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Spinal Cord Stimulation for Chronic Neuropathic Pain in Adrenomyeloneuropathy: A Case Report

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Background: Neuropathic pain in adrenomyeloneuropathy (AMN) is a poorly understood phenomenon, with no consensus on treatment options. We report for the first time the successful treatment of medication-refractory neuropathic pain in AMN with thoracic spinal cord stimulation (SCS).

Case Report: A 33-year-old man with AMN presented to clinic with a 10-year history of progressive bilateral distal leg pain and numbness, and a diagnosis by electromyoneurography of demyelinating polyneuropathy, refractory to best medical therapy. After a successful percutaneous trial, he underwent insertion of a paddle system spanning T10-T12. At 3 and 12 months, validated questionnaires revealed improved pain and psychosocial functioning.

Conclusions: We therefore advocate for prompt referral to pain specialists for further workup and management, including consideration of SCS.

Key words: Adrenomyeloneuropathy, diabetic neuropathy, neuromodulation, neuropathic pain, spinal cord stimulation

Background

Adrenoleukodystrophy (ALD) is a rare genetic disorder caused by a mutation of the ABCD1 gene on the X chromosome encoding a peroxisomal membrane transporter (1). This mutation causes very long-chain fatty acid accumulation in the adrenal cortex, central nervous system myelin, and testicular Leydig cells (2). As an X-linked recessive disorder, the disease mostly affects men. While there are no symptoms at birth, a number of clinical phenotypes vary in frequency and age of presentation (3).

Adrenomyeloneuropathy (AMN) is one phenotypic subtype of ALD, affecting just under half of ALD patients. AMN is a noninflammatory axonopathy of the thoracolumbar corticospinal tracts and dorsal columns and peripheral nerves. AMN presents in the third and fourth decades with weakness, spasticity, and loss of vibratory sense. AMN in heterozygous women can present with milder, later, and more insidious spasticity and pain, although accumulating evidence shows symptoms in this group are underrecognized, and that the majority, if not all, will develop neurological involvement (4). Bowel and bladder symptoms are also common in AMN, in the form of constipation, urinary urgency, and urge or stress incontinence (5). Magnetic resonance imaging (MRI) has shown spinal cord atrophy; diffusion tensor imaging has shown reduced diffusion parameters in the corticospinal tracts (6). Electrophysiological studies (7) have revealed primarily axonal sensorimotor abnormalities affecting legs more than arms. Approximately 20%

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of patients with AMN develop an inflammatory cerebral disease, which is considered an independent process (3).

Patients with AMN can develop painful peripheral neuropathy like diabetic neuropathy. Diabetic neuropathy is a well-recognized symptom of diabetes with a wide variety of effective conservative, pharmacological, and neuromodulatory treatments (8,9). However, neuropathic pain in AMN is a less understood phenomenon, with no consensus on treatment options, and no published treatment of AMN with spinal cord stimulation (SCS). Here, we present a case of chronic neuropathic pain in a patient with AMN, who we successfully treated with SCS.

The patient's written consent and Health Insurance Portability and Accountability Act authorization were obtained. The University [masked for review] Institutional Review Board reviewed this report and determined it exempt. This case report adheres to the Case Report (CARE) Guidelines (10).

Case Presentation

At 18 years old, a male patient was diagnosed with AMN. At age 23, he developed progressive bilateral leg pain from the bilateral mid-thigh distally. The pain was described as aching, throbbing, sharp, burning, shooting, and tingling. Pain was constant throughout the day, worse in cold weather and sitting, and alleviated by heat, massage, walking, and stretching. The patient noted numbness involving the bilateral legs, greater distally.

Administration of the Visual Analog Scale (VAS) identified 80/100 mm pain rating. Administration of the 36-Item Short-Form Survey (SF-36) demonstrated poor self-rated general health, severe functional limitations, poor emotional health, and negative effects on social activities (11) (Table 1). Prior to discussion of surgical options, he underwent a full psychological evaluation that elicited symptoms of depression and chronic pain.

Examination was remarkable for diminished light-touch sensation in bilateral stocking distribution, worse distally, without allodynia or hyperalgesia, brisk reflexes (3+ left bicep, brachioradialis, patellar, Achilles, 2+ right), and high-stepping gait, but full strength in all muscle groups. Electromyoneurography at age 27 revealed a primarily motor, demyelinating peripheral polyneuropathy, and MRI revealed no abnormalities in the spinal cord.

