Erythromelalgia: New theories and new therapies

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Erythromelalgia is a rare condition that has remained an enigma diagnostically and therapeutically for decades. It has been assumed that erythromelalgia, which is characterized by hot, red, intensely painful feet or hands, may be the opposite of Raynaud's phenomenon. However, new research suggests that these two disorders are more similar than dissimilar. Erythromelalgia usually follows a chronic, sometimes progressive and disabling course. New evidence suggests that this may not be a disease entity at all, but a syndrome of dysfunctional vascular dynamics; recent studies demonstrate that this dysfunction is reversible in some patients. This review article presents the latest theories and successful treatments for erythromelalgia, and data from a survey of members of The Erythromelalgia Association, which was formed to provide information about erythromelalgia to doctors and patients. (J Am Acad Dermatol 2000;43:841-7.)

The incidence and prevalence of erythromelalgia in the United States are unknown. Kvernebo[1] estimates an incidence of 0.25/100,000 and a prevalence of 2/100,000 in Norway.

Erythromelalgia can be primary or secondary. Primary erythromelalgia begins spontaneously at any age. Secondary erythromelalgia has been reported with many disorders but most often with polycythemia, thrombocythemia, neuropathies, and autoimmune diseases[1-19] (Table I[1-36]). Unlike Raynaud's phenomenon (RP), patients with primary erythromelalgia do not typically experience autoimmune diseases in subsequent years.

The onset of erythromelalgia may be gradual with some cases remaining mild and unchanged for decades, or erythromelalgia may begin acutely, spreading or becoming disabling within weeks (Table II).

Abbreviations used:

CRPS:	complex regional pain syndrome
PGE:	prostaglandin E
RP:	Raynaud's phenomenon
TEA:	The Erythromelalgia Association

DESCRIPTION

Erythromelalgia is characterized by intense burning pain, marked erythema, and increased skin temperature. Most patients experience erythromelalgia in the feet, but the hands may be the primary sites (Table II). Although typically bilateral, erythromelalgia may be unilateral, especially in secondary cases. Severe erythromelalgia may spread up the legs or arms, from lower to upper limbs or vice versa, or to the face or ears (The Erythromelalgia Association [TEA] survey), typically bilaterally.

In mild cases, erythromelalgia's constellation of symptoms may be apparent only during a flare, which is characterized by acute erythema, heat, swelling, and pain. Flaring typically occurs late in the day and continues through the night, impairing sleep. Flaring is improved by elevating the affected limbs. In severe cases, patients elevate the limbs continuously. Some patients complain of severe tingling or neuropathy-like pain when flaring.

EFFECTS OF TEMPERATURE

Heat intolerance and relief with cooling are hallmarks of erythromelalgia. Exposure to warmth can trigger flaring and increase its severity. Patients quickly learn that their erythromelalgia is triggered at a specific temperature, which varies considerably between individuals.

Relief of pain with ice water immersion is so common that it is almost pathognomonic. Others buy air conditioners or blow fans across their affected areas. In severe cases, patients perform ice water immersions nearly constantly, which may trigger reactive flaring, and a vicious cycle can occur. Frequent immersion can lead to maceration of the skin, nonhealing ulcers, infection, necrosis, and amputation.[4,37]

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0190-9622/2000/$12.00 + 0 **16/1/109301**
doi:10.1067/mjd.2000.109301

