Practical Pain Management

Letters to the Editor

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Trial & Error for Treating Erythromelalgia

Dear PPM,

My friend has erythromelalgia and has been informed it is incurable. Her neurologist hasn't given up, but told her she has the most pain of any of his patients and it would be a "miracle" for her to become pain-free. With such a bleak outcome, she had to go on disability, which with no relief, will result in her early retirement.

During her year of disability, it would be helpful to have a medical list of modalities she could try. It's an opportune time without the pressure of keeping her feet in ice water during her waking hours and fumbling with ice packs while trying to sleep. If there was a checklist, she could try each remedy in turn with the hope of achieving a significant reduction in pain in order to go back to work. She has a high tolerance for pain, so some level of pain would be manageable but not the extreme pain she is suffering with now.

Could you provide a helpful checklist? A more educated patient is always helpful for the doctor. A plan can be visualized and an orderly trial and error begun. If all treatments fail, then a patient like my friend will know that everything has been attempted.

–P. Cumming

Dear Mr. Cumming,

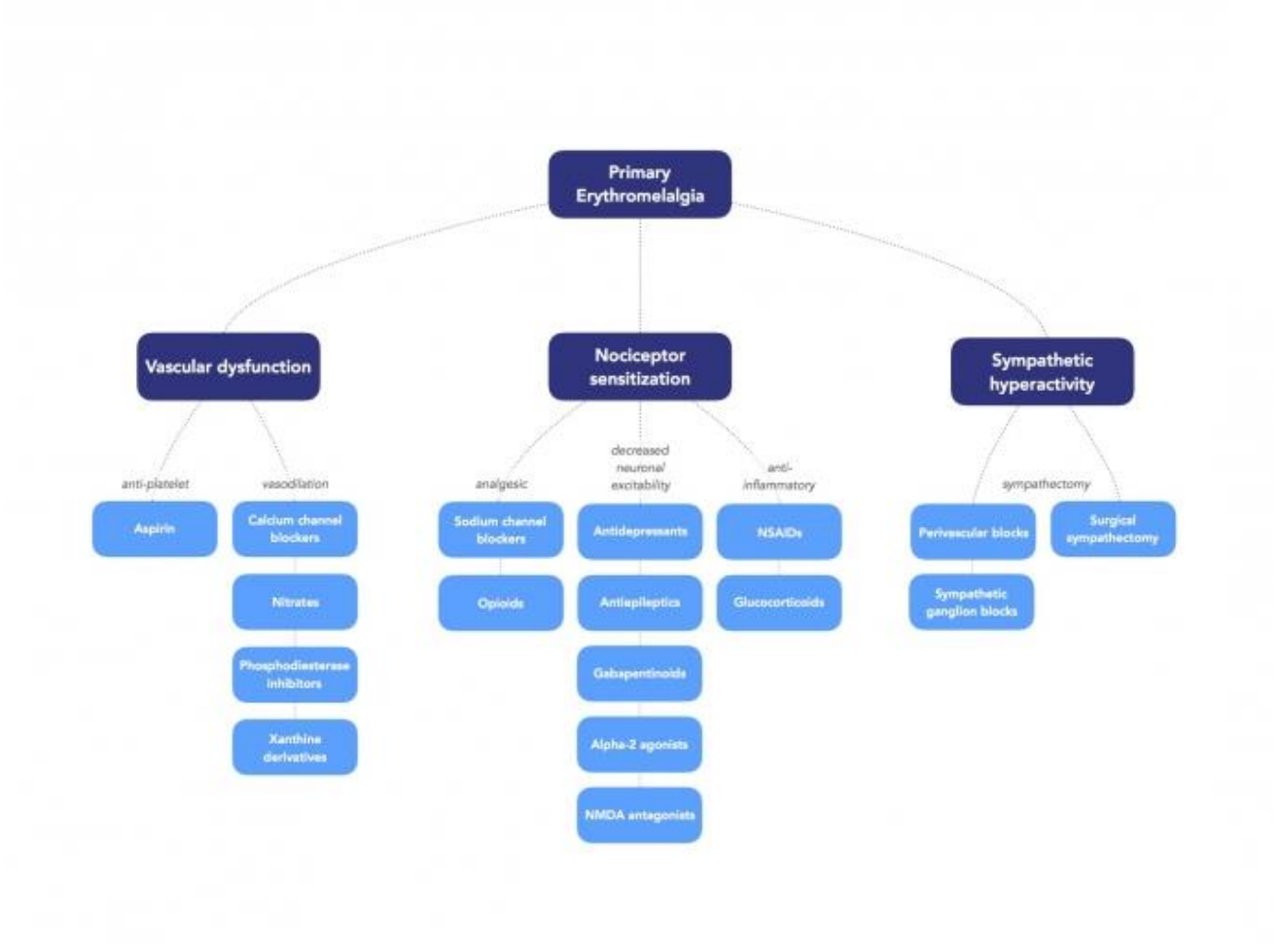
Erythromelalgia (EM) is a rare neurovascular disorder characterized by swelling, erythema, and burning in the extremities. The first step in the management of EM is to ensure that all secondary causes have been ruled out. The most common causes of secondary EM include hematologic disorders involving thrombocytosis, certain immunological disorders, and vasoactive medications.[1]

