

# Erythromelalgia pain managed with gabapentin.

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## CASE REPORTS

ERYTHROMELALGIA is a rare syndrome characterized by episodic burning pain, erythema, and elevated temperature of the feet, hands, or both.[1,2] The syndrome can occur alone or with myeloproliferative or other diseases.[3-5] Attacks may last from minutes to days and can persist indefinitely in the absence of treatment. The pathophysiology of erythromelalgia is poorly understood. Case reports in the literature have implicated abnormalities of arterioles, platelets, and peripheral nerves. [6-11] Patients typically obtain relief from elevating and cooling the involved extremity. This relief usually is temporary, with some patients developing immersion injury from prolonged exposure to cold water. Symptomatic responses have been reported to aspirin therapy, [12,13] vasodilators,[14] beta blockers,[15] tricyclic antidepressants,[16] and regional local anesthetic techniques.[17,18]

Gabapentin, an anticonvulsant, has been reported to be effective in managing a variety of chronic pain states.[19,20] We report two patients for whom several previously described treatments for the pain of erythromelalgia were ineffective and whose symptoms resolved after the institution of therapy with gabapentin.

## Case Reports

### *Case 1*

A 42 yr-old man was admitted to our hospital for management of severe bilateral leg pain. His pain began 3 months before admission in his toes bilaterally and progressed to involve the feet, ankles, and lower legs. There was no known antecedent trauma to his feet or legs. He also complained of swelling of his feet and legs. The severity of this pain prevented the patient from bearing weight on his feet.

Previous therapies included aspirin, prednisone, and acetaminophen and oxycodone, none of which dramatically reduced his pain. The pain was transiently relieved by soaking his legs in ice cold water.

His past medical history is significant for the diagnosis of multiple sclerosis made 9 months before admission by a magnetic resonance imaging study of his head after developing vertigo, tinnitus, and stocking-glove hypoesthesia of his hands and feet. This hypoesthesia resolved after 2 weeks.

On admission, the patient was alert, conversant, and complained of 9/10 pain in his feet and legs. His legs were elevated and wrapped in a cooling blanket. His lower extremities were erythematous, warm, edematous, and tender. Mechanical allodynia and hyperpathia were present in his feet, ankles, and lower legs. Pulses were easily palpable bilaterally at dorsalis pedis and posterior tibial arteries. The remainder of his examination was normal.

Laboratory studies were unremarkable except for an erythrocyte sedimentation rate of 25 mm/hr. A dermatology consultation supported the diagnosis of erythromelalgia. Hematologic workup did not reveal any evidence of myeloproliferative disease. Duplex ultrasound examination of the lower extremities

revealed increased flow.

The patient was treated with intravenous morphine up to 240 mg/ day administered via a patient-controlled analgesia device. This was ineffective in controlling his pain and resulted in marked sedation.

He was then started on gabapentin, 100 mg given orally three times daily, and imipramine, 10 mg given every night. Thirty minutes after the first dose of gabapentin, the patient had dramatic pain relief that lasted 4 h. The pain then returned to 80% of its previous intensity. After the second dose of gabapentin, the pain resolved for 6 h. The gabapentin dosage was increased to 300 mg three times daily, and the pain resolved except for some minor discomfort around the areas that had been most severely macerated from prolonged cold water soaks. This residual pain responded to treatment with oral acetaminophen and oxycodone combination (325 mg/7.5 mg) taken four to six times per day. After 2 days of the previous therapy plus leg elevation, his edema largely resolved, and he was allowed to lower his feet. At this point, he again could tolerate the touch of his clothing without pain. His pain then returned approximately 1 h before his next scheduled gabapentin dose and resolved 30 min after each dose. This cycle repeated for three doses. Pain relief was sustained after his dosage was increased to 400 mg three times daily. The patient has remained pain-free for 4 months.

