Refractory idiopathic erythromelalgia.

by Richard L. Ratzck, MD, Francisco Naveira, MD, Kevin L. Speight, MD, and Beth P. Smith, PhD


Departments of Anesthesia and Orthopedics, The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina

Erythromelalgia was first described by Mitchell in 1878 (1) and named from three Greek words: erythros (red), melos (extremities), and algos (pain). Through the years, the condition has been extremely rare, and Lewis (2), in 1933, felt that it lacked any precise criteria for definition and should be abandoned. Soon thereafter, Smith and Allen (3) reported a series of patients and described the condition in either primary or secondary idiopathic forms.

Erythromelalgia can be characterized as a condition of painful, swollen, erythematous extremities. Intense burning pain and increased temperature of the involved extremities are hallmark features. Although it is a disease of the extremities, the lower extremities are more frequently involved than the upper. Males are more frequently affected than females at a ratio of 2:1.

Primary or idiopathic erythromelalgia occurs more frequently than secondary erythromelalgia, which is most commonly associated with a myeloproliferative disorder such as thrombocythemia or polycythemia vera (4). Other Conditions, such as myelogenous leukemia, hypertension, venous insufficiency, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, lichen sclerosus et atrophicus, gout, spinal cord disease, multiple sclerosis, astrocytoma, and pericarditis anemia, have been found in association with secondary erythromelalgia (5-10).

Primary erythromelalgia occurs most commonly in patients less than 30 years of age. The etiology of primary erythromelalgia remained elusive. A defective prostaglandin metabolism may explain the red discoloration and burning pain seen in most patients (11).

The following two case reports of idiopathic erythromelalgia in adolescent males demonstrate the need for aggressive techniques to manage the extraordinary pain symptomatology seen in these patients. These case reports are intended to provide an understanding of the pathophysiology of microvascular disturbances seen in these patients through the use of an Ice Cold Stress Test (ICST) and the protracted treatment course necessary to effect remission in certain patients.

CASE REPORT

Case 1
A 17-yr-old, 68 kg male presented with swollen red, painful hands; the pain was relieved only by immersion of the hands in cold water. One month earlier, he had
sprained an ankle playing baseball; his prior medical history was otherwise unremarkable. On physical examination, both hands demonstrated erythema, edema, and allodynia. Erythromelalgia was diagnosed clinically based on this presentation. A cervical epidural catheter at C7-T1 was placed, and 3 mL 2% lidocaine and 5 mL 0.25% bupivacaine were injected. The patient initially reported complete relief of and a continuous infusion of 0.003% morphine sulfate MSO-4 and 0.125% bupivacaine at 10 mL/h was begun. The following day, the patient had bilateral weakness in his upper extremities, relief of stinging pain, but a return of burning pain. He kept his hands in ice water during much of the day. An ICST was obtained (Figure 1). Occupational therapy was started, and his epidural infusion was increased to 20 mL/h over several days secondary to increased pain. A decrease in cold water immersion was noted. Confusion resulted from MSO-4 and epidural infusion was changed to 0.1% meperidine and 0.25% bupivacaine with mild to moderate relief. Serotonin reuptake inhibitors including nortriptyline trazodone, and doxepin were tried without benefit. EMLA® cream (Astra Pharmaceutical Products, Inc., Westborough, MA) topical clonidine, and aspirin were administered without relief. A nitroprusside infusion was begun at 1 μg. kg(-1) min(1) and nitrated to 4 μg - kg(-1) · h (-1) over 72 h with some relief in symptoms. The patient was evaluated by specialists including rheumatology, dermatology, neurology, orthopedic hand specialist, medical psychology, and psychiatry. No other etiologies for his pain were found. He continued to use ice packs and ice water on his hands when allowed. However, there was a definite gradual improvement in his symptoms, which continued over 9 days. The epidural and nitroprusside infusions which had provided the best relief of symptoms, were gradually discontinued. The Patient was discharged home wearing compression hand gloves, receiving transdermal clonidine 0.1 mg. bilaterally, pentoxifylline 150 mg three times a day, doxepin 50 mg at bed time, and oxycodone 5 mg with acetaminophen 325 mg 1-2 tablets by mouth every 4 h as required. Over a period of 1 mo, his, symptoms decreased, his medications were discontinued, and he returned to playing recreational softball. Of note, he had sustained a 12-kg weight loss over this period. A repeat ICST revealed continued high flow rates in vasomotion (Figure 2). At 10 mo after the hospitalization, the patient was asymptomatic, had regained his weight and was once again playing baseball for his high school team. A repeat ICST 16 mo later had normal results: flow rates and vasomotion were normal (figure 3). The patient has remained asymptomatic 2 yr after his presentation.