He was trialed on gabapentin, baclofen, oxycodone, and methadone with no improvement. He experienced some benefit from heat and ice packs. Botulinum toxin injection to bilateral biceps femoris was performed on 2 occasions to target muscle tightness during walking, but relief was partial and temporary, lasting approximately 3 days on each occasion. Physical therapy provided ongoing partial relief. At the time of the stimulation trial, he was taking 650 mg acetaminophen 2-3 times per day, and 10 mg oxycodone 2-3 times per day.

At age 33, he underwent a one-week percutaneous dorsal column stimulator trial. Two 16-contact leads were placed with the tips at T9, and elicited paresthesia in the abdomen and lumbar spine. He reported 80% relief in leg pain and increased function. One month later, he underwent permanent paddle electrode and generator implantation (12-14). The procedure was performed under general anesthesia with fluoroscopic guidance. The patient underwent superior T12 laminotomy, and a 4 x 16 contact SCS paddle was inserted in the epidural space in the cranial direction. Fluoroscopy confirmed paddle placement in the midline spanning the bottom of T10 to top of T12 (Fig. 1). The paddle was secured to the dura with a 4-0 braided nylon suture followed by a fibrin sealant (Fig. 2). A subcutaneous pocket was created in the right buttock, and the implantable pulse generator (IPG) was inserted into the pocket. The electrode tails were tunneled to the IPG pocket and connected to the IPG. Both incisions were closed in layers, and the skin was closed with a 4-0 monofilament poliglecaprone-25 suture. The patient tolerated the procedure without complication and was discharged in stable condition on postoperative day one.

At both 2- and 6-week follow-ups, the patient reported improvement in neuropathic pain and complete resolution of surgical pain. The SCS system was programmed to a proprietary stimulation-free paradigm with full parameters in Fig. 3.

The SF-36 questionnaire administered at 3 and 12 months revealed improvement in almost all questions, as shown in Table 1.

On VAS, pain decreased from a preoperative 80mm to a 3-month postoperative 46mm. On administration of the SF-36 at 3 months, general health was "much better," functional limitations were reduced or disappeared, emotional health improved, and negative effects on social activities were reduced (Table 1).At one year, VAS rating had increased to 71 mm. SF-36 answers were similar to 3-month responses, but with slightly worse self-reported health and functional limitations, specifically in lifting, but improved emotional

Table 1. SF-36 patient-reported outcomes by average percentage.

SF-36 Domain	Preoperative (mean %)	3 mo (mean %)	12 mo (mean %)
Physical Functioning	25	55	45
Role Limitations due to Physical Health	0	50	0
Role Limitations due to Emotional Problems	0	33	67
Energy/Fatigue	25	50	40
Emotional Well-Being	64	88	96
Social Functioning	63	50	75
Pain	10	32.5	27.5
General Health	70	95	70

Abbreviations: SF-36, 36-Item Short-Form Survey; mo, month.

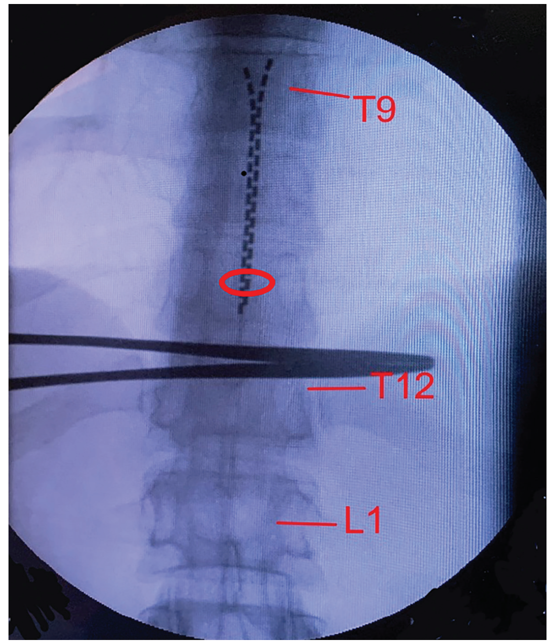

Fig. 1. Intraoperative anteroposterior fluoroscopic image of the placement of the SCS trial. Red circle represents site of optimal stimulation during trial. SCS, spinal cord stimulator.

