens, she noticed one-sided numbness and weakness in her more active arm and hand after movement, and the symptoms improved spontaneously after a few days. Transient pain of the back then appeared.

In her twenties, these symptoms continued to come and go. Moreover, symptoms of transient pain with dysesthesia and muscle weakness of bilateral legs appeared. She visited many hospitals and departments where various were examined. Laboratory and imaging examinations detected no clear abnormalities. Screening for rheumatoid factors and anti-nuclear antibodies were also negative. Nerve conduction studies were performed annually, and they detected a decrease in sensory conduction velocity and amplitude in multiple nerves, including bilateral median, ulnar, and sural nerves. Motor conduction velocities and bilateral peroneal and left median nerve amplitudes were also decreased. Somatosensory evoked potential examination showed that the conduction times of the peripheral nerves were prolonged, although those of central nerves were normal. Other examinations, such as needle electromyography, repetitive nerve stimulation test, and central motor conduction time, showed normal findings. These findings were consistent with HNPP.

In her early thirties, muscle weakness and pain with dysesthesia of all four limbs became persistent. Then, a peripheral left peroneal nerve biopsy was performed. Histopathological examination showed focal thickening of the myelin sheath, known as tomacula, a characteristic pathological feature of HNPP. There were localized thin parts of the myelin sheath, although no findings of active demyelination were observed. There were no findings of vasculitis, inflammatory cell infiltration, or abnormal deposits. Genetic testing detected PMP22 gene deletion. She was finally diagnosed as having HNPP. Several courses of steroid pulse therapy improved her symptoms. Although the effects were

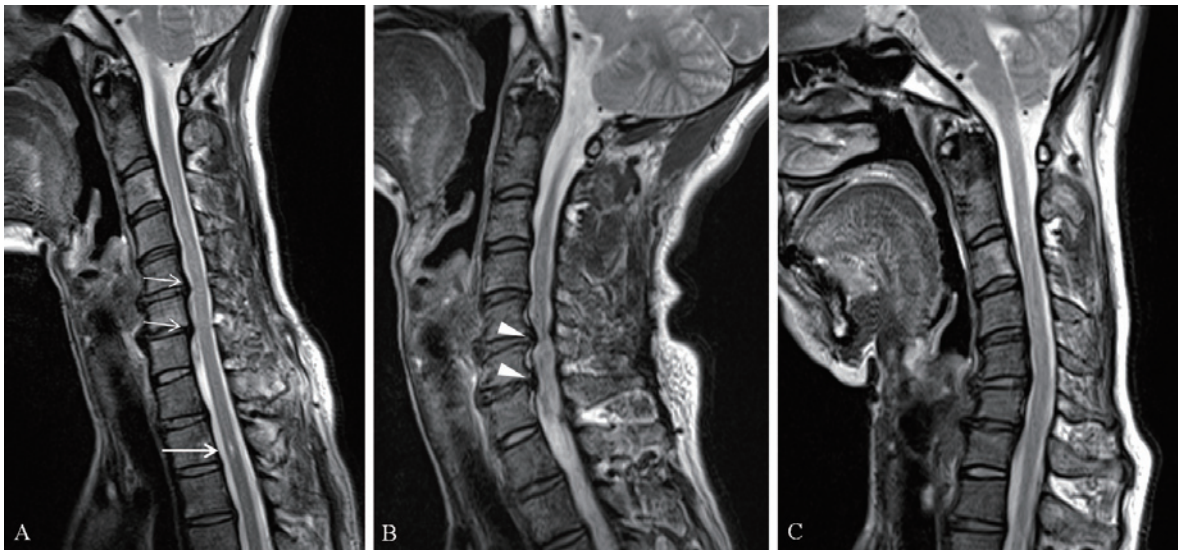

Fig. 2 A: Magnetic resonance image shows disc herniations at C5/6 and C6/7 (thin arrow) and syringomyelia at the Th2 level (thick arrow). B, C: Dynamic magnetic resonance images demonstrate protruding disc herniations compressing the spinal cord (B: retroflexion, C: anteflexion).

temporary, she returned to her original condition. Immunoglobulin therapy did not have an effect.