Table I. Disorders associated with erythromelalgia*

- Hematologic disorders
  - Polycythemia, thrombocythemia[2,3,5-8,15]
  - Leukemia, particularly chronic myeloid leukemia[2,3]
  - Hereditary spherocytosis[3]
  - Pernicious anemia[4,8]
  - Thrombotic thrombocytopenic purpura[9]
- Cardiovascular disorders
  - Atherosclerosis[3]
  - Hypertension[2,10-12]
  - Venous insufficiency[4]
- Embolic disease
  - Cholesterol crystal emboli syndrome[3]
  - Metabolic disorders
  - Diabetes mellitus, types 1 & 2[2,3,13]
  - Hypercholesterolemia[3]
  - Gout[2,14]
  - Familial nephritis[2]
- Connective tissue disorders
  - Rheumatoid arthritis[2,3]
  - Systemic lupus erythematous[2,3,15,16]
  - Mixed connective tissue disorder
  - Sjogren's syndrome
  - Vasculitis[17,18]
- Infectious diseases
  - AIDS[3]
  - Recurrent bacterial infections[3]
  - Viral infections[1,19]
  - Syphilis[2]
- Musculoskeletal disorders
  - Sciatica[3]
  - Carpal tunnel syndrome, peritendinitis[3]
  - Back trauma or surgery[1-3]
  - Neck and other trauma
- Neurologic disorders
  - Neuropathies[1,13,20,21]
  - Multiple sclerosis[4]
  - Spinal cord disease, sciatica[3,22]
- Drug induced
  - Iodide contrast injection[3]
  - Vaccines: influenza, hepatitis[23,24]
  - Oral medications: nifedipine, felodipine, nicardipine, bromocriptine, norephedrine, pergolide, ticlopidine[1-3,23-33]
- Other conditions
  - Carcinoma: abdominal,[34] colon,[3] thymoma,[1] astrocytoma[35]
  - Frostbite[3]
  - Conversion disorder[1,3]
  - Mercury poisoning[36]

*A causal relationship has not been established for some of these conditions.

Table II. Results of informal survey of TEA members

- Total responses = 41
- Age at which erythromelalgia appeared:
  - Mean age = 41.6
  - Age of onset per decade: 0-9 years old = 3 cases; 10-19 = 4; 20-29 = 6; 30-39 = 3; 40-49 = 8; 50-59 = 8; 60-69 = 4; 70-79 = 5.
  - (Many members had prodromal symptoms of burning pain, heat intolerance, or facial flushing for months or years before the appearance of characteristic vasomotor symptoms.)
- Areas afflicted:
  - Lower limbs only or mainly = 21
  - Upper and lower limbs = 17
  - Face or ears also sometimes involved = 17
- Unilateral or bilateral:
  - Bilateral = 40
  - Unilateral = 1
- Erythromelalgia episodic or active most of the time:
  - Episodic (worse in late afternoon, evening, nighttime) = 26
  - Active most of the time = 13
- Flaring:
  - Flaring (paroxysmal hyperemia, increased warmth, swelling, pain) = 39
- Presence of redness or hyperemia:
  - Red most of the time = 19
  - Episodic redness (with activity or flaring) = 14
  - Hardly any redness = 4
- Pain:
  - Severe = 21
  - Moderate = 16
  - Mild = 4
- Coolness in affected limbs when not flaring and in a cold environment:
  - Diagnosed with Raynaud's phenomenon = 4
  - No Raynaud's, but involved areas get colder than normal = 14
- Erythromelalgia primary or secondary:
  - Primary = 26
  - Secondary = 13
  - Uncertain = 2

IMPACT ON NORMAL FUNCTIONING

Even mild erythromelalgia can greatly affect normal functioning and quality of life. Patients avoid warm weather and limit their activities to cool or air-conditioned locations. Some move to cooler climates. Evening activities are avoided. Many patients cannot wear socks or closed shoes even in winter. In severe cases, patients become virtually housebound by continuous flaring and pain. Standing and even sitting with the legs down become increasingly intolerable, and constant elevation becomes necessary. Work and social functioning are disrupted, which in turn affects family functioning.

REACTIVE HYPEREMIA IN ERYTHROMELALGIA AND RP

Erythromelalgia has some similarities with RP. RP's most prominent symptom is the whiteness of digits from cold-induced vasoconstriction, but the greatest

discomfort sometimes occurs with warming, which is described in terms that resemble erythromelalgia: intense heat, redness, vasodilation, and burning pain. It is hypothesized that similar dynamics underlie this aspect of RP and erythromelalgia: the hyperemia phase is more prominent in erythromelalgia, whereas the constriction phase is more prominent in RP. This might explain the puzzling reports of erythromelalgia and RP in the same patients.[28,38,39]

