Hot feet: Erythromelalgia and related disorders.

By Robert B. Layzer, MD

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From the Department of Neurology, University of California-San Francisco, San Francisco, CA.

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Address correspondence to Dr Robert B. Layzer, Box 0114, University of California-San Francisco, San Francisco, CA 9414:3. Tel: 41.6-476-9206; fax: 415-476-3428; rlayzer@ix.netcom.com

Abstract

Erythromelalgia is an extraordinary pain syndrome first described by S. Weir Mitchell in 1878. Episodes of severe burning pain in the distal limbs, accompanied by striking redness and warmth of the skin, are precipitated by heat or activity and can be terminated only by cooling the affected part. Primary erythromelalgia is a sporadic or autosomal-dominant hereditary disorder whose symptoms begin in childhood. Secondary erythromelalgia occurs in association with thrombocythemia, collagen-vascular diseases, diabetes mellitus, peripheral neuropathy, and use of certain drugs. Aspirin is effective for patients with thrombocythemia, but most other cases are very resistant to treatment. The pathogenesis of erythromelalgia has remained puzzling, especially the peculiar switch-like manner in which symptoms are turned on by heat and turned off by cold. Following Ochoa's description of the ABC (angry backfiring C nociceptors) syndrome, it seems plausible to regard erythromelalgia as a problem of sensitized skin polymodal C-fiber receptors. C-fiber threshold to activation by heat would be lowered to 32°C to 36°C; activated C fibers would cause vasodilation via axon reflexes with redness, heat, and swelling. Cooling would bring the nociceptors below threshold. Secondary erythromelalgia may result from Immoral factors released from platelets or ischemic tissues or from C-fiber injury in some cases of neuropathy, whereas primary erythromelalgia could be due to a mutation of the capsaicin receptor. (J Child Neurol 2001;16:199-202).

In 1878, S. Weir Mitchell, the great American neurologist who first described causalgia, reported an extraordinary new pain syndrome that he named erythromelalgia, from the Greek words erythros (red), melos (extremity), and algos (pain).[1] A preliminary report had been published in 1872. Mitchell's 1878 article, "On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confused," described a heterogeneous group of patients who suffered from episodes of burning pain

in the distal limbs, brought on or aggravated by standing, walking, or heat and relieved by the horizontal position and by cold. During attacks, the painful areas were red, hot, and throbbing, with engorged veins.

Mitchell's description has held true to this day. Erythromelalgia is one of the most unpleasant of all pain syndromes. Patients must often keep their feet uncovered during the day, and they sleep with their feet outside of the bedclothes. Their activities are restricted because pain and redness are provoked by exercise such as standing or walking. Often, they carry a pail of ice water with them, in which they plunge their feet when pain intensifies. Prolonged soaking in ice water may lead to cold injury of the skin, ulceration, and even amputation.

Classification

By the middle of the twentieth century, it was apparent that erythromelalgia occurs in several different clinical settings. Various authors proposed somewhat contradictory clinical classifications,[2] even suggesting that the naive be changed to *erythermalgia*.[3] I prefer to retain Weir Mitchell's original name, and Table 1 offers a simple classification, which fits the clinical data reasonably well.

Primary erythromelalgia is unassociated with any known underlying cause and usually becomes symptomatic in childhood or adolescence. Some cases are familial, with an autosomal-dominant pattern of inheritance.[4] The symptoms are usually confined to the feet and legs, sparing the toes. Patients remain symptomatic throughout life, although the severity fluctuates. There is no consistently effective treatment.

Essential thrombocythemia is the most important cause of secondary erythromelalgia. This myeloproliferative disorder is characterized by overproduction and abnormal function of platelets, which have an increased tendency to aggregate. Erythromelalgia also occurs in polycythemia vera but not in reactive thrombocytosis, where platelet function is normal. The symptoms of erythromelalgia may precede the diagnosis of a myeloproliferative disorder by several years. In these patients, the symptoms of erythromelalgia occur in a patchy, localized distribution in the distal upper and lower extremities, including the fingers and toes.[5] Livedo reticularis, petechiae, ecchymoses, and purpura may also be present. In one series, 26% of patients with essential thrombocythemia had erythromelalgia, which was usually the initial complaint.[6]

Laboratory studies have shown that thrombocythemic erythromelalgia is associated with intravascular platelet aggregation, but thrombin generation does not occur.[7] Skin biopsies show endothelial cell damage and microvascular occlusions.[7]

Table 1. Classification of Erythromelalgia

1.	Primary erythromelalgia
	a. Sporadic
	b. Familial
2.	Secondary erythromelalgia
	a. Thrombocythemia
	b. Collagen-vascular diseases
	c. Drugs
	d. Diabetes mellitus
	e. Neuropathies

A striking and diagnostic feature is the fact that administration of a single dose of

aspirin, sometimes as little as 50 mg, provides marked relief in less than an hour, and the relief may last for several days.[5] Other antiplatelet agents such as dazoxiben, ticlopidine, and dipyridamole are ineffective, as are heparin and warfarin. This suggests that the cyclooxygenase-inhibiting action of aspirin is responsible for its beneficial effect. Reducing the platelet count by pheresis or chemotherapy is also helpful for the long-term control of thrombocythemia. Untreated patients may develop ischemic ulcers, gangrene, or strokes.

