Behavioral therapy ceased cold water immersion dependence in a patient with familial erythromelalgia caused by *SCN9A* mutation

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INTRODUCTION

Erythromelalgia is characterized by a triad of symptoms, which include symmetrical burning sensations in the limbs, particularly in the soles and legs; erythema; and an elevated skin temperature. Prolonged burning sensations are often triggered by thermal stimulation, exercise, or infection, which patients may alleviate by immersing their legs in cold water. However, extended immersion often results in skin ulcers and refractory infections, creating a vicious cycle. Erythromelalgia is classified into familial (primary) and acquired (secondary) forms. A missense mutation of *SCN9A*, which encodes a voltage-gated sodium channel, is the known cause of the familial type of erythromelalgia.

CASE REPORT

A 19-year-old Japanese man experienced frequent pain in his soles from 4 years of age. At approximately 8 years, bilateral burning sensations developed in his legs during exercise and bathing, and he had to cool his feet with an electric fan even in winter. From about 12 years, he had been unable to sleep deeply because of the severe pain, and at 17 years, erythromelalgia was diagnosed based on genomic *SCN9A* mutation. Although he received various analgesic medications, including pregabalin, serotonin-noradrenaline reuptake inhibitors, anxiolytics, sedatives, and epidural blocks, his symptoms were not relieved by these treatments. To alleviate the burning sensations, he immersed his legs in ice cold water for extended periods. He visited our department because of the acute exacerbation of pain in his toes and suspected concomitant cellulitis. His father, monozygotic twin brother, and younger sister also experience similar symptoms but with differing severities.

At his initial visit to our department, inflamed reddening and edema were observed extending from the extensor surface of both lower extremities to both feet. His skin was whitely macerated from the ankle joints to the soles, and yellowish keratinous material, necrotic tissue, and multiple skin ulcers were observed. His toes, soles, and nails showed a thickened corneum, severe maceration, and cracking (Fig 1). His neurologic findings were normal.

Abnormal laboratory tests were as follows: white blood cell count, 19.1 $\times$ $10^3/\mu$L (neutrophils, 91.0%); creatine phosphokinase, 904 U/L; and C-reactive protein, 10.74 mg/dL. Bacterial cultures obtained from the leg ulcers showed the presence of *Staphylococcus aureus* 3+, *Klebsiella oxytoca* 3+, *Citrobacter freundii* 3+, *Delftia acidovorans* 2+, and *Aeromonas hydrophila/caviae* 1+. Direct sequencing using DNA extracted from peripheral blood lymphocytes confirmed a heterozygous mutation at c.406A>G, resulting in the amino acid substitution of p. I136V in *SCN9A*. Based on these analyses, a diagnosis of familial primary

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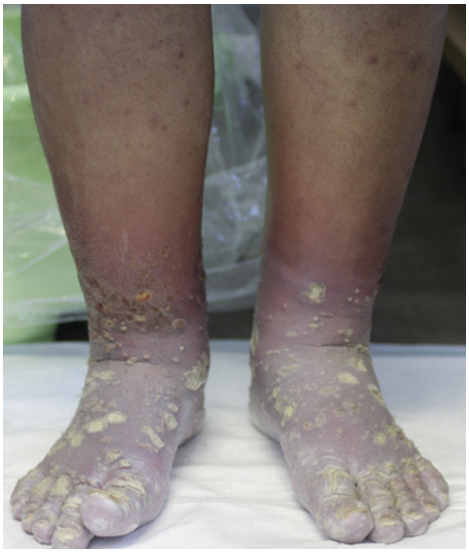

Fig 1. Clinical image taken at the patient's initial visit. Erythema and edema are visible on both legs. From the ankle joints to the feet, the patient's skin is markedly macerated, and multiple ulcers are present.

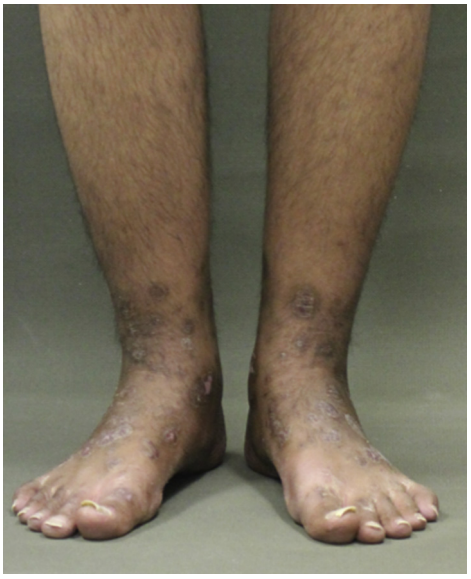

Fig 2. Clinical image taken at the time of discharge (hospital day 85). The redness and edema on his legs and feet have visibly improved. The leg ulcers have re-epithelized, and pigmentation alone remains.