Case 2
A 12 yr old, 63-kg male patient with no prior history of systemic illnesses presented with a chief complaint of intractable pain, redness, swelling, and increased temperature in both and feet of 6 weeks' duration. There was a positive family history of connective tissue disorder on the mother's side. History revealed a barring pain that began in the "balls of his feet" followed 2 weeks later by bilateral hand symptoms. The pain was relieved by ice water and worsened by warm or hot water.

The patient's physical examination demonstrated marked bilateral hand edema, redness and nondermatomal hyperalgesia of the affected areas. The feet demonstrated only mild signs of edema and redness without pain.

Tests for Lyme disease and inflammatory arthritis were negative. A monospot test was positive. Prior to admission, the patient had received prednisone 20 mg by mouth twice
daily, pentazocine naloxone by mouth every 4 h, tolmentin sodium, amitriptyline, meperidine intramuscularly, chloral hydrate, aspirin, ketoprofen, and several other nonsteroidal anti inflammatory drugs.

On admission, MSO-4 patient-controlled analgesia (PCA) at a concentration of 2 mg/mL with a dose of 0.5 mL per injection and basal rate of 0.5 mL/h was started. Soon after admission, the symptoms in the patient's feet disappeared, while those of the hands worsened, necessitating the placement of a cervical epidural catheter at C7-T1 and the infusion of 0.125% bupivacaine at a rate of 5 mL/h, which was subsequently increased to 0.25% bupivacaine at 9 mL/h. The PCA basal rate was increased to 1.0 mL/h. At this point, the patient seemed to tolerate not having his hands constantly submerged in ice water. The results of an ICST slowed high flow rates and significant vasomotor instability, similar to the results in Case 1. Four days later, the patient developed a fever, requiring the removal of the catheter and the start of intravenous (IV) antibiotics. The IV PCA was switched to fentanyl 50 μg/mL plus a ketoralac solution of 0.3% (3 mg/mL), In addition to nifedipine 10 mg orally, twice daily, and a 0.1-mg clonidine patch on the dorsal aspect of each hand. None of these modalities alleviated his pain. Eventually, he again began to submerge his hands in ice water in an effort to obtain relief from now unbearable pain.

Four days after the discontinuation of the first epidural catheter, with the fever subsiding and a negative result from the culture of the fast catheter tip, a second epidural catheter was placed at the level of C6-7 and a continuous epidural infusion using 0.25% bupivacaine at 8 mL/h was begun. IV PICA using fentanyl 50 μg/mL at a basal rate of 1.0 mL/h, a dose of 1.0 mL per injection, a delay of 6.0 min, and a 1-h limit of 7.0 mL was continued, along with Amitriptyline 25 mg by mouth at bedtime and ketoralac 30 mg intramuscularly every 6 h as required for breakthrough pain. Acupuncture was initiated, and the patient had four 20-min sessions during which both hands were treated over a period of 4 days. This also proved unsuccessful. During this period, whenever the patient's epidural infusion was decreased he had recrudescence of his pain. Finally, 26 days after his admission, the patient was taken to the operating room, where a long-term cervical epidural catheter was placed. The next day he was discharged home using a portable epidural infusion pump with fentanyl 40 μg/mL plus 0.25% bupivacaine at a rate of 5.0 mL/h with 1.0 mL boluses. Ten days later, the infusion rate was decreased to 3.0 mL/h because the pain had slowly diminished. Eleven days later, the pump dose was decreased to 1 mL/h and subsequently was discontinued because the patient's symptoms further resolved. The epidural catheter was removed 37 days after placement, and the patient has remained asymptomatic for 16 mo.