Less commonly, erythromelalgia is associated with collagen-vascular diseases, vasculitis, diabetes mellitus, frostbite, and other conditions that may cause microvascular occlusive disease in the distal limbs.[8] These patients do not usually respond to cyclooxygenase-inhibiting drugs. However, a patient with thrombotic thrombocytopenic purpura developed typical erythromelalgia, which responded easily to aspirin, suggesting that platelet aggregation rather than microvascular occlusion was the inciting factor.[9] Certain drugs, especially calcium-channel blockers, pergolide, and bromocriptine, have precipitated the syndrome[10]; symptoms resolve on discontinuing the drug. Peripheral neuropathies and nerve injuries have been known to cause erythromelalgia,[8] although this is a rare complication. More often, warmth and redness of the feet in a painful polyneuropathy result from damage to sympathetic nerves; pain and redness are constant rather than episodic and are not triggered by heat. The same distinctions apply to patients with acral arterial insufficiency or reflex sympathetic dystrophy, which could be confused with erythromelalgia.

Pathophysiology

In 1933, the distinguished cardiovascular physiologist Thomas Lewis studied several patients in an attempt to clarify the pathophysiology of erythromelalgia.[11] He was unable to explain the connection between the pain and the vasodilation, but he drew several important conclusions, which have held true to this day: (1) the reddening of the skin results from a "relatively toneless condition of the minute cutaneous vessels"; (2) burning pain is induced whenever the temperature of the skin rises to a certain level, a temperature that normally would be insufficient to produce pain; (3) there is no evidence of unusual discharge or inhibition of sympathetic impulses; and (4) the tissues are in a "susceptible state" that makes blood vessels more "disposed to dilate to vasomotor and other influences."

A few years later, Smith and Allen[3] made detailed clinical observations of the relationship between local skin temperature and the occurrence of pain and redness. They found that, in susceptible areas of the distal lower extremities, attacks were triggered by skin temperatures between 32°C and 36°C. With temperatures higher than this, the distress persisted; when skin temperature was lowered below the critical point for that patient, the pain and redness gradually subsided. These observations confirmed the existence of a switch-like phenomenon in erythromelalgia: warming the skin triggers a state of pain and vasodilation that can be switched off only by cooling the skin.

Many recent authors have suggested that microvascular damage, as seen in patients

with thrombocythemia or collagen-vascular diseases, is somehow involved in the pathogenesis of erythromelalgia. However, the fact that aspirin relieves symptoms so promptly in thrombocythemia suggests that chemicals released from aggregating platelets, rather than microvascular occlusion, are the trigger in that condition. Furthermore, patients with erythromelalgia secondary to peripheral neuropathy do not have microvascular damage.

Given these considerations, three basic questions must be addressed when attempting to clarify the pathophysiology of erythromelalgia:

1. Is there a common mechanism in the different varieties of erythromelalgia?
2. What is the connection between the key symptoms of pain, vasodilation, and heat sensitivity?
3. What explains the switch-like behavior, whereby symptoms are triggered by temperatures above a certain threshold and abolished by temperatures below that threshold?

I believe that there is a common mechanism that links the different varieties of erythromelalgia and explains the interconnected symptoms and the switch-like behavior. It
is the axon reflex, first described (ironically enough) by Thomas Lewis and recently invoked by Ochoa and colleagues to explain pain and skin vasodilation in patients with sensitized C fibers.[12]

Ochoa's ABC Syndrome

Under this designation (angry backfiring C nociceptors), Ochoa described four patients with extremity pain induced by low-level mechanical and thermal stimuli, sometimes associated with spontaneous pain.[12] Decreasing the skin temperature abolished both spontaneous and stimulus evoked pain, and raising the skin temperature aggravated the symptoms. When pain occurred, it was accompanied by cutaneous vasodilation in a pattern precisely corresponding to the hyperalgesia. One patient had a patch of sensitive skin on the back of one hand, resulting from an old episode of photo-dermatitis. Another patient (Ochoa himself) had a plantar neuroma, another had polyneuropathy due to vitamin B-12 deficiency, and a fourth had acute diabetic small fiber polyneuropathy.

Investigations of the first patient with nerve blocks and microneurography showed that the pain was mediated only by C fibers, that C-polymodal nociceptors had abnormally low thresholds, and that activated C fibers produced prolonged after-discharges.[13] The authors postulated that sensitization of polymodal C-fiber nociceptors was the basic abnormality in the ABC syndrome and that C-fiber axon reflexes not only caused vasodilation (the flare in Lewis's triple response) but also boosted the sensitization of adjacent nociceptors. Skin warming due to hyperemia also activated the sensitized nociceptors, in a vicious circle.

