

## Clinical Summary



### Erythromelalgia

#### By

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Dr. Abuzetun has no relevant financial relationships to disclose.

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#### ICD codes

ICD-9:

Erythromelalgia: 443.82

ICD-10:

Erythromelalgia: I73.8

#### OMIM

Erythromelalgia, Primary: #133020

#### Synonyms

Erythromelalgia; Mitchell disease

#### Historical note and nomenclature

Erythromelalgia, or "Mitchell disease," was first described by Dr. Wier Mitchell in 1878 (Mitchell 1878). Erythromelalgia, which literally means red, painful extremities, describes an exceedingly rare, chronic condition that is characterized by the clinical triad of pronounced erythema, painful burning, and elevated skin temperature usually around the extremities (Davis 2004; Waxman and Dib-Hajj 2005a; 2005b). Clinically, erythromelalgia presents as intense redness (erythros) and severe pain (algia) in the extremities (melos). Erythromelalgia, the alternative name of the condition, describes the elevated temperature (thermos) that is often noticed in the affected areas.

Although first described in 1878, the first major study reporting the incidence of erythromelalgia was conducted in 1932 at the Mayo Clinic. The study estimated the incidence of the disease to be in the range of 1 case per 40,000 patients (Brown 1932). In the mid 1980s, an epidemic outbreak of erythromelalgia occurred among rural inhabitants in China, prompting medical professionals to investigate the characteristic

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distribution of the disorder (Zheng et al 1988). A comprehensive study undertaken in Norway in 1997 estimated the incidence of erythromelalgia to be 0.25/100,000 and prevalence 2/100,000, further strengthening the notion that the original Mayo Clinic study may have underreported the overall incidence of the disease (Kvernebo and Seem 1987; Kalgaard et al 1997).

Studies in experimental animals have shown that the Nav1.7 sodium channel plays a major role in inflammatory pain (Black et al 2004; Nassar et al 2004), but until the demonstration of mutations of Nav1.7 in patients with erythromelalgia, there was no definitive evidence for a role of this channel in pain in humans. Erythromelalgia is the first known human pain syndrome to be examined at a molecular level. Interestingly, primary erythromelalgia is also the first known human disease that involves the Nav1.7 sodium channel.

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### Clinical manifestations

The disorder is classified as a primary or secondary form, depending on whether there is a known causative factor. Primary erythromelalgia can further be subdivided into familial (inherited as an autosomal dominant trait) or sporadic forms. Moreover, familial and sporadic forms of erythromelalgia can be defined as juvenile (onset of symptoms occurring before the age of 20 years; often manifesting itself before the end of the first decade of life) or adult onset. These patients experience episodic vasodilation of the extremities in association with burning pain of the feet or lower extremities (Michiels et al 2005; Waxman and Dib-Hajj 2005a; 2005b; Waxman 2007). Occasional sporadic cases of juvenile-onset erythromelalgia have been reported to occur as a result of a de novo founder mutation in the SCN9A gene of the proband (Han et al 2006; Harty et al 2006). In these cases, although the mutation is present only in the proband and would be passed on to 50% of the offspring, it is not present in the proband's parents.

Secondary erythromelalgia oftentimes presents as a symptom of an underlying disease. It is most commonly associated with myeloproliferative diseases such as polycythemia vera and essential thrombocythemia but can also be seen in association with systemic conditions including diabetes, rheumatoid arthritis, collagen vascular diseases, thrombotic thrombocytopenic purpura, hypertension, multiple sclerosis, cutaneous vasculitis, and gout as well as with the use of certain drugs (Drenth et al 1993; Layzer 2001; Tefferi 2003; Jeffcoate et al 2004). Interestingly, in the secondary form of erythromelalgia, a 2:1 predominance of females has been reported (Kalgaard et al 1997).

Although it is a chronic condition, symptoms tend to be more episodic than continuous and often occur following exposure to certain stimuli (Buttaci 2006; Choi et al 2006). Attacks are described by patients as severe burning pain with accompanying redness in the extremities in response to warm stimuli or moderate exercise (van Genderen et al 1993; Nathan et al 2005). The lower extremities are more commonly involved than the upper extremities, and involvement is usually symmetrical (Davis 2004; Waxman 2007). There have been reports that the symptoms of this debilitating condition also tend to become worse as the patient ages (Mandell et al 1977). Furthermore, the affected areas may expand to include greater parts of the extremities, sometimes as far as the knee, as a person gets older (Mandell et al 1977). Increased age in patients with the condition correlates with