Littleford, Khan, and Belch[40] measured the skin temperature of patients with erythromelalgia, which, when not flaring, was lower than that of control subjects. This suggests a subclinical vasoconstriction during the day with subsequent reactive hyperemia at night. Littleford, Khan, and Belch state: "We believe that, in erythromelalgia, vasoconstriction precedes reactive hyperemia, similar to that seen in Raynaud's phenomenon." (p 588) This may explain why some patients have noticeably cool, yet still erythematous limbs during the day as their symptoms progress. Normal skin temperature may disappear entirely, and the affected areas go from cool during the day to hot at night. Other patients do not exhibit this diurnal variation; instead they display typical symptoms of erythromelalgia and heat intolerance continuously.

VASCULAR ABNORMALITIES IN ERYTHROMELALGIA

Blood perfusion through skin capillaries primarily serves nutritional needs, whereas arteriovenous anastomoses facilitate heat and temperature regulation.[1] Recent research suggests that in erythromelalgia, some precapillary sphincters may be constricted while the arteriovenous shunts are open, creating an imbalance of increased total perfusion yet deficient nutritive perfusion.[1-4,17] The result is "the coexistence of hypoxia and hyperemia in affected skin."[3] (p 191) The products of tissue hypoxia trigger increased local blood flow, worsening the redness, warmth, and pain. This may explain why higher ambient temperatures exacerbate symptoms of erythromelalgia.

DIAGNOSIS

Erythromelalgia's intermittence can make diagnosis difficult. Because symptoms typically appear late in the day, the patient may appear normal during daytime examinations. Confirmatory tests are lacking. Thus many patients are misdiagnosed or are undiagnosed for years. However, patients with erythromelalgia can usually provide good descriptions of their symptoms, from which a tentative diagnosis may be made. If doubt remains, immersing an affected area in hot water for 10 to 30 minutes sometimes (but not always) provokes flaring. Alternately, the patient can take pictures during a flare, or the patient can be directed to an after-hours facility for examination when flaring occurs.

Other telltale symptoms and signs may help in making the diagnosis. Some patients report tingling pain or exhibit allodynia during flaring. Severe cases may develop numbness in some digits. Several TEA members report curled or hyperextended toes, but it is not clear whether this association is causal or incidental. Skin injury from repeated immersion may be apparent.

Primary versus secondary erythromelalgia must be differentiated. In all new cases, underlying causes should be sought. Erythromelalgia may be an early sign of polycythemia or thrombocythemia,[2,3,5-8,15] and appropriate laboratory studies should be performed periodically.

DIFFERENTIAL DIAGNOSIS

With a good history and classic findings, the diagnosis of erythromelalgia is easily made. Nevertheless, erythromelalgia may be confused with some types of complex regional pain syndrome (CRPS1, reflex sympathetic dystrophy). The latter also produces abnormal heat, erythema, and burning pain, and these patients sometimes soak affected limbs in ice water. Although CRPS1 usually occurs after an injury, some cases appear spontaneously. Conversely, although erythromelalgia typically occurs spontaneously, it can appear subsequent to injury. However, erythromelalgia usually is bilateral and spreads bilaterally. Pain is reduced or absent between flares.

The tingling and burning nature of erythromelalgia pain may resemble a neuropathy, and because burning pain sometimes precedes erythema for months, differentiation can be difficult. Secondary erythromelalgia is linked to several types of neuropathies,[1,13,20,21] and skin biopsy specimen studies conducted by the Mayo Clinic have revealed "both small- and large-fiber neuropathies in a high proportion of patients."[41] (p 1448) Electromyographic studies are usually normal for erythromelalgia not associated with neuropathies.

Menopausal symptoms and medication reactions may produce flushing or sensations of intense heat, but they do not cause the profound, localized redness and pain of erythromelalgia.

TREATMENT

The following therapies apply to primary erythromelalgia and to secondary erythromelalgia that is unresponsive to treatment of the underlying disorder.