## Case 2

A previously healthy 9-yr-old girl was admitted for the evaluation and treatment of incapacitating bilateral foot pain. She had suffered from gradually increasing pain for approximately 1 month before admission. There was no history of trauma to the feet or legs. She described her pain as burning and stinging. It persisted around the clock, preventing the patient from sleeping more than a few hours each night. The pain was most intense in her feet but also was present in her hands. It had been unrelieved by aspirin, opiates, and benzodiazepines. She could only obtain relief by immersing her feet in buckets of ice water.

Evaluation for malignancy, immune disease, and blood dyscrasia was negative. There was no family history of similar pain.

Physical examination on admission revealed a well-developed girl with obvious distress with her feet immersed in ice water. She was afebrile with normal vital signs. Both feet were edematous, erythematous, warm to touch, and exquisitely tender. The swelling and tenderness extended to her lower calves. Her hands exhibited the same signs to a lesser degree. Dorsalis pedis and posterior tibial and radial pulses were all brisk bilaterally.

A lumbar epidural catheter was placed, and bupivacaine, 0.25%, produced dense sensory blockade extending to T10. Despite absence of foot pain, the patient became distraught with the loss of all sensation. She refused further epidural trials. An infusion of intravenous nitroprusside was begun. Infusion rates of up to  $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$

Within several days, she was seen as an outpatient in the Pain Management Center. Her pain had at this point persisted for 6 weeks, and she had developed trench foot as a result of prolonged immersion in ice water. She was started on gabapentin, 100 mg three times daily, and her amitriptyline was maintained. During the following week, the gabapentin dosage was increased to 300 mg three times daily. After 1 week, her symptoms began to resolve, and her dosages were not changed further. During the next several weeks, her symptoms continued to improve, and within 1 month she was pain-free. She was maintained on the same regimen for 4 months and subsequently slowly weaned from both medications without recurrence. She has remained pain-free for 6 months.

## Discussion

Despite a variety of proposed etiologies, the pathogenesis of erythromelalgia remains poorly understood. In addition, erythromelalgia pain often is resistant to a range of analgesic therapies. This has resulted in recommendations for various invasive therapies, including lumbar and cervical local anesthetics and the

continuous infusion of vasodilators. Despite these aggressive therapies, pain relief is not predictable.

Erythromelalgia, like the complex regional pain syndrome (CRPS, also known as reflex sympathetic dystrophy), is characterized by chronic incapacitating pain in the extremities. CRPS appears to be associated with increased sympathetic activity. Patients typically present with cool, mottled extremities that have poor pulses. In contrast, patients with erythromelalgia present with warm, erythematous extremities that have normal or even bounding pulses. Consequently, these patients would not be expected to benefit from sympathetic blockade as many patients with CRPS do.

The possibility of a neuropathic pain mechanism in patients with erythromelalgia is suggested by the presence of mechanical allodynia in the affected areas and the ineffectiveness of opiate analgesics. Gabapentin is an anticonvulsant that also has been used successfully for a variety of chronic pain conditions.[19,20] Its safety has been well established.[21,22] The most common side effect is sedation; patients generally develop tolerance to this effect in a few weeks if the dosage is increased slowly.

The first patient demonstrated an immediate response to gabapentin administration. The duration of his pain relief was dose-dependent; at 400 mg three times daily, his relief was continuous. His initial rapid and dramatic response to a 100-mg dose was surprising and may have reflected a degree of placebo effect. The disappearance of allodynia after larger dosages suggested a neuropathic mechanism. In addition, it is possible that the gabapentin actually was ameliorating the symptoms of multiple sclerosis. There are no reports, to our knowledge, regarding the use of gabapentin in the management multiple sclerosis.

The second patient was a child and treated as an outpatient; her gabapentin dosage was increased slowly, and her improvement was more gradual. Although it is possible that it was unrelated to her gabapentin therapy, her improvement occurred coincident with achieving dosages of gabapentin reported to be therapeutic for neuropathic pain states.

In conclusion, we report the successful management of erythromelalgia pain with gabapentin in two patients. Because it is safe and generally well tolerated, it would appear reasonable to initiate therapy for erythromelalgia with gabapentin before administering more aggressive alternatives.

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