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A case of inherited erythromelalgia

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SUMMARY

Background A 15-year-old boy presented with recurrent episodes of erythema and burning pain in the distal extremities, which he had experienced since early childhood. The episodes were triggered by heat or exertion. His medical history revealed an extensive six-generation family history of similar symptoms.

Investigations Neurological examination, MRI brain scan, electromyography, skin biopsy, laboratory blood testing, and DNA analysis.

Diagnosis Juvenile onset primary erythromelalgia.

Management Genetic counseling, and symptomatic management of neuropathic pain.

KEYWORDS erythromelalgia, mutation, neuropathic pain, neuropathy, sodium channel

CME

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THE CASE

A 15-year-old boy presented to his primary care physician with a lifelong history of episodic erythema, mild swelling, and painful burning sensations in the distal extremities that affected his hands, feet (Figure 1), ears, and at times his face. Over the years, the episodes had increased in frequency and severity, and he now experiences multiple daily episodes of burning, stinging and throbbing pain, each lasting minutes to hours.

The episodes were triggered by exertion or an increase in the ambient temperature or humidity, and the symptoms were relieved by cooling the affected extremities. The patient preferred to wear open-toed sandals or to be barefoot, and he slept uncovered and attempted to keep his environment cool. He would relieve his symptoms by placing his extremities in front of a cool fan, and would sometimes resort to submerging his hands and feet in ice water—despite being counseled against this. Physical exertion—even brisk walking or running short distances—provoked his symptoms, and he therefore avoided physical activity. His episodes could be triggered by consuming small amounts of alcohol or caffeine, large amounts of sugar, and occasionally melon. His family history revealed that, over a period of six generations, many of his relatives had experienced similar symptoms (Figure 2).

The patient reported no symptoms of orthostatic hypotension, and no gastrointestinal problems or perspiration abnormalities. He had experienced hypertension in his early teenage years, but this had not required treatment.

Physical examination revealed diffuse blanching erythema over the patient's feet extending to his ankles, and healed ulcerations. Neurological examination revealed a mild subjective decrease in pin-prick sensation to the ankles bilaterally, with normal vibration and soft touch. Deep tendon

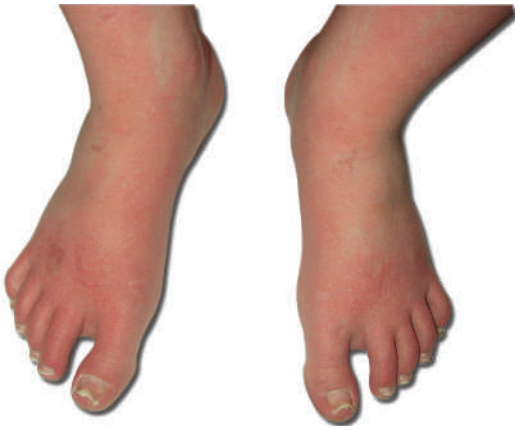

Figure 1 Photograph of the patient's feet showing erythema.

reflexes were reduced at the ankles but were normal and symmetrical elsewhere. Neurological examination was otherwise normal.

An evaluation of the patient 2 years previously had included an MRI brain scan, skin biopsy, and sensory and motor nerve conduction studies of the lower extremities, all of which were normal. Complete blood count, platelet count, and antinuclear antibodies were normal. Four other family members (two male, two female) with the same symptom complex were tested for Fabry's disease—an X-linked disorder that can cause burning pain in the extremities—with negative results.[1] After his evaluation, the patient underwent genetic testing and was found to have a mutation (F1449V) in the Nav1.7 sodium channel, which was also present in all affected family members who were tested.[2]

On the basis of the patient's family history and negative work-up for an underlying cause, he was given a clinical diagnosis of juvenile onset primary erythromelalgia. Management of his pain involved counseling regarding the maintenance of a cool environment, how to safely cool his lower extremities, and the avoidance of triggers. To date he has not been given any trials of symptomatic pharmacological treatment.

DISCUSSION OF DIAGNOSIS

Erythromelalgia (sometimes called erythermalgia) is characterized by episodes of burning pain, skin redness, and swelling of the extremities, ears and face. The pain can be severe, and is sometimes described as "searing" or "like hot lava". The pain is triggered by physical exertion or ambient heat, and is relieved by cooling the extremities. Other less consistently reported precipitating factors include wearing socks or tight shoes, consuming alcohol or spicy foods, and use of vasodilating agents. The episodes can be disabling, and can interfere with sleep and limit activity—especially in warm weather. Affected individuals prefer air-conditioned environments, and will sometimes move to a cooler climate. As in the present case, involvement of the lower extremities is more common than upper extremity involvement, and the pattern of symptoms is typically symmetrical.