Nonmedicinal approaches

Putt[42] reported pain reduction in one patient using biofeedback. This approach provided modest benefit

Table III. Therapies used by members of the erythromelalgia association (TEA)

Medication	No. of users	No. benefited
Gabapentin	16	16
Aspirin	14	1
Diltiazem	8	6
Amitriptyline	8	5
Sertraline	6	3
Fluoxetine	5	3
Misoprostol	5	2
Opiates (oral)	5	2
Phenoxybenzamine	5	2
Imipramine	4	3
Pentoxifylline	4	1
Carbamazepine	4	1
Antihistamines	3	2
Clonazepam	3	2
Cyproheptadine	3	0
Venlafaxine	2	1
Tramadol	2	2
Paroxetine	1	1
Fluvoxamine	1	1
Topicals:		
OTC capsaicin cream	4	0
EMLA cream	3	0
Doxepin cream	1	1
Invasive therapies:		
Morphine pump	2	1
Spinal cord stimulator	2	2
Nonmedicinal therapies:		
Acupuncture	4	1
Biofeedback	4	2
Hypnosis	3	0
Magnets	2	0

for 2 of 4 TEA members (Table III). Hypnosis was reported as useful in 2 cases of erythromelalgia associated with hypertension.[10,43] Three nonhypertensive TEA members tried hypnosis with little benefit.

Topical treatment

Standard capsaicin cream has been reported to help erythromelalgia,[44] but often causes increased pain and redness. Robbins et al[45] have used high-potency (10%) topical capsaicin, given with the patient under epidural anesthesia, for CRPS and neuropathic pain syndromes. This approach led to dramatic improvement in a TEA member with severe, incapacitating erythromelalgia for 40 years.

Oral medications

Isolated cases of remissions have been reported with propranolol (10 mg 3 times daily),[46,47] clonazepam,[16] cyproheptadine,[48] methysergide,[13] piroxicam,[49] pizotifen,[50] and others, but TEA members report that these drugs usually do not work or, at best, work only modestly.

Aspirin. Early reports suggested that aspirin promptly relieved erythromelalgia, but this appears true only for cases involving thrombocythemia, polycythemia, or other blood dyscrasias.

Drugs inhibiting serotonin reuptake. Rudikoff and Jaffe[51] reported 3 remissions achieved through use of venlafaxine and sertraline. Several TEA members have obtained substantial improvement with venlafaxine (18.75 to 75 mg twice daily), and others have improved with sertraline (25 to 200 mg/day) but no complete remissions have been achieved. Improvement has also been reported with paroxetine, fluoxetine, and tramadol. Some erythromelalgia patients are quite sensitive to these drugs and require very low doses initially.

Tricyclic antidepressants. Herskovitz et al[20] reported remission of secondary erythromelalgia in 1 patient using 75 mg of amitriptyline. Several TEA members use amitriptyline for pain reduction, but no remissions have occurred. Imipramine is also used.

Anticonvulsants. McGraw and Kosek[52] reported a remission in a child using gabapentin. Gabapentin (400-3600 mg/day) reduces erythromelalgia pain for many TEA members, but no remissions have occurred. One TEA member has improved with carbamazepine used in combination; another did not respond to valproic acid.

Calcium antagonists. Belch[2] recommends extended release nifedipine for some patients with erythromelalgia to attenuate the vasoconstriction phase of erythromelalgia, thereby lessening the reactive hyperemia.[1] Nifedipine may also improve nutritional capillary flow. Interestingly, calcium antagonists, including nifedipine, have also been implicated in the onset of erythromelalgia.[25-28] One TEA member experienced mild improvement with nifedipine, but others experienced intolerable adverse effects. Five TEA members have obtained improvement with diltiazem (60 to 300 mg/day) without adverse effects, and one patient has achieved virtual remission. Several other patients did not respond to diltiazem.

Misoprostol. Prostaglandins can improve nutritive blood flow via relaxation of precapillary sphincters. Mork obtained improvement in 17 of 22 patients with erythromelalgia, including one remission, after 3 months of misoprostol compared with improvement in 5 of 22 with placebo (article in press). Doses up to 400 μg twice daily were used, in contrast to a usual dose of 200 μg 4 times daily for nonsteroidal anti-inflammatory drug–treated gastropathies. There is one report of misoprostol precipitating bilateral burning hand pain.[53] Except for one patient, use of misoprostol among TEA members has generally been disappointing.

