

### ORIGINAL ARTICLE

#### **Juvenile onset erythromelalgia with neuropathy. Report of three patients and a review of the literature.**

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#### **Abstract**

Erythromelalgia (EM) is a syndrome characterized by redness, increased temperature of the skin, and severe extremity pain. EM is rare in children, in part due to underdiagnosis. EM may be classified as primary or secondary to other conditions. We report 3 patients with juvenile erythromelalgia associated with peripheral neuropathy. The three adolescent patients developed an illness characterized by edema, redness and severe extremity pain that improved only with immersion of the affected extremities in freezing water. Each teen varied in pain severity and in response to analgesics. The most severe patient required intrathecal infusion of drug in the morphine class of analgesic for pain control, and also developed gangrene requiring toe amputations. All three patients had peripheral neuritis with demyelination on nerve biopsy. A review of the literature documented a small number of EM patients in the juvenile age range. Most had neuropathy or other associated conditions. We conclude that this syndrome should be considered in the differential diagnosis of severe limb pain in children along with trauma, infection,

vasculitis, Raynaud's phenomenon, reflex sympathetic dystrophy, antiphospholipid syndrome, and other conditions. Clinicians must be vigilant for the neuropathy and other associated pathology, especially the possible complication of rapid, severe vascular compromise. In those cases resistant to usual analgesics, the use of intrathecal infusion of anesthetics and vasodilators should be considered. Diagnostic criteria, severity scores, and more research in this area are needed.

## **Introduction**

Erythromelalgia was first described by Mitchell in 1878. EM is a syndrome characterized by redness, increased temperature of the skin, and very severe pain, mostly in the extremities. EM is thought to be either primary or secondary. [1-2] The idiopathic or primary EM is more frequent than the secondary and begins spontaneously at any age, although it is more common in patients under 30. It is of unknown origin. The secondary form has been reported associated with several conditions such as diabetes, lupus or hypertension, but is most frequently secondary to myeloproliferative diseases. [1-2, 3, 5-7] In juvenile patients the prevalence is reported as low but the condition may be underdiagnosed. The purpose of this paper is to report 3 adolescents with erythromelalgia and a neuropathy that were seen at the Hospital de Pediatría "Pedro de Elizalde" between October 2000 and November 2001 and to review the pertinent literature..

## **Case 1**

A thirteen year old boy was initially seen with a 10 day history of very severe pain in his feet. His feet were warm. He could not walk. He also had referred pain in his arms and fine tremors in his hands as well as erythema and swelling. The recent history was not helpful with absence of recent infections, fevers, rashes, or other problems. The family history was non-contributory as well. The pain, swelling, and redness of his hands did not improve with NSAID's but did show an immediate improvement with his immersion of hands and feet in cold water. Physical examination revealed edema and erythema in his hands and feet with severe pain on movement and tenderness on palpation. He had a distal, fine tremor and enhanced reflexes without focal neurological signs. His ophthalmologic examination was normal. He had no arthritis, rash, other skin changes, or other significant physical findings.

During followup the patient worsened progressively, developing paraesthesias in his hands and feet with an increase of extremity pain. He also demonstrated hyperreflexia in his lower limbs, dysphonia secondary to paralysis of the left recurrent nerve, and the appearance of ulcerated lesions on his legs (Figure 1). No evidence of vasculitis was noted.

Figure 1. Erythromelegia affecting the feet of a thirteen year old boy including skin ulcerations



A brain and spinal cord MRI was normal while an electromyelogram showed a mononeuritic lesion of the radial nerve, fasciculations, and axonal damage with loss of 30% of the neural parenchyma. The patient became severely depressed, refused to eat, and required parenteral nutrition. The pain was managed with several combinations of drugs including calcitonin, dipirone, paracetamol, ibuprofen, diazepam, dextropropoxifen, carbamazepine, tricyclic antidepressants and prednisone. Psychotherapy and intense physical therapy were also utilized. The patient improved gradually with complete recovery after a period of 52 days.