As shown in Table 1, erythromelalgia can be either primary or secondary. In a case series of 87 patients with erythromelalgia, Kalgaard *et al.*[3] reported that approximately two-thirds of the cases were primary and approximately one-third were secondary, occurring in the context of hematological disease such as polycythemia vera, secondary polycythemia or leukemia, metabolic disease such as diabetes, connective tissue disease such as systemic lupus erythematosus or rheumatoid arthritis, musculoskeletal disease such as sciatica, or neoplastic disease, and with a 2:1 predominance of females.

The symptoms in erythromelalgia have been suggested to arise from a neuropathic etiology, and might involve increased local cellular metabolism.[4] Another suggestion is that the symptoms result from microvascular arteriovenous shunting, possibly caused by impaired autonomic regulation.[5] In non-inherited erythromelalgia, however, the precise contributions of vascular, neuropathic and metabolic changes are still speculative.

Drenth *et al.*[6] provided an important insight into the pathogenesis of inherited erythromelalgia when they localized the disease locus to chromosome 2 (2q31–32). Researchers subsequently identified missense mutations in the *SCN9A* gene—which encodes the Nav1.7 sodium channel—within this region in two families with inherited erythromelalgia.[7] In 2004, Cummins *et al.*[8] showed that these mutations, I848T and L858H, shift the activation voltage dependence of Nav1.7 in a hyperpolarizing direction thus facilitating activation of the channel, slow deactivation of the channel so that it remains open for longer, and increase the response of the channel to small slow depolarizations such as generator potentials. Each of these changes should increase nociceptor excitability. In 2005, Dib-Hajj and colleagues described the F1449V mutation,

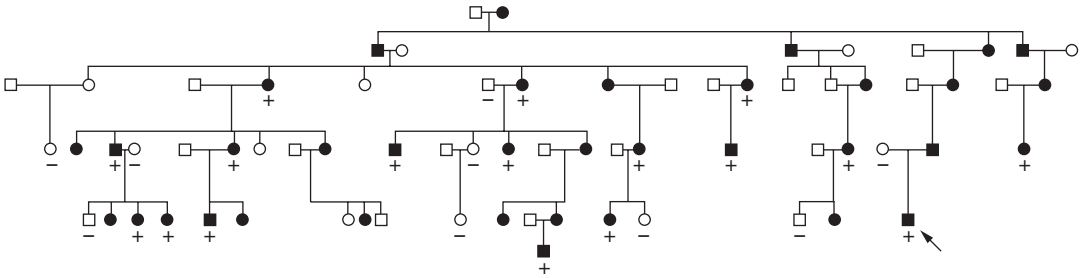

Figure 2 The patient's family pedigree. Circles denote females; squares denote males. The proband is shown by an arrow. Blackened symbols indicate subjects affected with erythromelalgia. + denotes subjects heterozygous for the F1449V mutation; – denotes subjects without the mutation. Permission obtained from Oxford University Press © Dib-Hajj *et al.* (2005) *Brain* **128:** 1847–1854.

which also shifts the voltage dependence of activation in a hyperpolarizing direction, and depolarizes steady-state inactivation so that more channels are available to open at any one time.[2] Additional erythromelalgia Nav1.7 mutations (Figure 3) and several polymorphisms have been identified since the discovery of these initial mutations.[9]

The Nav1.7 channel is selectively expressed in the nervous system within dorsal root ganglion (DRG) and sympathetic ganglion neurons. When mutant F1449V and L858H Nav1.7 channels are expressed within nociceptive DRG neurons, the action potential threshold is reduced and the cells fire at a higher than normal frequency (Figure 4). The hyperexcitability produced by these *SCN9A* mutations in DRG neurons appears to account, at least in part, for the pain experienced by patients with inherited erythromelalgia.[2,10] Interestingly, Nav1.7 also appears to mediate acquired inflammatory pain.[11,12]