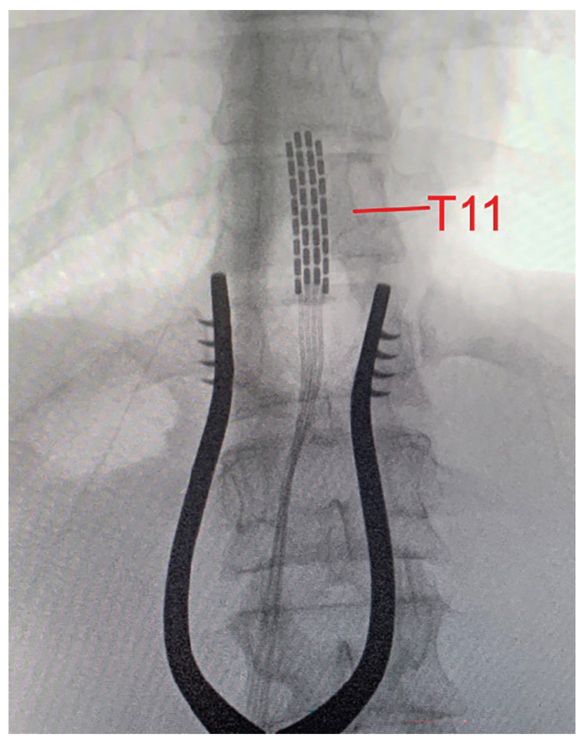

Fig. 2. Intraoperative anteroposterior fluoroscopic image of SCS paddle electrode. SCS, spinal cord stimulator.

health and social functioning. The patient was taking the same dose of acetaminophen (650 mg 2-3 times per day) and oxycodone (10 mg 2-3 times per day), as reported in Suppl. 1.

DISCUSSION

Chronic neuropathic pain in AMN is both common and debilitating, interfering with quality of life, activities of daily living, and psychosocial health. Indeed, previous studies (4) have reported chronic pain in almost half of patients with ALD, including 80% of women and 30% of men, the majority of whom had AMN. Reported pain descriptions include headaches and musculoskeletal pain, as well as a neuropathic "burning" (4). Pain described as burning and tingling occurs most commonly in the feet. Studies (15,16) employing electrophysiological and quantitative sensory testing have implicated small Aδ nerve fibers in ALD patients. AMN patients exhibit thermoalgesic hypoesthesia (15,16), as well as impaired windup to repetitive noxious stimulation, compared to nonmyeloneuropathic ALD patients, in keeping with a loss of small Aδ fibers carrying pain-related signals (4). Like large-fiber dysfunction, Aδ fiber dysfunction is more prevalent in the legs, consistent with a length-dependent neuropathy (4). Interestingly, some patients show small fiber dysfunction despite normal intraepidermal density, which may implicate the spinothalamic tracts (15).

Painful diabetic peripheral neuropathy shares several similarities with AMN. Clinical symptoms include hypoesthesia, paresthesia, and distal neuropathic pain,

A Right

Area Status	Stimulation: ON
Amplitude	2.3 mA
Pulse Width	320 µs
Rate	90 Hz
Cycle	Continuous
Min mA	0.0 mA
Max mA	4.8 mA
Ramp Up	3.0 sec

Port A	Port B	Port C	Port D	Case
		+ 15	+ 29	
	- 11	+ 39		
	+ 10	- 31	- 34	
	+ 7	- 24		

B Left

Area Status	Stimulation: ON
Amplitude	1.6 mA
Pulse Width	320 µs
Rate	90 Hz
Cycle	Continuous
Min mA	0.0 mA
Max mA	4.1 mA
Ramp Up	3.0 sec

Port A	Port B	Port C	Port D	Case
	+ 14	+ 16		
	+ 30	+ 34	- 7	
			+ 6	
	- 24	- 28		
	- 19	- 22		

Fig. 3. SCS parameters. SCS, spinal cord stimulation.

classically described as sharp or burning. Electrophysiological studies (17) demonstrate a length-dependent, predominantly sensory axonopathy, which also affects sympathetic and, later, motor nerves. Quantitative sensory testing has revealed a similar pattern to AMN, implicating small nerve fibers early in the disease (18). Several treatment options exist for diabetic neuropathy, including the medications gabapentin, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and antiepileptic drugs. Given the similarities between diabetic painful neuropathy and pain in AMN, these same medications have been trialed with variable efficacy (19). Beyond pharmacological intervention, treatments for diabetic painful neuropathy have extended to include neuromodulatory strategies, such as transcutaneous electrical nerve stimulation, intrathecal medication infusion, SCS, or dorsal root ganglion stimulation, with randomized controlled trials and meta-analyses proving strong evidence for efficacy (20-22).