C Nociceptors And The Axon Reflex

Table 2. Sensitizers and Activators of C Nociceptors

Acid pH	Prostaglandins
K^+ ions	Leukotrienes
Adenosine triphosphate	Nerve growth factor
Serotonin	Cytokines
Adenosine	Substance P
Bradykinin	

Polymodal nociceptors on the terminals of C pain fibers respond to heat, pressure, and a variety of chemical stimuli.[14] The many different chemical transducers that have been identified (Table 2) act as either sensitizers, stimulators, or both. The threshold for activation by heat is around 42 to 45°C, above which the firing rate of C fibers and the intensity of pain rise exponentially. Recently, Julius and coworkers[15] have shown that the neural receptor for capsaicin (the active ingredient of hot chili peppers) is a heat-activated nonselective cation channel, which is probably the heat transducer in C fibers.

When histamine or capsaicin is injected into the skin, it produces pain, a local wheal, and a slowly spreading surrounding flare or redness.[16] As Lewis showed in 1927, the latter is caused by dilation of arterioles and capillaries, produced by retrograde impulses in sensory nerve branches that innervate blood vessels at a considerable distance from the main nerve.[16] This phenomenon is known as an axon reflex. Local anesthetic nerve block in the skin within the potential flare area prevents the spread of the flare beyond the block. Secondary hyperalgesia also develops in the flare region, probably because of nociceptor-sensitizing chemicals released from dilated capillaries (eg, bradykinin) and from nerve endings (eg, substance P).

Mechanism of Erythromelalgia

The above properties of C fibers offer a plausible explanation of several of the clinical features of erythromelalgia. In particular, as diagrammed in Figure 1, a state of sensitization of polymodal C nociceptors could lower the temperature threshold for activation of C fibers from a normal value of 42°C to 45°C to the threshold of 32°C to 36°C encountered in patients. Skin temperatures above threshold would trigger both burning pain (from activated C fibers) and vasodilation (via the axon reflex mechanism). Vasodilation would keep the skin temperature elevated and sustain the symptoms until external cooling is introduced.

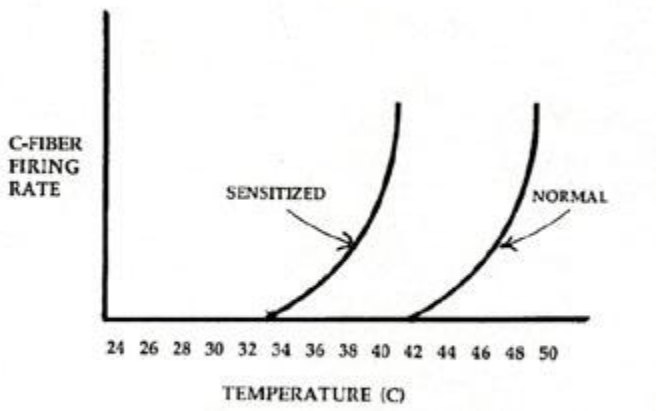

Figure 1. Proposed trigger mechanism of erythromelalgia. The threshold for activation of C fibers is shifted to a lower temperature, close to normal skin temperature.

The reasons for sensitization of C nociceptors would vary with the etiology. In thrombocythemia, aggregation of abnormal platelets may release serotonin and other chemical sensitizers and activators. Aspirin would prevent this process. In microangiopathies due to collagen-vascular disease, diabetes mellitus, or frostbite, tissue

ischemia may generate chemical transducers, including hydrogen ions, which are among the most potent sensitizers of C nociceptors. In most cases of small-fiber sensory polyneuropathy, damage to C fibers would prevent the operation of the mechanisms outlined above. In rare cases, however, C nociceptor sensitization may precede nerve degeneration, causing erythromelalgia. Finally, primary and familial erythromelalgia could be a genetic disorder of the C nociceptor-perhaps even of the capsaicin receptor itself.

Treatment

Erythromelalgia is very resistant to treatment. Aspirin and other cyclooxygenase inhibitors work in platelet-induced cases, and drug-induced cases respond to removal of the offending agent; otherwise, no medication or regimen has been consistently effective. The symptoms of erythromelalgia often wax and wane, and severe exacerbations may resolve if the patient can be nursed through the crisis. In two recent pediatric cases, long-term epidural infusion of morphine and bupivacaine was employed successfully.[18] As mentioned earlier, tissue damage from repeated icing of the skin may exacerbate the problem, and prolonged epidural anesthesia may help to wean the patient away from cold therapy.

Recently, high-dose topical capsaicin cream has been used in several unpublished cases, following a protocol described by Robbins et al.[18] The rationale is based on the fact that huge doses of capsaicin actually damage C fibers, which may take months to regenerate. If the present hypothesis is correct, this rationale is plausible. The results are said to be promising, but controlled studies have not been done.

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