By contrast, within sympathetic ganglion neurons, expression of the L858H erythromelalgia mutation has been shown to have the opposite effect to that in DRG neurons, rendering the cells hypoexcitable.[10] This mechanism appears to contribute to the impaired cutaneous sympathetic vasomotor control in patients with this mutation. The opposing functional effects of the L858H erythromelalgia mutation in DRG neurons and sympathetic neurons are the result of the different ensembles of channels in these two types of neurons and the depolarization produced by the mutation: in addition to expressing Nav1.7, DRG neurons express the sensory-neuron-specific Nav1.8 sodium channel, which is not present in sympathetic ganglion neurons. The sodium channels within sympathetic neurons are inactivated by the depolarization imposed by the L858H Nav1.7 mutant channels, so that excitability is decreased in these cells. The Nav1.8 channel, however, is relatively resistant to inactivation by depolarization, and depolarization renders DRG neurons hyperexcitable by bringing their resting potential closer to the threshold for activation of Nav1.8 channels.[10]

Nav1.7-specific sodium channel blockers would be expected to reduce nociceptor hyperexcitability in erythromelalgia, but might also have unwanted adverse effects on sympathetic neurons. The selective expression of Nav1.8 within DRG neurons suggests that the use of Nav1.8-specific blockers might ameliorate the hyperexcitability of these sensory neurons without inducing autonomic side effects. At present, however, only nonspecific sodium channel blockers are available.

DIFFERENTIAL DIAGNOSIS

A number of conditions can display symptoms similar to those seen with erythromelalgia. Complex regional pain syndrome (CRPS) can present with burning neuropathic pain associated with hot swollen limbs, but unlike erythromelalgia, in which symptoms are distally symmetrical, CRPS symptoms are often unilateral and can be proximal or distal. In addition, episodes that are triggered by heat and relieved by cool temperatures are less common in CRPS than in erythromelalgia.

Small-fiber neuropathies can also produce neuropathic pain and autonomic skin changes, and typically occur in a distal symmetrical pattern. The symptoms of most small-fiber neuropathies, however, tend to be less episodic

Table 1 Classification and causes of erythromelalgia with relevant diagnostic tests.

Erythromelalgia classification and cause	Diagnostic test
Primary erythromelalgia	
Juvenile onset familial	Assess for Nav1.7 mutations
Juvenile onset sporadic	Assess for Nav1.7 mutations
Adult onset familial	Assess for Nav1.7 mutations?
Adult onset sporadic	None
Secondary erythromelalgia	
Myeloproliferative disease	Complete blood count, platelet count, response to aspirin
Cholesterol emboli, hypercholesterolemia	Blood lipid evaluation, magnetic resonance angiography, angiography as indicated
Autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, vasculitis, idiopathic thrombocytopenic purpura)	Antinuclear antibodies (ANA), erythrocyte sedimentation rate, rheumatoid factor, C-reactive protein, antineutrophil cytoplasmic antibodies (ANCA), complete blood count
Diabetic neuropathy	Fasting glucose, 2 h oral glucose tolerance test
Fabry's disease	α-Galactosidase A enzyme assay in males; DNA testing is more reliable in females
Small fiber neuropathy	Nerve conduction study, skin biopsy
Inorganic mercury poisoning	Serum mercury level
Mushroom poisoning	None
Paraneoplastic syndrome	CT scanning for primary neoplasm
Medications: verapamil, nifedipine, ciclosporin, bromocriptine, ticlopidine	NA
HIV-1-positive/AIDS	HIV-1 screening
Sciatica	Neurological examination, electromyography, neuroimaging

Abbreviation: NA, not applicable.

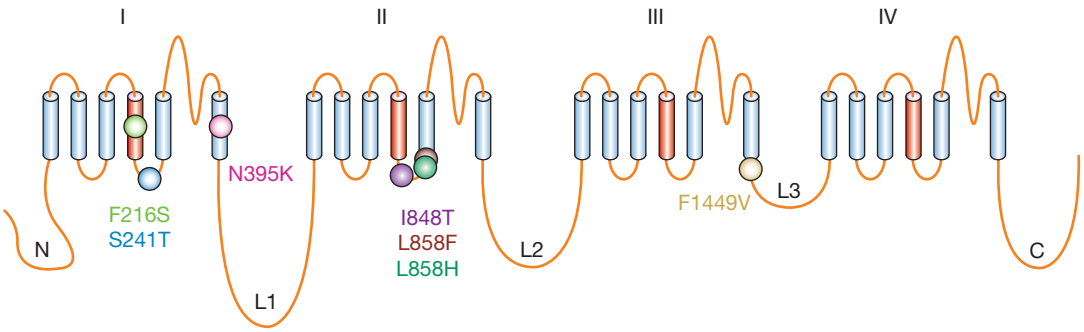

Figure 3 Schematic diagram of a sodium channel showing the locations of the known mutations in Nav1.7 in erythromelalgia. The S4 transmembrane segments, which serve as a voltage sensor, are indicated in red. Note the location of the F1449V mutation in the present patient's family in L3, which carries the inactivation gate for sodium channels.

than those of erythromelalgia, and they are not exquisitely temperature-sensitive. Patients with erythromelalgia can display damage to small nerve fibers, but other common causes of small fiber neuropathy such as diabetes mellitus should also be ruled out in such patients.