In her late thirties, she presented with new symptoms of muscle weakness and numbness of her arms when moving her neck. Magnetic resonance imaging (MRI) showed cervical disc herniations at C5/6 and C6/7 and syringomyelia at the Th2 level (Fig. 2A). Dynamic MRI demonstrated that the disc hernias protruded and compressed the spinal cord with neck retroflexion (Fig. 2B, C). Anterior cervical decompressions and fusion were performed using instruments. After the surgery, the new symptoms induced by moving her neck disappeared.

In her forties, the pains in her back and four limbs persisted. Furthermore, she also presented with muscle weakness and abnormal neurological findings of all limbs with muscle atrophy (Table 1). Anesthesiologists treated the pain with various medications, including oral morphine (30 mg daily), fentanyl patch (1 mg daily), duloxetine (40 mg daily), pregabalin (450 mg daily), and non-steroidal anti-inflammatory drugs on an as-needed basis. The numerical rating scale (NRS) scores for the pain of the back, arms, and legs were 8, 5, and 6, respectively.

The patient continued to have severe pain despite administering many medications at sufficient doses. Therefore, an SCS trial was performed using two percutaneous cylinder-type leads (Model 977A190; Medtronic Inc). Only DTM stimulation was applied during the SCS trial because tonic stimulation induced uncomfortable paresthesia. The SCS trial result showed pain relief by DTM stimulation. One month later, two new leads at the C3-5 levels and an implantable pulse generator (Intellis; Medtronic Inc.) were implanted under general anesthesia, referring to the previous X-ray of trial lead placement (Fig. 3A, B). The back and arm pain decreased from 8 to 1 and 5 to 3 on the NRS score, respectively. The pain relief has continued for 6 months after implantation. Cervical SCS did not provide relief of the leg pain, although the frequency of spastic muscle contractions of bilateral legs decreased. After the first implantation, the medication dosages were reduced: pregabalin from 450 to 150 mg daily and fentanyl patch from 1 mg daily to none. Oral morphine could not be stopped because the bilateral leg pain persisted. Since the patient demanded that her pain be alleviated, a second SCS trial was performed using two leads placed at the Th8-9 levels. Additional DTM stimulation at Th8-9 during stimulation with the cervical implanted SCS system showed add-on effects for pain relief of the bilateral legs. Therefore, one month later, an additional SCS system was implanted similarly (Fig. 3C, D). Accordingly, four leads and two implantable pulse generators were implanted (Fig. 3E). The back, arm, and leg pain decreased from 8 to 1, 5 to 1, and 6 to 2 on the NRS score, respectively. With the relief of pain of both legs, regular use of oral morphine 30 mg daily was tapered to 10 or 20 mg on an as-needed basis. The pain relief effect has continued for three months since the second implantation. Since the first implantation, this patient was followed up for 12 months.

Using the Short-Form McGill Pain Questionnaire-2, the score decreased from 156 (pre-operatively) to 115 (6 months after the first SCS implantation), then to 64 (12 months after the first SCS implantation). The score on the Quick Inventory of Depression Symptomatology decreased from 27 (pre-operatively) to 22 (6 months after the first SCS implantation), then remained at 22 (12 months after the first SCS implantation). The score on the Pain Catastrophizing Scale decreased from 44 (pre-operatively) to 33

Table 1 All four limbs' muscle weakness and neurological findings

		Rt	Lt	Median
MMT				
Neck	anteflexion			4
	retroflexion			4
Deltoid		3	3	
Biceps		3	3	
Triceps		3	3	
Wrist	flexion	2	2	
	extention	2	2	
Fingers	flexion	2	2	
	extention	2	2	
Opponens pollicis		2	2	
Iliopsoas		3	3	
Quadriceps		4	4	
Hamstring		4	4	
Tibialis anterior		3	3	
Gastrocnemius		3	3	
EHL		3	3	
FHL		3	3	
Grasping power Reflex		3.5 kg	3.5 kg	
Biceps		+	+	
Brachioradialis		±	±	
Triceps		+	+	
PTR		+	+	
Ankle		±	±	
Hoffmann		-	-	
Tromner		-	-	
Babinski		-	-	
Chaddock		-	-	
Sensory				
Touch		LE ↓	LE ↓	
Algesia		LE ↓	LE ↓	
Temperature		LE ↓	LE ↓	
Vibration		LE ↓	LE ↓	
Joint position		Normal	Normal	

EHL: extensor hallucis longus, FHL: flexor hallucis longus, LE: lower extremity, Lt: left, MMT: manual muscle test, Rt: right, PTR: patella tendon reflex

(6 months after the first SCS implantation), then to 14 (12 months after the first SCS implantation).