significantly decreased survival when compared with individuals in the general population without the condition (Davis et al 2000; Drenth et al 2005; Sandroni and Davis 2006). Clinicians should raise their index of suspicion for the disorder in patients who present with burning pain in the extremities that are red or purple in color and hot to the touch (Davis et al 2003). It is important for clinicians to remember that erythromelalgia shares a number of clinical features with, and is often confused with reflex sympathetic dystrophy because both are characterized by severe pain and vasomotor disturbances, but in contrast to reflex sympathetic dystrophy, erythromelalgia is bilateral and symmetric (Mitchell 1878; van Genderen et al 1993; Novella et al 2007).

Increases in environmental temperature seem to provoke exacerbation of the condition (Han et al 2007). Thus, exercise, exposure to warmth (including the summer months), and long periods of standing can possibly trigger attacks in at-risk individuals (van Genderen et al 1993; Nathan et al 2005; Han et al 2007). Given this finding, exposure to environments with cooler temperatures tends to mitigate symptoms in individuals with erythromelalgia (Davis et al 2006; Han et al 2007). Environmental factors, including certain foods, alcoholic beverages, and spices, have been reported to aggravate symptoms in patients (Novella et al 2007). Moreover, a characteristic feature is relief obtained by immersing the extremities in ice, which can lead to ulceration and gangrene. In the absence of a clear etiology, treatment has been empirical and only partially effective in most cases.

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## Clinical vignette

**Vignette #1: Primary inherited erythromelalgia.** The patient was a 40-year-old male who presented to a neurologist with the complaint of episodic erythema, mild swelling, and painful burning sensations in his feet and hands bilaterally. He reported that his symptoms began when he was about 5 years of age, although his mother stated that he has had trouble with "red, hot feet" since he was about 1 or 2 years of age. His symptoms initially only affected his feet; however, he later had similar symptoms involving his hands. Over the years, the patient had noticed that his episodes had increased in frequency and severity. At the time of presentation, he experienced multiple daily episodes of burning, throbbing pain that lasted minutes to hours.

The pain episodes were triggered by exercise or an increase in the ambient temperature. Summer months seemed to cause an increase in the frequency of painful attacks, especially if the day was hot and humid. The pain was relieved by cooling the affected extremities by using a fan or submerging the areas in ice water. In fact, during the winter months, the patient often walked outside without shoes to help relieve his pain. He preferred to wear open-toed shoes or to ambulate barefoot, even in the winter months; he slept uncovered and often kept the room cool through the use of an air conditioner. Because physical exertion, such as walking uphill or running, triggered his symptoms, the patient avoided most physical activities. He also felt that his symptoms could be triggered by alcohol or caffeine consumption, spicy foods, and sometimes melon; therefore, he began to avoid these things as well.

A review of systems was unrevealing. A review of his family history revealed that over 3 generations, multiple relatives had experienced similar symptoms beginning approximately at the same age. This

included 2 of his children, his mother, his brother, his maternal aunt and uncle, and his uncle's son and daughter. Of note, due to the severity of her symptoms, his aunt had decided not to have children. He had one maternal uncle without any symptoms.

Physical examination showed diffuse erythema over the patient's feet and hands, extending to the ankles or wrists respectively. Neurologic examination, including motor, reflex, and sensory examinations, was normal.

Evaluation of this patient included an MRI brain scan as well as sensory and motor nerve conduction studies of the right arm and leg, all of which were normal. Complete blood count, platelet count, blood chemistries, and antinuclear antibodies were within normal range; testing for Fabry disease was negative. Evaluation of the SCN9A gene in this patient revealed a single amino acid substitution, which was also present in all of the tested affected family members.

On the basis of the patient's clinical presentation, his family history, and the negative work-up, he was given the diagnosis of primary inherited erythromelalgia. Management included a trial of symptomatic pharmacological relief, as well as pain counseling. He was advised to not submerge his extremities in cold water. He was counseled on how to maintain a cool environment, how to safely cool his affected extremities, and how to avoid triggers.

**Vignette #2: Adult onset, sporadic erythromelalgia.** The patient was a 41-year-old female who presented with an 8-month history of intermittent tingling, and erythema as well as painful throbbing, burning sensations in her lower extremities. Her symptoms extended to approximately mid-calf, bilaterally. She noticed that her symptoms began approximately 8 months prior to presentation, while driving home from her first day at an aerobics class she had recently joined. She had never noticed any pain or erythema on her hands or face. Her symptoms were intermittent, lasting minutes to hours, and occurred approximately 2 or 3 times per week. She occasionally had multiple episodes during the span of 24 hours.