The mechanism of SCS is poorly understood, but there is evidence to suggest that SCS has an inhibitory effect on the transmission of pain-related signals ascending from second-order neurons in the spinal dorsal horn. Early mechanistic theories that led to the development of SCS postulated that antidromic activation of larger sensory Aβ fibers activated inhibitory interneurons that close the “gate” to pain (23). Other theories and evidence (24) suggest that smaller unmyelinated C fibers carrying pain-related information may be stimulated. Additional theories regarding mechanisms of action include direct blockade of transmission along spinothalamic tracts (25), activation of descending supraspinal pain-modulating signals (26), vasodilatory effects mediated by increased release of substance P or calcitonin gene-related peptide (27), other alterations in neurotransmitter balance (e.g., serotonin or inhibitory gamma-aminobutyric acid) (28-30), direct activation of spinal inhibitory neurons to block pain transmission (31,32), or even higher-order alterations in pain perception in the brain (33,34). In any case, the mechanism of action of SCS in AMN may be similar to that in diabetic neuropathy, because the therapy acts centrally in the spinal cord, reducing the transmission of pain signals arising primarily from the peripheral nerves (35). The identical symptoms, patterns of electrophysiology, and quantitative sensory testing between diabetic neuropathy and AMN suggest that this application of electrical neuromodulation and the multifactorial mechanisms described above, now US Food and Drug Administration approved for painful diabetic neuropathy, should also be widely successful for AMN. Acting upon a converging or shared physiologic pain pathway is likely to produce similar clinical benefits between diabetic neuropathy and AMN, as demonstrated in our case presentation.

Therefore, we hypothesize that some patients with AMN may benefit from SCS, and possibly other neuromodulatory treatments. We advocate for patients with refractory neuropathic pain to be referred early to pain specialists for further workup and consideration of neuromodulatory strategies. A strength of this case report is the application of SCS in a genetically determined and electrodiagnostically confirmed cause of peripheral neuropathy (clear diagnosis), application of commercially approved SCS system and stimulation patterns (broad applicability), and quantifiable measures of pain and quality of life. However, limitations include the inherently subjective and fluctuating nature of pain assessment, including the discrepancy between the 12-month VAS and other SF-36 measurements. Without a randomized, prospective, blinded, sham-stimulation-controlled study, the placebo effect could be a major confounder. This remains a barrier even in larger randomized studies of SCS (36). Despite the patient's positive endorsement (Suppl. 1), strong conclusions may not be inferred from a single case report, and further data are needed.

CONCLUSIONS

We report an inaugural, successful treatment of medication-refractory neuropathic pain in AMN with thoracic SCS. Given the paucity of data, other experiences of treating neuropathic pain in AMN are needed. Electrophysiological and quantitative sensory testing evidence offers hope that AMN patients with neuropathic pain may benefit from neuromodulatory strategies used in diabetic neuropathy, including SCS.

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Suppl. 1. Patient correspondence to senior author detailing postoperative experience.

Patient Correspondence to Senior Author Detailing Postoperative Experience

I wanted to say thank you so much for helping me out a few weeks ago. I do not know what happened, but I had a pretty massive increase in the pain I deal with every day. I "think" there was a progression with the disease, but I do not know? I was doing really great managing and going about the "day to day" life. [Name redacted], who I met with, seemed to get the stimulator programmed to help with decreasing the pain that spiked during the week of [Date redacted].

I am doing better since I got to meet with [Name redacted]. My pain levels are not near what it was when I contacted you. I can't thank you enough for responding as quickly as you did. This stimulator really has made a major impact on my life. I can say it takes the pain down to a more manageable level for myself. I believe that I have a very high pain tolerance so I cannot imagine what life would be like right now if I did not have the surgery to have the stimulator installed. I am still moving around pretty good since [Date redacted]. I am just moving at a bit slower pace. I am sure I will get back out walking again next week. I try to do my best to stay walking every day, I have hope there will be some new technology to help myself further in the future dealing with neuropathy. Here are some details about what I was doing daily before that week in [Date redacted].

I had been doing really well. I was walking with my 4 wheel walker around my block in [Location redacted] about 2-3 times a week about a half a mile each time. As well as swimming to keep my muscles moving. When I do not move enough during the day, the muscles in my legs get VERY stiff and won't allow me to move very well. I have found that even though it hurts, to walk and move around. It's in my best interest for my future to keep moving no matter how much nerve pain I am in. I have to keep moving!

I am back in [Location redacted] now for a while to have my annual "checkups" with my doctors back home. Please let me know if there is anything I can do to help you with your research. As well, please keep me in mind if you hear of anything that could help me deal with this neuropathy pain I am dealing with. I am 100% sure that if we wouldn't have done this surgery, I would be in a wheel chair today. So, I cannot thank YOU enough. I will always keep fighting the battle, thank you Dr. [Name redacted]!