## Case 2

A twelve year old boy developed very severe pain in his hands and feet that only improved with the immersion of the extremities in cold water. He also had hand and foot edema, redness (Figure 2), increased temperature of the extremity skin, and progressive ulcerative skin lesions on the distal extremities. No contributory recent or family history was noted. The patient was admitted to the hospital 21 days after the onset of his extremity pain with transient vision loss, difficulty walking and a recent tonic/clonic seizure. Edema and skin lesions of the feet worsened and the pain was very difficult to control with analgesics such as NSAID's.

Routine laboratory tests, clotting assays, and hypercoagulability tests were normal. The following tests were normal or negative: ESR, CRP, ANA, antiDNA, rheumatoid factor, C3, C4, serology for bacteria and viruses including HIV 1-2, toxic (thallium, mercury, lead). Brain and spinal cord CT scan and magnetic resonance were normal as were venous and arterial doppler studies. A bone marrow biopsy showed only a mild megakaryocytic hyperplasia. Porphyria and malignancy were thought to be very unlikely.

Upper and lower limb EMG showed moderate to severe polyneuropathy. An external saphenous nerve biopsy including electronic microscopy demonstrated only a mild involvement of myelin fibers and vasculitis was not seen. Muscle biopsy also did not reveal vasculitis and only showed a selective atrophy of fibers type 2 likely secondary to decreased physical activity.

Several analgesics such as aspirin, dextropropoxifen plus dipirone, carbamazepine 800mg/ per day, enalapril 5 mg/ per day, amitriptiline 40mg / per day were tried but failed. Vitamins B1,B6, and B12 were added without response. By the 8th day of admission, the patient was put on gabapentin with a rapidly increasing dose up to 1500 mg/day without change in the pain. Ketanserine, tramadol, and mexilitine were also used without relief of pain. Finally, after failure of all therapies used, it was decided to place an epidural catheter in the lumbar spine with continuous infusion of 0.5% bupivacaine and morphine with good control of pain. Unfortunately, cyanosis of the third right toe and the forefoot (Figure 2) was observed and quickly progressed to severe ischemia with necrosis.

Figure 2. Erythromelegia in a 12 year old boy with necrosis of several toes

PLACE Figure 2

Iloprost and hyperbaric chamber improved the lesions but surgery with amputation of 2nd to 5th right toes was required (Figure 3).

Figure 3. Erythromelegia in a 12 year old boy: Sequelae after amputation

PLACE Figure 3

During followup, physical therapy and psychotherapy were needed. The total disease duration was 130 days. The patient was discharged able to walk and with almost full functional ability.

**Case 3**

A seventeen year old female developed EM two months after a miscarriage. She had been diagnosed with primary Sjögren Syndrome associated with autoimmune thyroiditis at the age of 12 years.

Her symptoms started with burning pain, heat, and erythema in both feet that improved only with immersion in cold water. The physical examination was normal except for redness and swelling of her feet with considerable pain and tenderness. The neurological examination was normal but an electromyogram showed signs of peripheral neuritis. Some psychological issues in the family were apparent. The pain was controlled with NSAID’s, physical therapy, and psychotherapy with complete recovery after 60 days.

**Discussion**

History

The word erythromelalgia comes from 3 Greek words: erythros (red), melos (extremity) and algos (pain). [2-4,6]. It was described for the first time by Weir Mitchell in 1878. Mitchell intended to restrict the term erythromelalgia to the secondary forms associated with myeloproliferative illnesses that respond to aspirin, and suggested the word *erythromelalgia* for the idiopathic forms without aspirin response. The symptoms of the illness are distinguished by the coexistence of increased temperature of the skin, marked redness, swelling and severe burning pain of the involved extremity. [1-2] These signs and symptoms typically improve when exposing the affected area to the cold and usually there is no response to analgesics.

Epidemiology

Kvernebo estimated an incidence in Norway from 2.5 to 3.3 per million of inhabitants a year and an annual prevalence of 18 to 20 /1,000,000. [4]. The incidence and prevalence of EM in pediatric patients is unknown. As this syndrome is not well known, we believe that EM is underreported and that the prevalence may be higher than appreciated.

The illness appears to be more frequent in females. Davis et al reported that 72.6% out of 168 cases were female (mean age was 55.8 years, range 5-91 years). [3] Kalgaard noted a male:female ratio of 1:2 (mean age 43.4 years, range 7.8-76.6 years). [8] The patients in both studies were mostly adults as only 7 cases began in childhood. However, in the reported series of juvenile patients, 66% were boys which is in agreement with our observation (Table 1).

