Erythromelalgia

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Contributor: Nicole Yin

Erythromelalgia is a condition characterized by episodes of pain, redness, and swelling in various parts of the body, particularly the hands and feet. These episodes are usually triggered by increased body temperature, which may be caused by exercise or entering a warm room. Ingesting alcohol or spicy foods may also trigger an episode. Wearing warm socks, tight shoes, or gloves can cause a pain episode so debilitating that it can impede everyday activities such as wearing shoes and walking. Pain episodes can prevent an affected person from going to school or work regularly.

Keywords: genetic conditions

1. Introduction

The signs and symptoms of erythromelalgia typically begin in childhood, although mildly affected individuals may have their first pain episode later in life. As individuals with erythromelalgia get older and the disease progresses, the hands and feet may be constantly red, and the affected areas can extend from the hands to the arms, shoulders, and face, and from the feet to the entire legs.

Erythromelalgia is often considered a form of peripheral neuropathy because it affects the peripheral nervous system, which connects the brain and spinal cord to muscles and to cells that detect sensations such as touch, smell, and pain.

2. Frequency

The prevalence of erythromelalgia is unknown.

3. Causes

Mutations in the *SCN9A* gene can cause erythromelalgia. The *SCN9A* gene provides instructions for making one part (the alpha subunit) of a sodium channel called NaV1.7. Sodium channels transport positively charged sodium atoms (sodium ions) into cells and play a key role in a cell's ability to generate and transmit electrical signals. NaV1.7 sodium channels are found in nerve cells called nociceptors that transmit pain signals to the spinal cord and brain.

The *SCN9A* gene mutations that cause erythromelalgia result in NaV1.7 sodium channels that open more easily than usual and stays open longer than normal, increasing the flow of sodium ions into nociceptors. This increase in sodium ions enhances transmission of pain signals, leading to the signs and symptoms of erythromelalgia. It is unknown why the pain episodes associated with erythromelalgia mainly occur in the hands and feet.

An estimated 15 percent of cases of erythromelalgia are caused by mutations in the *SCN9A* gene. Other cases are thought to have a nongenetic cause or may be caused by mutations in one or more as-yet unidentified genes.

3.1. The Gene Associated with Erythromelalgia

- SCN9A

4. Inheritance

Some cases of erythromelalgia occur in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In some of these instances, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

5. Other Names for This Condition

- erythermalgia
- familial erythromelalgia
- primary erythromelalgia

References

1. Cregg R, Laguda B, Werdehausen R, Cox JJ, Linley JE, Ramirez JD, Bodi I,Markiewicz M, Howell KJ, Chen YC, Agnew K, Houlden H, Lunn MP, Bennett DL, WoodJN, Kinali M. Novel mutations mapping to the fourth sodium channel domain ofNav1.7 result in variable clinical manifestations of primary erythromelalgia.Neuromolecular Med. 2013 Jun;15(2):265-78. doi: 10.1007/s12017-012-8216-8.
2. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. From genes to pain: Na v 1.7 andhuman pain disorders. Trends Neurosci. 2007 Nov;30(11):555-63.Review.
3. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal andpathological pain. Annu Rev Neurosci. 2010;33:325-47. doi:10.1146/annurev-neuro-060909-153234. Review.
4. Drenth JP, te Morsche RH, Guillet G, Taieb A, Kirby RL, Jansen JB. SCN9Amutations define primary erythermalgia as a neuropathic disorder of voltage gatedsodium channels. J Invest Dermatol. 2005 Jun;124(6):1333-8.
5. Emery EC, Habib AM, Cox JJ, Nicholas AK, Gribble FM, Woods CG, Reimann F.Novel SCN9A mutations underlying extreme pain phenotypes: unexpectedelectrophysiological and clinical phenotype correlations. J Neurosci. 2015 May20;35(20):7674-81. doi: 10.1523/JNEUROSCI.3935-14.2015.
6. Estacion M, Han C, Choi JS, Hoeijmakers JG, Lauria G, Drenth JP, Gerrits MM,Dib-Hajj SD, Faber CG, Merkies IS, Waxman SG. Intra- and interfamily phenotypicdiversity in pain syndromes associated with a gain-of-function variant of NaV1.7.Mol Pain. 2011 Dec 2;7:92. doi: 10.1186/1744-8069-7-92.
7. Han C, Dib-Hajj SD, Lin Z, Li Y, Eastman EM, Tyrrell L, Cao X, Yang Y, Waxman SG. Early- and late-onset inherited erythromelalgia: genotype-phenotypecorrelation. Brain. 2009 Jul;132(Pt 7):1711-22. doi: 10.1093/brain/awp078.
8. Waxman SG, Dib-Hajj S. Erythermalgia: molecular basis for an inherited painsyndrome. Trends Mol Med. 2005 Dec;11(12):555-62.