Her pain episodes were triggered by exercise or an increase in environmental temperature. In fact, she stated that bathing in her Jacuzzi, a favorite pastime, always triggered the symptoms. She preferred to sleep without blankets covering her feet and often had a fan blowing on her lower extremities during the night hours. She often wore sandals and avoided any tight-fitting pants or hosiery in an attempt to prevent the start of her symptoms.

On review of systems, she had diet-controlled hyperlipidemia. She had no history of orthostatic hypotension, gastroparesis, labile blood pressure, palpitations, or other signs of autonomic dysfunction. There were no family members with similar symptoms over the last 4 generations.

The patient had a normal neurologic examination. No abnormalities were seen on nerve conduction studies or electromyography. No abnormalities were noticed on laser Doppler flow examination. Subsequent quantitative sudomotor axon reflex test yielded normal findings. All of the patient's blood work was within normal limits.

On the basis of the patient's clinical presentation and negative work-up, the patient was given the diagnosis of adult onset, sporadic erythromelalgia. Management for this patient is the same as the above patient.

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## Etiology

No information was provided by the author.

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## Pathogenesis and pathophysiology

The SCN9A gene on 7.94 cM interval of chromosome 2q has been identified as the locus of mutations that cause the primary, hereditary form of erythromelalgia (Drenth et al 2001; Yang et al 2004). The SCN9A gene encodes the alpha subunit of the voltage-gated sodium channel, which is predominantly expressed within both sensory and sympathetic neuronal cells (Toledo-Arai et al 1997). Primary erythromelalgia is due to missense mutations of the Nav1.7 sodium channel, which result in single amino acid substitutions in the channel alpha subunit protein and cause gain-of-function changes (lowered threshold for activation; prolonged opening after activation; enhanced response to small stimuli) at the level of the channel (Cummins et al 2004; Waxman and Dib-Hajj 2005a; 2005b; Waxman 2007). Thus, primary erythromelalgia is an autosomal dominant disorder; penetrance appears to be 100% for inherited mutations (Yang et al 2004; Dib-Hajj et al 2005). Sympathetic peripheral fibers, or C fibers, have been recognized as being adversely affected by the mutations (Layzer 2001; Kazemi et al 2003). At a physiological level, erythromelalgia mutations in Nav1.7 typically result in hyperexcitability of the nociceptive DRG neurons in which Nav1.7 is normally present, causing these cells to generate inappropriate action potentials that are relayed to the brain, signaling the presence of a painful stimulus even when one is not there (Dib-Hajj et al 2005; Waxman and Dib-Hajj 2005b). However, these same mutations produce hypoexcitability within sympathetic ganglion neurons, which also express Nav1.7 (Rush et al 2006), providing a basis for the abnormality of sympathetic vasomotor control that is seen in these patients (Rush et al 2006).

Although paroxysmal pain disorder (previously known as familial rectal pain syndrome) has also been shown to involve mutations in the SCN9A gene, recent findings have concluded that the characteristic phenotypes of the erythromelalgia and the former are distinctive and easily distinguishable clinically (Fertleman et al 2007). Whereas erythromelalgia most often presents as episodic vasodilation of the extremities in association with burning pain of the feet and lower extremities, paroxysmal pain disorder most often presents as recurrent bouts of burning rectal and ocular pain in association with tonic, nonepileptic seizures (Fertleman et al 2007). It has been suggested that the different clinical presentations are related to different physiological effects of erythromelalgia mutations (which enhance Nav1.7 channel activation) and paroxysmal pain disorder mutations (which impair Nav1.7 inactivation).

In contrast to primary erythromelalgia, no genetic basis has been identified thus far in secondary erythromelalgia (Yang et al 2004). In fact, secondary erythromelalgia is a distinct, acquired disorder whose development is believed to be associated with rheumatologic and autoimmune factors (Stricker and Green 2001). Secondary erythromelalgia is often seen in association with a myriad of systemic conditions, most particularly with myeloproliferative disorders. Its development is likely related to the release of humoral components from platelets or ischemic tissues that tend to be exacerbated in the