Discussion

PMP22 gene deletion could lead to small fiber neuropathy affecting mainly thinly myelinated Aδ fibers or terminal Schwann cells of subepidermal free nerve endings.[8] The clinical presentation of HNPP classically involves acute onset, painless, single or multiple sensory or motor deficits at nerve entrapment sites.[13,14] Symptoms are usually transient and last several hours to months. Features of the electrodiagnostic examination of HNPP are slowed nerve conduction, increased distal motor latency, or conduction blocks.[7] These findings are not specific to HNPP, and electrodiagnostic examination alone cannot diagnose HNPP.[2,3] HNPP diagnosed through peripheral nerve biopsy and detection of a gene deletion of PMP22.[1,2] HNPP has historically been considered pain-free neuropathy.[2,6] However, recent cohort studies showed that many people with HNPP had pain and experienced persistent pain.[7-9] The pain of HNPP consists of neuropathic and/or musculoskeletal pain. Neuropathic pain is more focal or distal pain with coexisting hypoesthesia or allodynia.[8] Changes in myelin have been identified, and it is one mechanism of the neuropathic pain in HNPP.[15,16] Altered peripheral processes in neuropathy have the potential to contribute to more nervous system-wide changes and sensitization.[17] Central sensitization has been proposed as a link between HNPP and pain.[8]

In this case, sensory and motor symptoms were initially localized and transient. These clinical symptoms were considered typical clinical presentations of HNPP. Then, muscle weakness with muscle atrophy and sensory disturbance, including persistent pain, were considered persistent neuropathy in advanced HNPP. The results of nerve conduction studies showed damage to multiple peripheral nerves. Meanwhile, the result of somatosensory evoked potential testing and central motor conduction time showed normal central nerve conduction. These changes in symptoms and various examination findings indicated multiple peripheral neuropathies. Furthermore, the pain mechanisms may involve peripheral neuropathy and central sensitization because the pain was refractory and persistent over many years. Unsurprisingly, the pain also included musculoskeletal and psychological mechanisms. Examined retrospectively, this case met the fibromyalgia syndrome diagnostic criteria. Fibromyalgia syndrome is a widespread pain disorder thought to have altered central pain processing.[18,19] HNPP with whole-body pain may overlap the fibromyalgia criteria and potentially delay the diagnosis of HNPP.[8]

Conventional tonic SCS delivers mild electrical pulses and elicits comfortable paresthesia.[20] The mechanisms of the analgesic effect of conventional tonic SCS are activation of the spinal GABAergic interneurons in the dorsal horn and descending pain-inhibitory pathways.[21,22] Meanwhile, DTM is one of the paresthesia-free stimulation methods. DTM stimulation uses multiple electrical signals and modulates glial cells and neurons, rebalancing their interactions.[12] DTM stimulation may show superior pain relief to conventional SCS.[11] Generally, SCS has greater effects on peripheral than central neuropathic pain. In this