When the cardinal symptoms of erythromelalgia are present (i.e. episodic burning pain, and symmetrical redness of the distal extremities that is triggered by heat and relieved by cooling) a diagnosis of erythromelalgia should be considered. Table 1 lists the causes of secondary

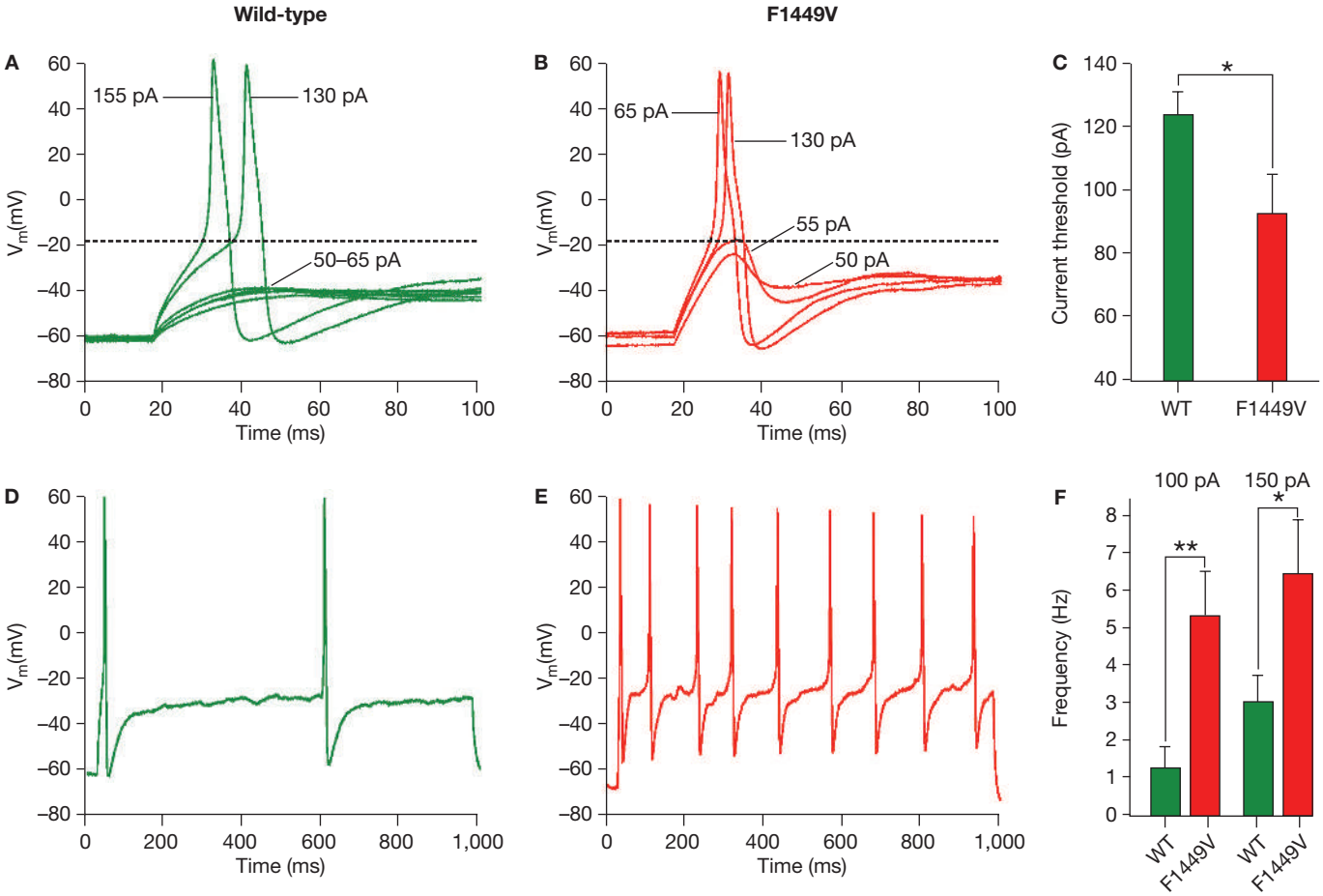

Figure 4 The effect of the F1449V mutation on the firing properties of dorsal root ganglion neurons. The current threshold for generation of single action potentials is reduced (**A**,**B**,**C**), and the frequency of firing in response to graded stimuli is increased (**D**,**E**,**F**) as a result of expression of mutant channels. Permission obtained from Oxford University Press © Dib-Hajj *et al.* (2005) *Brain* **128:** 1847–1854. Abbreviations: V_m, membrane potential; WT, wild-type. **P* <0.05; ***P* <0.01.

erythromelalgia that should be excluded before arriving at a diagnosis of primary erythromelalgia. The signs and symptoms of secondary erythromelalgia can also precede, and herald, the clinical onset of the causal disorder.

Management of secondary erythromelalgia can require specific treatment for the underlying cause. In cases of erythromelalgia that are secondary to hematological or myeloproliferative disease, symptoms can respond dramatically to treatment with aspirin, with patients experiencing several days of pain relief from a single dose. Primary erythromelalgia, by contrast, does not respond to aspirin. Patients in whom the pain is responsive to aspirin should be periodically monitored for myeloproliferative disease.

Primary erythromelalgia can be classified as either familial (inherited as an autosomal dominant trait) or sporadic. Familial and sporadic erythromelalgia can also both be further classified as either juvenile (onset before the age of 20 years, and frequently before the age of 10 years) or adult onset. Familial juvenile onset erythromelalgia, as in the present patient, is in some families associated with mutations to the Nav1.7 sodium channel. Clinical genetic testing for the condition, however, is not yet available. There is also to date no confirmatory laboratory test. Some sporadic juvenile cases are the result of *de novo* founder mutations.[13] Sporadic juvenile cases and familial cases (either juvenile or adult) might benefit from genetic screening for Nav1.7 mutations, although it should be noted that to date a Nav1.7 mutation has not been found in families with adult onset erythromelalgia.

Competing interests
The authors declared they have no competing interests.

TREATMENT AND MANAGEMENT