DISCUSSION

Both patients exhibited the six criteria necessary for diagnosis by Brown in 1932 (12): 1.) localized redness, congestion, vasodilatation, burning pain, and increased-temperature: 2.) bilateral manifestation, although symmetry may be lacking; 3.) a condition produced and then aggravated by exercise and heat; 4.) symptomatic relief provided by cold, rest, and elevation of the extremities: 5.) absence of an associated disease, and 6.) a condition refractory to treatment: The only treatment that uniformly helps patients is immersion of the afflicted extremity in an ice-cold environment (13). Thompson et al. (14) reported that patients exhibit 2 critical skin thermal threshold above
which exacerbation of symptoms is noted. This temperature ranged in patients from 32 to 36°C (5). Both of the patients presented here insisted on using ice water throughout much of their disease course.

Several articles import that prolonged exposure to cold in these patients can lead to maceration and infection ultimately requiring amputation (14). Both of our patients demonstrated some skin breakdown secondary to prolonged cold water immersion. We were only able too get them to bring their extremities out of the ice water through use of cervical epidural infusions of local anesthetics and, opioids. Although the epidural infusions could not provide complete relief of pain, they did allow the patients to spend more "ice free" time.

Aspirin has been the treatment of choice in erythromelalgia, although neither of our patients responded to the drug (15-17). This finding agrees with other articles that note that many cases of erythromelalgia without underlying thrombocytemia do not respond to aspirin. Our patients were both considered to have Idiopathic erythromelalgia unconnected to an underlying disease process potentially treatable with aspirin.

As observed in our two cases, treatment of primary erythromelalgia can be frustrating and difficult. Our experience with this disease demonstrates the necessity to be aggressive and supportive in refactory cases. Although neither epidural analgesia nor other multiple medical. regimens could provide complete relief of symptoms, both patients experienced worsening of their pain, erytherma, and swelling if treatment intensity was reduced.

Two cases of idiopathic erythromelalgia were successfully treated with sodium nitroprusside (18). In both cases by Ozsoyulu and Coskun (18), the patient responded with complete or near-complete resolution of symptoms and no recurrence at an infusion rate between 1 and 5 μg - kg(-1) - min(-1) for 48 hours. Our first patient received a nitroprusside infusion for 72 hours with some resolution of symptoms, but symptoms returned after the infusion was stopped.

Increased skin temperature has been recorded since the initial description by Mitchell (1). The mechanism of this elevated temperature has not been elucidated. We used an ICST with laser Doppler fluxmetry to examine the mechanism of elevated temperatures seen in this disease. Isolated ICST was developed as a noninvasive method to evaluate digital cutaneous perfusion (19,20). With this technique, thermistors and laser Doppler fluxmetry probes are attached to the digital pulp. The thermistors monitor digital temperatures and provide an index of total digital blood flow. Laser Doppler fluxmetry technology used laser light and the Doppler principle to measure the flux of red blood cells in the skin, thus providing an assessment of cutaneous microvascular perfusion. Laser Doppler fluxmetry permits assessments of vasomotor activity of the cutaneous microvasculature.

In order to perform an ICST, thermistors are attached to all five digits and laser Doppler probes are attached to one digit of each extremity. The thermistors and laser Doppler probes are interfaced with a computer that collects measurements of digital temperature and cutaneous perfusion over the 45-minute testing period. Baseline measurements are collected for five minutes, then the hands are placed within a refrigeration unit (6 to 8°C) for 20 minutes while the response to cold exposure is monitored. After the 20-minute cooling period, the hands are removed from the
refrigeration unit and are allowed to rewarm to room temperature for 20 minutes. A printout of the test results can be made, and the results can be analyzed by time period, i.e., baseline period, cooling period, and rewarming period.