Table 1 – Reported series of patients with juvenile onset erythromelalgia

AUTHOR	SEX	AGE	ANTECEDENT EVENT	TREATMENT	EVOLUTION
Rabaud C et al	M	17 y	Hepatitis B vaccine	Propanolol, aspirin,	Favorable

				propoxiphen, acetaminophen, steroids, IV $\gamma$ globulin, hypnotherapy	
Confino et al	F	4 ½ y	Influenza Vaccine	Aspirin, carbamazepine and propranolol	Favorable
Kasapcopur O, et al	M	7 y	Hypertension and leukocytoclastic vasculitis	Prednisolone fenoxibensamine	Favorable
Zenz W, et al	M	5 y	Gastroenteritis	sodium nitroprusiate	Favorable
Stone JD, et al	F	15 y		sodium nitroprusiate	Favorable
Cimaz R, et al	M	10 y	Growth hormone deficiency and skin ulcers	Growth hormone	Favorable
Mc Graw T, et al	F	9 y		aspirin, opiate, benzodiazepine, epidural bupivacaine, nitroprusside, amytriptiline, gabapentin	Favorable
Rauch RL, et al	M	17 y		Cervical epidural infusion of analgesic and anesthetics	Favorable
	M	12		Cervical epidural infusion of analgesic and anesthetics	Favorable

Kurzrock and Cohen differentiate two categories: a) an adult form, which can be idiopathic or secondary; b) an early idiopathic childhood form. [4, 6-7] EM is considered acute when the symptoms last less than 1 month and chronic if greater than 1 month. [4-8] All 3 patients in our series had the chronic form with a mean duration of 80 days (range 52 -130 days). Table 2 illustrates differences between the adult and child forms of EM.

Table 2 – Erythromelalgia: Differences clinical features between adults and children

Adults	Children
Primary or idiopathic in 60% of the cases; 40% are secondary, mainly to myeloproliferative illnesses.	Mainly secondary
Lower limbs in 65% Upper and lower limbs in 25%.	Either lower or upper limbs in 62% All four limbs in 38% of the cases
Bilateral in most of the patients, but it can also be asymmetric	Always bilateral and symmetrical.
Better response to treatment	Usually resistant to treatment.
Primary forms should be followed closely because of possible evolution into secondary forms	

### Classification

A classification of EM has been proposed and three forms were described: a) a thrombocytosis/hyperviscosity form, b) vasoconstrictor form and c) vasodilator form. The different forms of EM suggested in this classification may explain the considerable variability of treatment responses. Most of the patients show the vasoconstrictor/reactive hyperemia form. The less common form is the vasodilator form that can respond to vasoconstriction with beta selective blockers such as propranolol, while it may worsen with other treatments. To distinguish these forms of EM, vascular studies are recommended. These studies are carried out in cold and hot environments using doppler, doppler fluxometry, thermography, and tissue oxygen pressure control.

### Pathology/pathophysiology

As EM can be primary or secondary, the search of underlying pathology is important. In our patients, a wide range of conditions were considered and eliminated. A notable point was that all of them

had both peripheral neuritis and psychological stress. Whether the psychological problems were just secondary to this painful condition or were an important part of the etiology, as may be seen in reflex sympathetic dystrophy in adolescents, remains unclear.

Recent studies attempting to explain the physiopathology of EM suggest that pre-capillary sphincters may close, leading to the opening of arterial-venous shunting. This imbalance may increase perfusion but decrease tissue oxygen, leading to both hyperemia and hypoxia in the affected skin. Tissue hypoxia leads to a reactive increase in blood flow thus worsening the erythema, heat and pain. [1-4,6,14] Acrocyanosis and ischemic ulcers can develop with risk of secondary infection, sometimes progressing to distal necrosis. [6] This vascular dysfunction could be potentially reversible in some cases but in others could lead to chronic ischemia in spite of the high perfusion of the limb. There could be due to a chronic dysregulation of the sympathetic nervous system, showing increased sympathetic tone in some patients with primary EM.