Medication combinations. Polypharmacy has helped some patients but not others.[1,8,13,23] A 33-year-old TEA member who had to keep his legs elevated 22 hours a day obtained substantial relief with dibenzyline 10 mg twice daily, atenolol 50 mg twice daily, amitriptyline 25 mg 3 times daily, and pentoxifylline 400 mg 3 times daily (after starting with lower doses). Currently he reports even greater improvement with misoprostol and gabapentin. One TEA member has obtained considerable improvement with sertraline and diltiazem, and another with diltiazem and imipramine. Persons have benefited from gabapentin combined with imipramine, amitriptyline, or venlafaxine. Drug combinations may be worth considering when single agents do not adequately control symptoms.

Parenteral approaches

Nitroprusside infusions. Nitroprusside infusions have been helpful in some children and adolescents[11,54] and may be the preferred treatment for severe erythromelalgia in these age groups. It is usually not effective in adults. One adult TEA member experienced increased pain and flaring with nitroprusside infusions.

Lidocaine infusions. Kuhnert, Phillips, and Davis[41] obtained a 90% reduction in pain and modest alleviation of redness in a man with long-term severe erythromelalgia. Improvement occurred with one lidocaine infusion and was maintained with oral mexiletine.

Prostaglandin infusions. Kvernebo[1] and Belch[2] have used prostaglandin E_1 (PGE1) infusion because of its ability to improve nutritive blood flow. Kvernebo[1] reported improvement in 8 of 9 patients, including 6 remissions, with one to three 72-hour PGE1 infusions. Belch[2] used 6- to 8-hour infusions on 3 to 5 consecutive days. The dose was low initially and was increased according to the patient's tolerance and the appearance of mild signs of flushing. Belch states that there is no difference in efficacy between PGE1 and PGI2 (prostacyclin), which is used more commonly in the United States. Two TEA members have received intravenous PGE1 therapy without improvement.

Invasive approaches

Sympathetic blocks and epidurals. Rauck et al[4] reported remissions in 2 adolescent boys receiving epidural infusions of bupivacaine and opiates. One patient received an epidural for 9 days, then was sent home with medications. The second patient received an implanted pump device for 37 days, as well as oral medications and a nitroprusside infusion; his symptoms cleared gradually. The medical literature contains reports of 3 other remissions with epidurals.[55-57] The oldest patient among these cases was 21 years old. Whether this procedure works for older patients with erythromelalgia is uncertain. Two TEA members, aged 45 and 67 years, received epidurals of 45 and 14 days, respectively, without significant improvement.

Zoppi et al[58] performed 10 daily lumbar sympathetic blocks using alternate sides on 3 adult patients. Two patients obtained remissions; the third obtained partial improvement. Several TEA members have had a single unilateral sympathetic block, and either no effect was noted or erythema was worsened.

Sympathectomies. Zoppi et al[58] reported mixed results with sympathectomies. In 1973, Postlethwaite[59] reported "excellent" results with bilateral lumbar sympathectomies in 4 of 4 erythromelalgia cases. In 1999, Shiga et al[60] reported a remission subsequent to bilateral thoracic sympathectomies in a patient with erythromelalgia of the hands. Belch[2] has told the author that her group has obtained very good results with lower extremity sympathectomies in some patients, but others have not improved with this treatment, and a few have worsened. Belch supports doing sympathectomies if a diagnostic sympathetic block produces improvement.

Kvernebo[1] described a patient made worse by a unilateral sympathectomy, and he considers sympathectomies contraindicated because he believes they increase thermoregulatory but not nutritive blood flow. However, Rauck et al[4] described epidurals as maximizing blood flow of all types. One would theorize that if some erythromelalgia patients display vasoconstriction before reactive hyperemia, as indicated by the work of Littleford, Khan, and Belch,[40] then thermoregulatory systems are involved. Moreover, the diurnal nature of erythromelalgia flaring may indicate autonomic involvement. The success of epidurals and sympathectomies supports this view, at least in some patients. Perhaps, as in RP, sympathetic and peripheral factors vary in importance in different patients with erythromelalgia.