erythromelalgia and secondary cellulitis was made. He was treated with intravenous cefazolin (3.0 g/d), oral minocycline (100-200 mg/d), and procyclin (120 μg/d). Oral pregabalin (75-300 mg/d), carbamazepine (200-400 mg/d), and flunitrazepam (2 mg/d) were also initiated to relieve his pain symptoms. However, the pain treatment was ineffective, and the patient continued to immerse his legs in cold water, even during hospitalization. Prolonged pain caused the patient to exhibit notably strange behaviors, such as constant shaking of his head and soliloquy; therefore, the antipsychotic drugs olanzapine (5 mg/d) and aripiprazole (3 mg/d) were administered by a psychiatrist. After 3 weeks of antibiotic therapy, swelling caused by cellulitis was reduced. The patient's legs were also wrapped in plastic bags during ice-cold water immersion, which gradually improved the skin maceration and ulcers.

Simultaneously, behavior therapy was administered by a psychiatrist and a clinical psychologist in whom they instructed the patient how to use breathing techniques to alleviate or prevent the pain. Moreover, he was clearly informed of the specific treatment goal of ceasing his dependence on cold water immersion and therapeutic strategies for discharge designed to help reduce his anxiety about the disease. We motivated him to adhere to the treatment plan, encouraged him to maintain a positive attitude, and urged him to change his habits and behaviors. As a result, he was weaned from his dependence on the cold water immersion treatment, enabling the leg ulcers to gradually re-epithelialize (Fig 2). The skin temperature of his foot was still markedly elevated when compared with the feet of healthy volunteers (Fig 3). Antipsychotic drugs had no effect and were discontinued. Currently, although he feels no urge to immerse his legs in cold water, he rates the burning sensation as approximately 4 on a visual analog scale compared to 10 on admission, which still limits his participation in outdoor activities and exercise.

DISCUSSION

SCN9A, the causative gene of familial erythromelalgia, encodes the α subunit of Nav1.7, the voltage-gated Na channel. Nav1.7 is preferentially expressed in the dorsal root ganglion and sympathetic ganglion neurons and their axons.[1] A heterozygous gain-of-function mutation in *SCN9A* prolongs hyperexcitation of the dorsal root ganglion neurons, which causes small-fiber neuropathy and results in burning sensations and long-lasting pain.[1] Twenty types of missense mutations have been identified in *SCN9A* causing familial primary erythromelalgia.[2] Homozygous or compound heterozygous loss-of-function mutations in *SCN9A* have been found to cause congenital insensitivity to pain.[3]

According to a review of the medical records of 168 patients with erythromelalgia, treatments included 84 different types of drugs, epidural blocks, and sympathetic neurectomy; however, all were

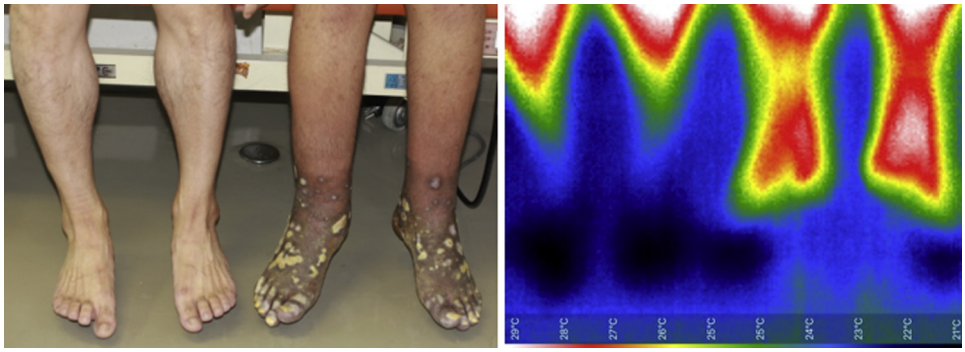

Fig 3. Thermographic images. These images show the temporal changes in the surface temperature of the legs at room temperature (25°C) after both legs were immersed in a bucket of water at 20°C for 20 minutes. The images on the left side show the legs of a healthy control, whereas those on the right show the patient's legs. Ten minutes after immersion, the skin temperature of the legs began to increase.

insufficient to alleviate the symptoms. Burning sensations were relieved by cooling in 67% of patients.[4] In this study, our patient could not stop immersing his legs in ice cold water because of the relief it provided from persistent burning sensations, which then resulted in skin maceration, persistent recalcitrant ulcers, and cellulitis. The sensation of heat associated with cellulitis caused by inflammation further exacerbated the pain postimmersion. Consequently, the patient immersed his legs in cold water more frequently to address the pain. In addition to antibiotic therapy for cellulitis, approaches used to avoid skin maceration included bathing his feet in isotonic sterile cold saline solution instead of tap water and wrapping his legs in plastic bags while cooling them in the saline. Furthermore, using behavioral therapy, he was successfully weaned from his dependence on cold water immersion despite the persistence of the burning sensations that adversely affected his daily life. The development of a fundamental treatment for this syndrome is warranted.

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