Genetic counseling and counseling on the chronic nature of the disease are essential for the management of primary erythromelalgia.[14] Patients should be advised to avoid triggers—especially heat and over-exertion, but also possible food triggers such as alcohol and spicy foods. A diary may help to identify food triggers. Although maintenance of a cool environment is essential, patients should be counseled against the use of ice or icy water baths to cool painful extremities, because this can lead to skin necrosis and ulceration. Use of a fan to cool the skin is a safer option.

Most of the available clinical evidence regarding treatment of erythromelalgia comes from anecdotal studies or small case series in which the majority of the reported patients had either secondary or sporadic adult onset erythromelalgia. Several case studies, such as that reported by Nathan *et al.*,[15] have described the efficacy of intravenous lidocaine (an acute, intensive-care-unit-based therapy) and oral mexiletine, both of which are powerful sodium channel blockers. One double-blind, placebo-controlled trial reported reduced microvascular arteriovenous shunting and symptomatic relief with the use of the prostaglandin E_1 analog misoprostol,[16] although this study included both patients with primary erythromelalgia and patients with secondary erythromelalgia, and there was no subgroup analysis. Improvement (although only partial in many cases) with gabapentin, lidocaine patches, venlafaxine, clonidine, ciclosporin, tricyclic antidepressants, calcium channel antagonists, oral magnesium, sympathetic blocks, and bilateral thalamic stimulation have also all been reported. A review by Davis and Rooke[17] summarizes the treatment approaches that have been used to date, although it does not discriminate between primary and secondary erythromelalgia.

CONCLUSION

This patient represents a typical case of juvenile onset primary familial erythromelalgia, a rare disorder that has been shown in some patients to be caused by a mutation to the *SCN9A* gene. Diagnosis of this condition is important, because proper counseling can enable the patient to minimize the severity and frequency of the painful episodes. Symptoms can be debilitating and can significantly impair quality of life, and they tend to be refractory to treatment. It is important to exclude treatable, secondary causes, a process that should include a thorough evaluation of the patient's medications. Although some treatment options—including sodium channel blocking agents and prostaglandin analogs—have shown promise, further research is needed to develop more-effective treatments for this condition.

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