Dorsal column stimulator. Graziotti and Goucke[61] reported the control of intractable pain in one patient via a dorsal column stimulator. Two TEA members have obtained moderate pain relief from this method, but no improvement in erythema.

Neurosurgery. Two Russian physicians have reported remissions via neurosurgery.[62,63] The author is not aware of similar work being done in North America or Western Europe.

DISCUSSION

The reversibility of erythromelalgia and its significance

It has now been amply demonstrated that erythromelalgia is a reversible condition in some patients. Once reversed, remissions may last

months, years, or indefinitely. These remissions support the statement of Kalgaard, Seem, and Kvernebo[3] that: "In our opinion erythromelalgia is not a separate disease entity but a pathophysiological response of the skin microcirculation." (p 195)

The hypothesis that erythromelalgia is a vicious cycle caused by a maldistribution of blood flow has gained plausibility via vascular studies and successful therapies that have been replicated. These therapies include nitroprusside infusions in children and adolescents, and prostaglandin and lidocaine infusions, 10% topical capsaicin, and bilateral sympathectomies in adults. None of these methods is consistently effective, suggesting multiple subtypes of erythromelalgia.

Different subtypes of erythromelalgia?

Belch[2] has categorized 3 subtypes: thrombocytosis/hyperviscosity, microvascular ischemia (vasoconstrictive), and vasodilatory. Whereas most patients exhibit the vasoconstrictive/reactive-hyperemia type that responds to the infusion or invasive approaches mentioned above, the less common vasodilatory type will worsen with these therapies. Conversely, the latter may respond to the vasoconstriction of unselective beta blockers like propranolol, whereas the former will worsen with such treatment. To differentiate these types, Belch recommends vascular studies performed in warm and cool environments that include Doppler pressures, laser Doppler flowmetry, thermography, and tissue PO_2 monitoring. The Mayo Clinic often performs nerve biopsies.

Treatment considerations

The most useful oral medications for erythromelalgia appear to be gabapentin, venlafaxine, diltiazem, sertraline, amitriptyline, imipramine, paroxetine, fluoxetine, and some antihistamines (diphenhydramine, cyproheptadine), usually begun at low doses. Response is quite variable and remissions are infrequent but through careful trial and error, substantial benefit can be achieved with most patients. Oral medications should be tried initially, especially in mild erythromelalgia cases, but 10% capsaicin (under epidural anesthesia), infusions, or invasive approaches may be necessary for intransigent and severe cases. The ideal therapeutic approach remains to be defined.

SUMMARY

Erythromelalgia is characterized by burning pain, marked erythema, swelling, and increased temperature in affected limbs. Symptoms are typically provoked by heat and reduced by cooling. The pathology underlying erythromelalgia appears to involve reduced nutritive blood flow coupled with increased arteriovenous shunting. This vascular dysfunction is potentially reversible even in long-term cases. Remissions have been reported with nitroprusside infusions or prolonged epidurals in children and adolescents, and with various medications, prostaglandin or lidocaine infusions, 10% topical capsaicin, and bilateral sympathectomies in adults. No single therapy has proved consistently effective, which supports the possibility that there are several subtypes of erythromelalgia. Although patients respond quite variably to medication therapy, careful trial and error often lead to substantial benefit. Patients and physicians can obtain information from a new organization, The Erythromelalgia Association (TEA),* which also runs an online support group.

ADDENDUM: After submission of this manuscript, 3 new articles on erythromelalgia have been published and are cited in MEDLINE:

Davis MD, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia: presentation and outcome in 168 patients. Arch Dermatol 2000;136:330-6.

Mork C, Asker CL, Salerud EG, Kvernebo K. Microvascular arteriovenous shunting is a probable pathogenetic mechanism in erythromelalgia. J Invest Dermatol 2000;114:643-6.

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