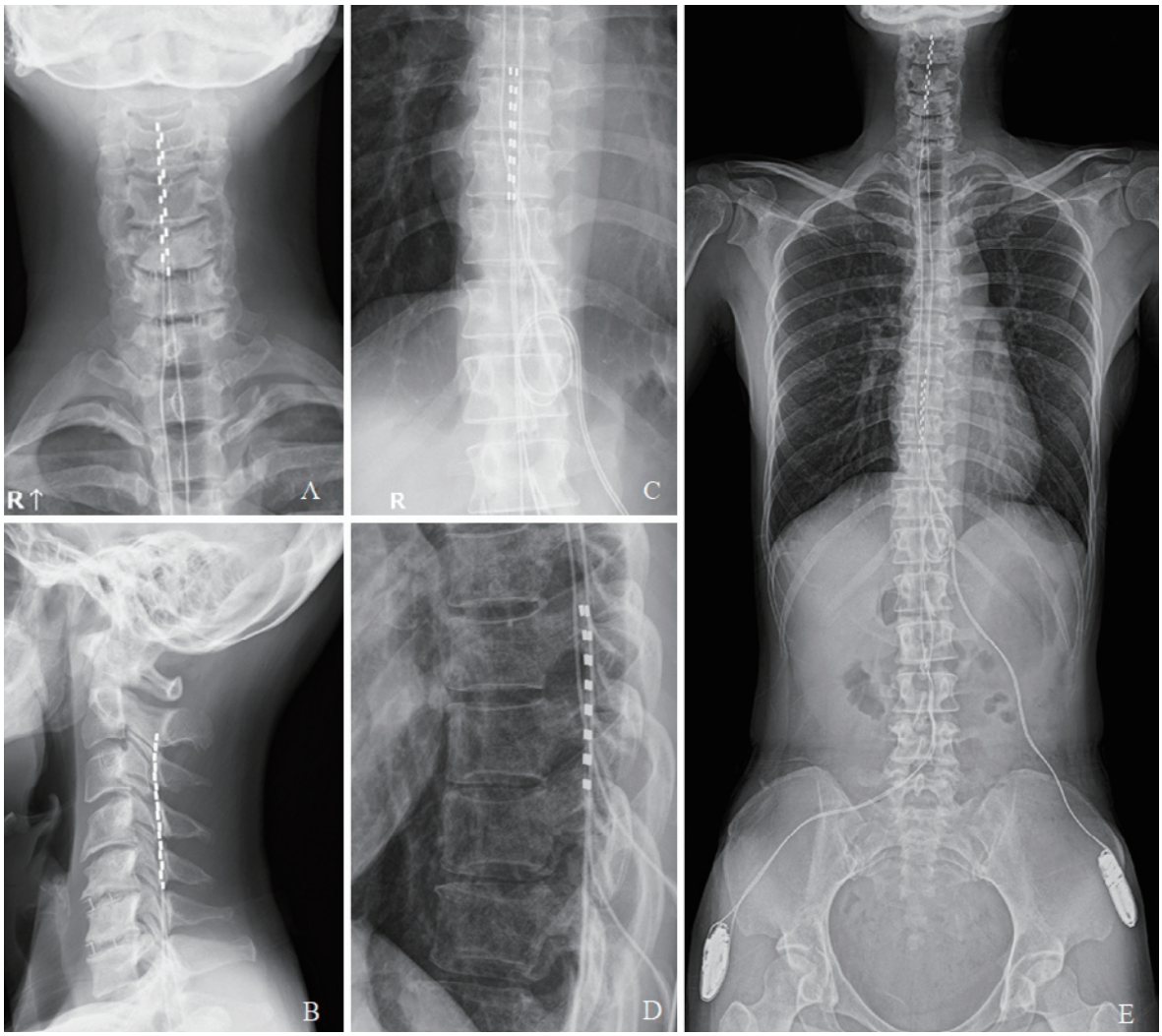

Fig. 3 A, B: Two percutaneous, 8-contact leads of the first implantation are located at the C3-5 levels (A: anterior-posterior view, B: lateral view). C, D: Two additional percutaneous 8-contact leads of the second implantation are located at the Th8-9 levels (C: anterior-posterior view, D: lateral view). E: Finally, four leads and two implantable pulse generators are implanted.

case, SCS using DTM stimulation provided pain relief and reduced medication use. One of the main reasons for achieving pain relief was that this patient's pain consisted mainly of peripheral neuropathic components. Intriguingly, the arm pain was decreased from 3 to 1 on the NRS score after the second implantation despite the lead being placed at the Th8-9 levels. Although the mechanism was unclear, SCS using DTM stimulation may act on the ascending side and modulate central sensitization. Some patients feel the paresthesia, induced by tonic stimulation, uncomfortable. This prevents applying it during an SCS trial. In such cases, paresthesia-free stimulation methods are available without inducing paresthesia.

HNPP, an autosomal dominant disorder coexisting with neuropathic and/or musculoskeletal pain, is a rare neuropathy.[1,2,7-9] The pain of HNPP has a complicated pathogenesis and is resistant to pharmacological treatment. SCS using DTM stimulation could be a treatment option for the intractable pain of HNPP. In this case, the first implanted SCS system has been effective for 12 months, and the second system remains effective after three months. Therefore, further follow-up is necessary for assessments of the clinical course of SCS effects and the amount of medication use.

Informed Consent

Informed consent for publication was obtained from the patient.

Conflicts of Interest Disclosure

The authors have no conflicts of interest directly relevant to this article's content.

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