presence of certain conditions and after ingestion of various drugs, including nicardipine, verapamil, bromocriptine, nifedipine, and pergolide (Dupont et al 1983; Levesque and Moore 1989; Drenth et al 1992; Mork and Kvernebo 2000; Layzer 2001). Unlike primary erythromelalgia, which is associated with alterations of critical sodium channels on the molecular level, secondary erythromelalgia has been suggested to be associated with acquired vascular changes that eventually lead to local hypoxia-induced symptoms in affected areas (Mork and Kvernebo 2000). Recent studies suggest that the condition arises in the setting of systemic disorders as a result of physiological responses to stimuli caused by systemic conditions that result in maldistribution of skin microvascular blood flow, leading to inadequate nutritive perfusion at the extremities. This presumably results in hypoxic conditions and is believed to lead to the symptoms of intense burning, unremitting pain, and other symptoms that have come to distinguish the condition (Mork and Kvernebo 2000). Thus, current findings point to a common pathogenetic mechanism prevalent in all cases of secondary erythromelalgia, namely, microvascular arteriovenous shunting secondary to systemic insults, some of which occur during exacerbations of systemic diseases (Kalgaard et al 1997; Mork and Kvernebo 2000; Ljubojevic et al 2004).

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## Epidemiology

Given the fact that few reported cases of primary erythromelalgia have appeared in the medical literature, accurately assessing the incidence and prevalence of the condition can pose a challenge. Despite the exceedingly rare nature of the primary subset, secondary erythromelalgia is less rare and is thought to appear in as many as 65% of all patients with myeloproliferative disorders. The overall incidence of both primary and secondary erythromelalgia is thought to be in the range of 1 case per 40,000 or 3.3 cases per million depending on the study (Brown 1932; Mork and Kvernebo 2000). A recent study suggested that the annual prevalence of the condition ranges between 18 and 20 cases per million (Kalgaard et al 1997; Mork and Kvernebo 2000). Although primary erythromelalgia is familial and often presents early in life, the secondary subset of the disorder can occur at any age and affects both genders equally. A comprehensive study undertaken in Norway in 1997 estimated the incidence of erythromelalgia to be 0.25/100,000 and a prevalence of 2/100,000, further strengthening the notion that the original Mayo Clinic study may have underreported the overall incidence of the disease (Kvernebo and Seem 1987; Kalgaard et al 1997).

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## Prevention

Given that erythromelalgia is precipitated via exposure to elevated temperatures, strict future avoidance of such environments should be encouraged (Mork and Kvernebo 2000; Davis 2004). For example, exercise regimens that require exposure to arid environments such as beaches or deserts should be avoided. Furthermore, recreational activities such as Jacuzzi or sauna bathing should be minimized on account of the contributory role they play in exacerbating symptoms. In cases of secondary erythromelalgia, immediate withdrawal of offending agent or treatment of underlying conditions is a prerequisite to

mitigating symptoms and minimizing risk of future exacerbation. Cooling the effected area has been shown to minimize pain and associated symptoms (Mork and Kvernebo 2000). However, patients should be cautioned not to immerse their limbs in ice water, which can cause gangrene, but rather to use a fan.

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### Differential diagnosis

The initial diagnosis of erythromelalgia can be challenging, particularly given the many other causes of painful erythematous extremities such as:

- Complex regional pain syndrome (reflex sympathetic dystrophy)
- Causalgia (only pain is the main finding)
- Thromboangiitis obliterans
- Raynaud phenomenon (primary and secondary forms)
- Burning hands and feet syndrome (idiopathic small-fiber neuropathy of elderly)
- Restricted forms of myofascial pain syndrome (fibromyalgia)
- ABC syndrome (Angry, Backfiring C nociceptors)
- Fabry disease (especially in males with associated clinical findings)
- Painful peripheral neuropathies
- Diabetic neuropathy
- Vitamin deficiency (B12/ B1)
- Vitamin excess (pyridoxine)
- Hypothyroidism
- Collagen vascular disease (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, vasculitis)
- Paraneoplastic syndrome
- Medications (amiodarone, cisplatin, colchicine, verapamil, nifedipine, bromocriptine, ticlopidine)
- Toxin or heavy metals (acrylamide, ethylene oxide, arsenic, thallium, mercury)
- Human immunodeficiency virus neuropathy
- Small-fiber neuropathy
- Sciatica

Thus, considering an appropriate differential diagnosis in at-risk patients can help eliminate misdiagnoses associated with this condition. Arriving at an accurate diagnosis necessitates paying careful attention to relevant medical history and clinical findings because no definitive laboratory criteria are currently available (Mork and Kvernebo 2000).