The denervation of the sympathetic system through epidural anaesthesia can explain the benefit obtained in some patients with this treatment, as in our second case. Genetic predisposition was also studied. A common haplotype located on the chromosome 2q31-32 has been described. [13]

#### Course of EM

Davis reported a disease duration between 1 month and 26 years. Symptoms were intermittent in 163 patients (97%) and persistent in 5 (3%). Gangrene has not been reported in Davis' study. [3] In 148 patients (88.1%), the feet were affected. In 43 patients (25.6%), the hands were affected, and in 23 (13.7%), the legs were involved. Other involved areas included the ears (1 case), face (4 cases), and neck (1 case). Among 63 patients who had only the lower limbs involved at onset, 9 reported progression to the upper limbs. No patients had progression from the upper limbs to the lower limbs. Almost all patients had symmetrical involvement. Only 1 out of 5 with unilateral symptoms at onset progressed to involvement on the other side. [3]

Relief of the symptoms is obtained by decreasing the temperature of the skin with immersion in freezing water, ice or snow, and this is so common that it is now considered characteristic of EM. All our patients described improvement of pain only with immersion of the limbs in a pail of cold water. In the severe forms, the patients carry out cold water immersion almost constantly. There are patients who permanently have a pail of cold water by their side and they immerse their feet for 15-30 minutes every hour and sleep with their feet in the cold water. [1,4,5-6] The pain relief with cold could be explained by the decrease of the metabolic index and therefore the oxygen requirement.

EM can significantly alter daily life activities. Davis reported that 50% of the patients could not walk long distances, 49% could not stand for long periods of time, 12.5% gave up their jobs, 12.5% were too disabled to drive, 3.1% were wheel chair-bound and 2.1% of the patients remained in bed. [3]

#### Primary and secondary forms

As noted above, when evaluating a patient with EM, it is essential to distinguish between the primary and secondary forms. Therefore, in all the new cases of EM, an underlying cause should be

sought. The most frequent associations are myeloproliferative illnesses [1-3,6-7] such as polycythemia vera and idiopathic thrombocytopenia. Sometimes EM precedes the diagnosis of these illnesses by an average of 2.5 years. Other associated diseases are diabetes mellitus type 1 and 2, hypercholesterolemia, amaurosis, connective tissue diseases, several infections including Epstein-Barr viral infections [9] and also post-vaccination reactions to influenza and hepatitis B. [1,11-12] Other associated entities include trauma, drug reactions, neuropathies [10] and genetic diseases. [3,6,8]

In our patients, peripheral neuropathy was the only condition that we could associate with the EM. Another interesting finding was that all of the children had had recent psychological stress. Though there are no evidence-based studies for confirmation, it is our belief that stress may be a trigger of EM as noted in cases of reflex sympathetic dystrophy.

#### Differential diagnosis of erythromelalgia

Table 3 summarizes the differential diagnosis of EM .

Table 3 – Erythromelalgia differential diagnosis

Phase of freezing recovery.  
Red phase of Raynaud's phenomenon.  
Cellulitis  
Vasculitis  
Reflex Sympathetic Dystrophy  
Causalgia  
Shoulder-hand Syndrome  
Thromboangiitis obliterans  
Peripheral Neuropathy  
Fabry's disease  
Angiodysquinesia, acrocyanosis and lipodermatosclerosis  
Drug reaction

#### Complications

There are several complications associated with EM that seem to be present more frequently in patients with platelet-mediated illnesses. [6] These can include maceration of the skin and skin ulceration. These chronic ulcers may develop secondary infection leading to digital necrosis or gangrene that may result in the amputation of the affected extremity [1-2,6-7]. Our second patient presented with gangrene leading to amputation of 4 toes. This can be explained on the basis of the existence of inflammatory and proliferative changes that can increase the ischemic dysfunctions, acrocyanosis and outlying gangrene. This is directly related to artery damage and an increase of platelet aggregation. [7] In the report of Kalgaard, several patients presented with severe complications leading in two of them to amputation of

lower limbs. [8]

### Diagnostic criteria

Several authors have proposed diagnostic criteria for this disease. Mitchell initially proposed three criteria: red, hot and burning extremities. [2] In 1932, Brown added other signs for a total of 6 criteria. [4] In 1979 Thompson proposed a new group of criteria [reference] and in 1988 Lazareth defined the current criteria (Table 4). A patient must have 3 major and at least 2 minor criteria for a diagnosis of erythromelalgia. [11]