Once a patient has been thoroughly tested, an EM diagnosis may be made clinically. based on the observation of burning and erythema in the extremities, relieved by cold and worsened by heat.

An overall understanding of the pathophysiology of a disease enables a focused diagnosis and treatment. The fact that we lack a single diagnostic test for primary EM speaks to the heterogeneous nature of its pathophysiology despite a common symptom profile. Although more than 19 mutations in the SCN9A gene have been implicated in an overactive sodium channel in primary EM,[2] mutations in this channel have not been sufficient to capture all of the individuals suffering from this syndrome. Thus, until science is able to comprehensively identify targets to direct the management of primary

EM, empirical therapy should be systematically conducted to manage the most life-altering symptoms.[3]

There are three major pathophysiological phenomena that clearly affect the extremities of EM patients: dysfunctional autoregulation of vascular tone, sensitization of nociceptive neurons, and unchecked sympathetic hyperactivity. It may be possible to mitigate symptoms or even achieve remission with the minimum possible trial period if carried out thoughtfully and systematically. We suggest a general approach to the empirical treatment of EM (see Figure 1).



The dysfunctional vascular tone in primary EM seems to stem from exaggerated constriction and dilation of arterioles, the small arteries that control blood flow into capillary beds, in response to environmental changes. Hyperdilation in the arterioles supplying the distal extremities gives rise to the classic red, hot feet/hands when exposed to heat or stimuli that induce dilation of peripheral vessels.

Conversely, hyper-constriction results in purple/dusky distal extremities and may even lead to ischemic necrosis of the skin due to the extent of exaggerated arteriole tone. Since these symptoms are largely restricted to the glove and stocking distribution in primary

EM, trialing topical agents that temper vascular tone (agents described in Figure 1) may be prudent so as to avoid high levels of circulating, systemic vasoactive agents.

The quest for effective, long-term analgesic agents for primary EM patients has been focused on targeting putative defective sodium channels found on peripheral sensory neurons. Sodium channel blockers (local anesthetics or antiarrhythmics), have varying, state-dependent affinities for nine different sodium channel subtypes.

Thus, the appropriate sodium channel blocker should be selected based on the intention to inhibit NaV1.7 channels as well as the desired delivery route (eg, parenteral lidocaine versus enteral mexiletine). Topical capsaicin should also be considered as a high-dose application may result in pruning of the small nerve fiber endings, leading to anesthetic areas that last until the endings regrow, which may take several months.

Sympathetic hyperactivity is a suspected to be a major component of the symptoms that manifest in the extremities of EM patients, giving rise to the swelling and redness that accompanies their pain. This hyperactivity is also the most evident link between vascular dysfunction and hyperalgesia, as it is known that sympathetic ganglia innervate both vascular beds and peripheral sensory neurons. Sympathetic innervation of dorsal root ganglia, where the cell bodies of the peripheral sensory neurons reside, can be potentiated by chronic hyperactivity. This suggests that early attempts at mitigating sympathetic activity may slow the progression of the intensity of characteristic EM symptoms.

This multimodal strategy to target vascular tone, neuronal excitability, and sympathetic hyperactivity provides a framework approach to treating the complex pain state in primary EM. Until the etiology of primary EM becomes clear, the use of medications targeting the clinical manifestations is the most likely route to improved quality of life.

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Erythromelalgia sources

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3-Low SA, Robbins W, Tawfik V, et al. Complex management of a patient with refractory primary erythromelalgia lacking a SCN9A mutation. *J Pain Res.* 2017:10;973-977.