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### Diagnostic workup

Although early recognition and treatment of the condition represent the best probability for successfully managing erythromelalgia, the lack of understanding of diagnostic modalities of the rare disorder represents a monumental challenge for clinicians (Buttaci 2006; Novella et al 2007). Although the diagnosis should be guided via a thorough history and physical examination, a battery of other interventions may assist in arriving at a definitive diagnosis. Current understanding of erythromelalgia suggests that the best diagnostic results can be achieved during a painful episode rather than during periods of remission (Buttaci 2006; Novella et al 2007). Furthermore, use of full neurologic examination, MRI scan of the brain, skin biopsy, nerve conduction studies, and electromyography are useful in preventing

misdiagnosis (Davis et al 2003; Novella et al 2007). Of note, clinical genetic testing for the condition is not yet available.

In patients who cannot be evaluated during a painful crisis, it is recommended that nerve function and vascular function tests be conducted after provoking symptoms via exercise or increases in local temperature (Davis et al 2003). In such patients, meticulous recording of skin temperature in affected areas along with transcutaneous oximetry and laser Doppler flow can be instrumental in arriving at an accurate diagnosis (Davis et al 2003). Furthermore, because small-fiber neuropathy has been reported in some erythromelalgia patients, thermoregulatory sweat testing can be a sensitive and effective marker in diagnosing patients with the disease (Davis et al 2006).

Erythromelalgia secondary to myeloproliferative disease can respond dramatically to aspirin (Michiels et al 2006). In fact, patients typically report pain relief for several days after a single dose. Therefore, patients who respond to aspirin should be worked-up for an associated myeloproliferative disorder (Novella et al 2007).

Although developing a broad, reflective differential is important, a thorough history and diagnostic evaluation are critical to prevent misdiagnosis. This is especially true of other neurologic syndromes that tend to mimic erythromelalgia such as complex regional pain syndrome, chronic mountain sickness, Anderson-Fabry disease, autosomal dominant burning feet syndrome, and chronic idiopathic axonal polyneuropathy. Unlike erythromelalgia, complex regional pain syndrome is often associated with trauma-related cytokine release resulting in exaggerated neurogenic inflammation and pain in the affected extremities (Birklein 2005). The recognition of such differences is critical to arriving at an accurate diagnosis in the setting of suspected erythromelalgia. Anderson-Fabry disease describes a condition that results in neuropathic pain in association with cerebrovascular, renal, and sensorineural deficits (MacDermot et al 2001). In fact, sensorineural deafness can be seen in as many as 78% of Anderson-Fabry disease patients (MacDermot et al 2001). Erythromelalgia rarely affects visceral organs and tends to primarily affect the distal extremities, primarily on a superficial level. Perhaps the disorder that most closely mimics erythromelalgia is chronic mountain sickness, which can only be distinguished via nerve biopsy (Thomas et al 2000). Like erythromelalgia, the most prominent clinical finding in chronic mountain sickness tends to be burning in the distal extremities (Thomas et al 2000). Nerve biopsy in a patient with chronic mountain sickness will demonstrate demyelination as well as the reduction of unmyelinated axons, whereas no such reduction in myelin is demonstrable in erythromelalgia patients (Thomas et al 2000; Davis et al 2006). Chronic idiopathic axonal polyneuropathy presents with burning pain in the distal extremities, but unlike erythromelalgia, idiopathic axonal polyneuropathy most commonly affects disabled elderly men (Hughes et al 2004).

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### **Prognosis and complications**

Erythromelalgia is a painful inherited neuropathy that can be difficult to treat (Waxman and Dib-Hajj 2005a; 2005b). Early recognition and diagnosis remains the cornerstone of treatment. Crucial to achieving this end is the ability of clinicians to recognize characteristic clinical signs. Diagnostic confirmation in suspected patients can be achieved



via full neurologic examination and verification with tests such as MRI scan of the brain, skin biopsy, nerve conduction studies, and electromyography (Davis et al 2006; Novella et al 2007). The condition does remit spontaneously in one third of patients (Davis 2004; Waxman and Dib-Hajj 2005a; 2005b).

