

# Erythromelalgia

Erythromelalgia (EM) is a rare, multisystemic disorder characterized by intermittent, intense burning pain, redness, and swelling of the skin, primarily affecting the extremities. The condition is exacerbated by high ambient temperatures and is relieved by cooling the affected area.

Erythromelalgia is often a dermatologic manifestation of various underlying systemic diseases, including hematologic, connective tissue, and vascular disorders, and its presence frequently warrants further investigation to identify and address the root cause.

## **Pathophysiology**

The pathophysiology of erythromelalgia is believed to involve a genetic mutation in the SCN9A gene, which encodes the Nav1.7 sodium channel. This voltage-gated sodium channel is crucial in the regulation of nociceptive (pain-sensing) neurons. Mutations in this gene lead to hyperexcitability of these neurons, particularly in response to thermal stimuli, causing excessive neurogenic inflammation and vasodilation, which in turn results in the characteristic burning pain, redness, and warmth of the affected areas. The abnormal response of blood vessels to nervous system signals is thought to be a key factor in the intense heat sensation and visible redness associated with the condition.

Erythromelalgia is frequently a secondary phenomenon, arising as a symptom of an underlying disease, rather than a primary condition. It has been linked to a variety of hematologic, connective tissue, and vascular disorders, including systemic lupus erythematosus (SLE), platelet disorders, and syphilis. Additionally, certain medications, particularly calcium channel blockers, have been identified as precipitants in genetically predisposed individuals. Therefore, a thorough clinical evaluation to identify potential underlying conditions is a key aspect of the diagnostic process.

## **Clinical Features**

The hallmark of erythromelalgia is intermittent and episodic burning pain in the extremities, often described as an uncomfortable and intense sensation of heat or fire. The pain is typically provoked by heat and alleviated by cooling the affected area or elevating the limbs. The most commonly affected regions are the feet and legs, with the hands and arms being less commonly involved. The affected skin may appear red or purple and may feel warm to the touch. In severe cases, individuals may experience additional features, such as cyanosis (bluish discoloration), livedo reticularis (a net-like mottling of the skin), and necrosis or ulceration in extreme cases.

The pain pattern in erythromelalgia is typically episodic, but a chronic, unremitting pain pattern can occur in some patients, especially in those with more severe disease. Such a presentation carries a worse prognosis and may require more aggressive management. Notably, about 10% of patients may experience spontaneous remission, with symptoms disappearing permanently.

## Diagnosis

The diagnosis of erythromelalgia is largely clinical, based on characteristic symptoms and exclusion of other possible conditions. Diagnostic criteria include:

- Burning pain in the extremities, often triggered by heat.
- Pain relieved by cooling and elevation of the affected area.
- Redness and increased temperature of the skin.
- In some cases, cyanosis, livedo reticularis, or necrosis may also be present.

To rule out secondary causes, a detailed medical history and comprehensive laboratory tests are essential. Testing for autoimmune conditions, hematologic disorders, and infectious agents is often indicated. Genetic testing for SCN9A mutations may also be considered, particularly in cases of idiopathic erythromelalgia or where familial inheritance is suspected.

## Treatment

Management of erythromelalgia focuses on both symptom control and addressing any underlying causes. There is no universally effective treatment, and therapeutic approaches must often be tailored to the individual. Key treatment strategies include:

- **Symptomatic Management:**
  - *Cooling and elevation:* Cooling the affected area with ice packs or other cooling methods can provide immediate relief. Elevating the affected limbs may also help reduce swelling and pain.
  - *Aspirin:* As an anti-inflammatory and antiplatelet agent, aspirin has been shown to provide relief in some patients by reducing the neurogenic inflammation associated with erythromelalgia.
  - *Serotonin reuptake inhibitors (SSRIs):* SSRIs, such as fluoxetine, have demonstrated efficacy in reducing pain and discomfort, possibly by modulating serotonin levels, which influence pain processing.
  - *Gabapentin:* This medication, typically used for neuropathic pain, can help manage the burning pain associated with erythromelalgia, possibly by modulating calcium channels involved in nerve excitability.
- **Advanced Therapies:**
  - *Misoprostol:* A prostaglandin analog, has been reported in some case studies to provide benefit in treating erythromelalgia by reducing pain and inflammation.
  - *Intravenous Immunoglobulin (IVIG):* This therapy has been shown to reduce symptoms in some patients, especially in those with autoimmune-related erythromelalgia.
- **Genetic and Targeted Treatments:**
  - A promising novel agent, *XEN402*, targets the Nav1.7 sodium channel and has demonstrated significant efficacy in preliminary studies, with some patients

experiencing up to 90% reduction in symptoms after a single infusion. This medication offers hope for more effective, targeted treatments in the future.

➤ **Addressing Underlying Causes:**

- If an underlying condition such as systemic lupus erythematosus, syphilis, or a platelet disorder is identified, specific treatment for the primary condition is crucial to improving the erythromelalgia symptoms. In some cases, discontinuing medications like calcium channel blockers may resolve the symptoms entirely.

## Conclusion

Erythromelalgia is a rare and complex disorder characterized by intense, episodic burning pain, redness, and swelling of the skin, most commonly in the extremities. While the condition may be a primary disorder, it is often a manifestation of an underlying disease, which necessitates a comprehensive diagnostic evaluation. Treatment is primarily symptomatic, though novel therapies targeting the Nav1.7 sodium channel hold promise for more effective management. Given the variability in responses to treatment, it is essential for patients to work closely with healthcare providers to identify the most effective approach to managing their symptoms.

## References

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