Table 4 – Erythromelalgia diagnostic criteria

<b>Major criteria</b>	<b>Minor criteria</b>
Paroxysmal attacks	Triggering factors (exposure to heat, effort)
Burning pain	Typical improvement with cold and rest
Redness of affected areas	Increase of local temperature during the attacks
	Improvement with aspirin

### Treatment

The treatment of EM is difficult and can often be discouraging. The use of a medication or group of drugs is sometimes insufficient and other therapeutic methods may be needed. In one survey by Davis et al, the patients received a total of 84 different drugs to treat their symptoms. [3] The first step in the treatment is to educate the patient so that he/she learns how to avoid excessive heat, limit vigorous exercises and overuse of the affected extremity, and also keep the affected extremity elevated as much as possible. [6] The patient should not use cold or icy water and should maintain excellent skin hygiene of the affected area to avoid infection. Also, in the secondary forms of EM, treatment of the underlying illness should improve the EM.

Different medications can be used for the control of the symptoms (Table 5). Several reports have advocated the effectiveness of aspirin for EM, likely due to the antiplatelet aggregation effect of this drug. Aspirin may only be effective in the cases associated with thrombocytosis, polycythemia or other blood dyscrasias. [1-2,6]

Table 5 – Drugs and other therapies used in the management of erythromelalgia

Selective inhibitors of serotonin receptors	Venlafaxine, sertraline, fluoxetine, paroxetine and tramadol. Some patients are very sensitive to these drugs and require low doses initially.
Tricyclic antidepressants	Amitriptyline, imipramine, nortriptyline and desimipramine

Anticonvulsants	gabapentín (400-3600 mg/per day), carbamazepine and valproic acid
Calcium channel antagonists	Nifedipine, diltiazem (60 to 300 mg/ per day)
Prostaglandin	Misoprostol 400 ugr TID
Drug treatment combinations	1) amitriptiline, benziline, atenolol and pentoxifiline. 2) misoprostol and gabapentín 3) gabapentín, imipramine, amitriptiline and venlafaxine. 4) sertraline and diltiazem 5) diltiazem and imipramine.
Topical treatments	Lidocaine and prilocaíne, doxepine, capsaicine (increase of redness and pain as adverse event)
Sodium Nitroprusside	Useful in children, ineffective in adults. Increase of heat and pain has been reported.
Lidocaine	Reduction of the pain in 90% and light relief of redness
Epidural blockades:	Rauck and Col reported the remission of 2 adolescents who received epidural infusion of bupivacaíne and opioids [2]
Surgery for disease itself or complications.	Unilateral or bilateral sympathectomy. Some patients with polycythemia benefit from phlebotomies. [6]
Non-drug therapies	Acupuncture, biofeedback, magnetic therapy and hypnosis

The response to medical treatment is unpredictable and remissions are uncommon. However, through careful trial and error, benefits can be obtained in many patients. Oral medications should initially be used especially in milder cases of EM, but infusions or invasive treatments may be necessary for the severe ones. The ideal therapy has not yet been defined.

### Conclusions

EM is a condition that requires a multidisciplinary team for its management. Diagnosis is often not easy. A patient may initially be classified as having primary EM, and may declare later that the EM is a secondary condition. It is important to be vigilant and watch for an associated condition. Diagnostic tests should be repeated if symptoms worsen in spite of therapy. In some patients, a hematologic evaluation

including bone marrow biopsy is necessary in order to diagnose associated myeloproliferative conditions that may precede or follow the diagnosis of EM.

Treatment is often unsuccessful but any treatment used must be closely monitored as progression of the disease can lead to several complications such as infections, tissue hypoxia and gangrene. In resistant cases, the possibility of intrathecal infusion of opioids should be considered since it appears to shorten disease evolution.

Multiple disease associations, varying degrees of disease severity, potential of severe complications, and inadequate treatment suggest a need for an international consensus to clarify nomenclature, develop severity and damage scores, and to encourage better research into the etiopathogenesis of this unusual but very painful disorder.

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