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## Management

As a result of the lack of studies on the condition, until recently, erythromelalgia was characterized as refractory to medical management (Stricker and Green 2001). Although recent findings have made great strides in treating the condition, many cases of erythromelalgia remain difficult and frustrating undertakings for many clinicians (Waxman and Dib-Hajj 2005a; 2005b). This is especially true of primary erythromelalgia, for which a myriad of medications including nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, tricyclic antidepressants, corticosteroids, calcium channel antagonists, and other drugs have been used--all with varying responses (Mork and Kvernebo 2000). Importantly, in patients with primary erythromelalgia, genetic counseling and counseling on the chronic nature of the disease is essential (Hisama et al 2006). Patients must be advised to avoid triggers, as well as how to properly cool painful extremities. Patients need to be warned against submerging their extremities in ice or in icy water due to the possibility of developing skin necrosis and ulceration. A safer option is using a fan to cool the skin. Moreover, recent attempts at surgical sympathectomies have also yielded conflicted results. The sodium channel blockers lidocaine and mexiletine have been reported to be helpful in some patients, although the beneficial effects are transient. The possibility of Nav1.7-specific sodium channel blockers, which target Nav1.7 but leave other sodium channel subsets unblocked, thereby minimizing side effects, is being explored (Waxman 2006). Although promising results have been reported via controlled trials using a topical gel compound containing amitriptyline and ketamine, further studies are required before this therapeutic option becomes more widely accepted by clinicians (Sandroni and Davis 2006). Further, the effectiveness of serotonin-reuptake inhibitors such as venlafaxine have demonstrated promising results both in the immediate alleviation of symptoms associated with erythromelalgia and in reducing their occurrence (DiCaudo and Kelley 2004; Firmin et al 2007). Overall, the most effective method of treating primary erythromelalgia is via medical management, which should include genetic counseling and symptomatic management of exacerbations (Novella et al 2007). Given the fact that the sodium channel gene SCN9A has been identified as the source of pain and inflammation in primary erythromelalgia, it should be considered for a molecular target of pain treatment for future therapies (Waxman and Dib-Hajj 2005a; Wada 2006; Waxman 2006).

In secondary erythromelalgia, treatment of the underlying disease often mitigates the symptoms and leads to remission of outbreaks. For example, phlebotomy in patients with polycythemia and effectively normalizing platelet counts in patients with essential thrombocytopenia will initiate a commensurate decrease in secondary erythromelalgia symptoms (Michiels et al 2005). In cases where an external stimulus such as heat is suspected of exacerbation, strict future avoidance of such stimuli should be recommended. In the event that a certain medication yields an eruption of symptoms, immediate withdrawal of

offending agent is recommended. Low doses of aspirin have been shown to reduce the incidence of both arterial and venous thrombosis, thereby improving symptoms associated with the disorder (Landolfi et al 2006). Thus, prophylactic use of low-dose aspirin is recommended to all patients with secondary erythromelalgia, particularly those with polycythemia vera-induced erythromelalgia (Landolfi et al 2006).

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### **Pregnancy**

No information is available.

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### **Anesthesia**

No information is available.

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### **Associated disorders**

polycythemia vera  
essential thrombocythemia  
diabetes  
rheumatoid arthritis  
collagen vascular diseases  
thrombotic thrombocytopenic purpura  
hypertension  
multiple sclerosis  
cutaneous vasculitis  
gout

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### **Related summaries**

Polycythemia and its neurologic manifestations  
Complex regional pain syndrome

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### **Differential diagnosis**

complex regional pain syndrome (reflex sympathetic dystrophy)  
causalgia  
thromboangiitis obliterans  
Raynaud phenomenon  
burning hands and feet syndrome  
restricted forms of myofascial pain syndrome  
fibromyalgia  
ABC syndrome (Angry, Backfiring C nociceptors)  
Fabry disease  
painful peripheral neuropathies  
diabetic neuropathy  
vitamin deficiency (B12/ B1)  
vitamin excess (pyridoxine)  
hypothyroidism  
collagen vascular disease (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, vasculitis)  
paraneoplastic syndrome  
medications (amiodarone, cisplatinum, colchicine, verapamil, nifedipine,

bromocriptine, ticlopidine)  
toxin or heavy metals (acrylamide, ethylene oxide, arsenic, thallium, mercury)  
human immunodeficiency virus neuropathy  
small-fiber neuropathy  
sciatica

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## Demographics

For more specific demographic information, see the Epidemiology, Etiology, and Pathogenesis and pathophysiology sections of this clinical summary.

### Age

0-01 month  
01-23 months  
02-05 years  
06-12 years  
13-18 years  
19-44 years  
45-64 years  
65+ years

### Population

None selectively affected.

### Occupation

None selectively affected.

### Sex

In the secondary form of erythromelalgia, a 2:1 predominance of females has been reported.

### Family history

family history typical

### Heredity

heredity typical

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