Blood flow in the hands and feet is primarily involved in thermoregulation, because the tissues in the hands and feet have very low nutritional requirements. The use of a cold stress test is important to assess any abnormalities in the sympathetic system, a major control of thermoregulation. The use of measurements of both digital temperature and cutaneous perfusion as measured by laser Doppler flowmetry provides quantitative data prescribing dynamic thermoregulatory function of the extremities over time.

Both of our patients demonstrated extremely high flow rates as measured by laser Doppler flowmetry (Figures 1 and 2). Epidural administration of local anesthetics and opiates did not further elevate flow but did reduce the vasomotion spikes seen in many high flow states and witnessed in Patient 1 after the epidural infusion was discontinued. Laser Doppler and clinical presentation suggest that patients with primary erythromelalgia have insufficient flow at the capillary level.

The use of epidural blockade with local anesthetics will ensure sympathetic denervation and enhance flow through the arterioles. Maximizing flow to the capillaries is essential to maintain nutritional support at the tissue level and allow restoration of flow through the arterioles. The increased skin temperature seen in patients and the complaints of red, swollen, and hot extremities suggest that flow is increased. This increased flow is currently thought not to occur at the tissue level, where nutrient exchange occurs. Investigations have hypothesized that the actual mechanism is shunting of blood to deep, sub-dermal arteriovenous shunts, a result of increased precapillary tone (21). This could render flow to the skin-or capillary level deficient and chronically ischemic despite high flow to the extremity itself. As in patients with other vascular ischemic diseases, the products of ischemic metabolism would continue to stimulate flow to the extremity, but the characteristics of the disease would limit nutritional flow.

Thus shunting may, in part, be under control of the sympathetic nervous system. Uno and Parker (22) observed changes in the autonomic nerve plexuses with a resultant increase in sympathetic tone in a patient with primary erythromelalgia. Denervation of the sympathetic system, via an epidural infusion may explain the benefit seen in our patients and others. (23) The dichotomy of increased total flow and ischemic tissue circulation is further supported by the histopathological findings of increased intravascular platelet aggregation. Platelet consumption has been significantly increased in some reports (24). Biopsies taken in these cases demonstrated arteriolar changes: thickened and swollen endothelial cells and a proliferation of smooth muscle cells resulting in a narrowed intraluminal diameter. These changes were seen to progress until there was complete fibrosis of the arterioles. These inflammatory changes and proliferative arteriolar lesions can lead to further ischemic circulatory derangements, acrocyanosis and peripheral gangrene (25). These vascular changes were restricted to the arteriolar level and were partially reversible with aspirin.

In conclusion, the etiology of primary erythromelalgia remains obscure, although the primary vascular abnormalities are becoming better understood (26,27). This study demonstrated further evidence of an underlying peripheral vascular ischemia despite increased total flow with the use of isolated cold stress testing. Aggressive symptomatic treatment is indicated in patients for whom the pain is extremely intense and unpleasant.
Children and young adults often do not have adequate coping mechanisms to deal with such discomfort. When extreme pain is unrelieved, the experience can be harmful to the patient, the family, the nursing staff, and anyone involved. Prolonged epidural analgesia, including cervical infusions at home for several weeks, may be necessary in refractory cases.

**References**


Accepted for publication January 10, 1996
Address correspondence and reprint requests to Richard L. Rauck, Pain Control Center, Bowman Gray School of Medicine, Medical Center Blvd. Winston-Salem NC 27157-1009
Figure 1. Initial Ice Cold Stress Test. Vasoconstriction dampened by epidural infusion. Flow rates are very high compared with normal values.

Figure 2. Ice Cold Stress Test after removal of epidural catheter. Executive vasoconstrictor activity has returned. Flow remains high.

Figure 3. Ice Cold Stress Test with return to normal flow rates and normal vasoconstriction.