Review article

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Review of primary and secondary erythromelalgia

N. Mann,[1] T. King[1] and R. Murphy[1]

[1]*Department of Dermatology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, UK*

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Summary

Erythromelalgia is a condition characterized by episodic pain, erythema and temperature of the extremities, which is relieved by cooling and aggravated by warming. It is useful to review this topic in light of recent discoveries of the genetic mutations that now define primary erythromelalgia, as opposed to secondary erythromelalgia, which is often associated with underlying medical disorders.

Introduction

Erythromelalgia is a rare disorder characterized by its clinical features of pain and erythema, usually in the extremities of the body. It was termed by Mitchell in 1878 from the Greek words *erythros* (red), *melos* (extremities) and *algos* (pain).[1,2] Primary and secondary forms exist, which both present with similar features, and therefore have been historically labelled with the same name. However, as the genetics and the subsequent mutated sodium channels behind primary erythromelalgia have been discovered, perhaps we should consider these as two completely separate conditions with different causes and potentially different approaches to treatment in the future.

Epidemiology

There is a lack of epidemiological data for the incidence of erythromelalgia in the UK. The incidence of all forms of erythromelalgia in a study in Olmsted County, Minnesota was 1.3 per 100 000 people per year, and it is generally accepted that there is a slightly higher female incidence.[3,4] The Olmsted County study reported separate incidence for primary and secondary forms, but the study looked at historical records from 1976 to 2005, and therefore the definitions of primary and secondary disease are outdated and probably no longer satisfy our modern classification in view of the genetic changes in primary erythromelalgia. The incidence figures are probably an underestimate as the condition often goes unrecognized.

Correspondence: Dr Thomas King, Department of Dermatology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK
E-mail: thomas.king2@sth.nhs.uk

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Aetiology and pathogenesis

Primary erythromelalgia is caused by an autosomal dominant mutation in the *SCN9A* gene, and was first described by Yang in 2004.[5] The *SCN9A* gene has been localized to the 7.94 cM region on chromosome 2q, and codes for voltage-gated sodium channels, NaV 1.7, which are expressed in small nociceptive neurones. The presence of voltage-gated sodium channels are thought to play a crucial role in causing neuropathic pain and pain perception, with the mutant gene altering the biophysical properties of the channel.[6–10]

By contrast, secondary erythromelalgia is a condition with multiple underlying associations. When associated with haematological conditions, the pathogenesis is related to changes to arterioles caused by platelet activation. It is thought that proliferation of the intimal cells and smooth muscle, coupled with thrombotic occlusions secondary to platelet aggregation, causes the symptoms experienced, particularly in the extremities of the body. Furthermore, prostaglandin production from the above activation leads to coagulation pathways being initiated, owing to the inflammatory nature of the condition.[11,12] Table 1 summarizes the key differences between primary and secondary erythromelalgia.

It has been hypothesized that erythromelalgia is a disorder of vascular dynamics, whereby there is

Table 1 Key differences between primary and secondary erythromelalgia.

Parameter	Type of erythromelalgia	
	Primary	Secondary
Gene involved	*SCN9A* gene	None identified
Disease association	Not applicable	Multiple disease associations
Distribution	Symmetrical distribution more likely	Asymmetrical distribution more likely
Age of onset	Younger age of onset	Older age of onset
Treatment	Standard treatment plus targeted treatment (e.g. mexilitine, novel selective $Na_v1.7$ modulators in trials)	Standard treatment plus diagnosis and treatment of associated disease

decreased capillary perfusion creating tissue hypoxia, while simultaneously, there is increased arteriovenous shunting within the skin, which therefore appears erythematous, warm and swollen. It is thought that erythromelalgia may be on the same spectrum as Raynaud phenomenon (RP), with RP having a more prominent vasoconstrictive phase and erythromelalgia having a more prominent reactive hyperaemia.[13,14]

Terminology and classification

There are many confusing and sometimes contradictory terms in relation to erythromelalgia, especially in the older literature prior to the *SCN9A* discovery in 2004. The term 'erythermalgia' in the past has been used interchangeably with 'erythromelalgia', while some authors have used erythromelalgia for the aspirin-responsive disease and erythermalgia for the aspirin-resistant disease.[15,16] Unfortunately, the term 'primary erythromelalgia' is sometimes still used to indicate idiopathic erythromelalgia.[1]

Presentation

There is a lack of accurate data comparing the presentations of primary and secondary erythromelalgia, and they share features, both presenting with pain, erythema, swelling and heat of the extremities.[14,17] A review of cases published long before the current understanding of the gene mutation in primary erythromelalgia reported that primary erythromelalgia is more likely to present in both upper and lower limbs, and is more likely to have a symmetrical distribution compared with erythromelalgia secondary to myeloproliferative disease.[2] Primary erythromelalgia tends to have a younger age of onset in comparison with secondary disease, presenting in the first decade of life, in contrast to a median onset of 49.1 years pain, which is often the most prominent and disabling feature of the condition, can vary between individuals; it may start as a mild burning or itching sensation and progress to a severe burning sensation.[8] Some case reports have observed that the pain tends to start quite suddenly, and can increase in severity and frequency with time.[1,18] However, the pain, along with the other symptoms, tends to occur intermittently, thus making diagnosis more challenging if presentation to a clinician is at a time of quiescence.[8]

The attacks can last from minutes to days, and tend to be precipitated by heat, exercise and physical dependency. As a result, cooling and elevation tend to relieve the symptoms.[1,2] Relief with ice-cold water immersion is so common it is almost pathognomonic of the condition, and can lead to severe tissue damage including nonhealing ulcers and infection necrosis, and can even lead to amputation[13] (Fig. 1). Flares tend to occur later in the day and into the night, causing difficulty in sleeping.[14] The affected distribution tends to be the extremities, most commonly the feet, followed by the hands; in more severe cases, this can go on to involve the arms, legs and even the ears or face, but this is uncommon.[13] Erythromelalgia has a profound impact on quality of life, and can severely limit normal

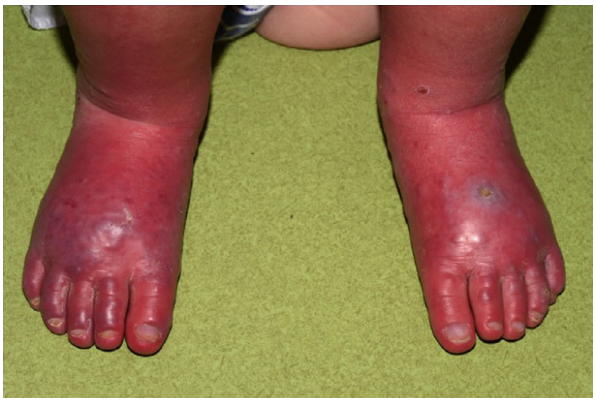

Figure 1 This 5-year-old girl has primary erythromelalgia, with a confirmed *SCN9A* (T647C) mutation. The picture demonstrates marked erythema and swelling of the feet. She had exquisite pain that was relieved with regular ice-cold water immersion, which led to ulceration and infections.

activities of work and social functioning; patients can even become virtually housebound.[13,17,19]

Diagnosis

Diagnosis of erythromelalgia is based on clinical criteria and exclusion of differential diagnoses, including peripheral neuropathies, vasculitis, the redness phase of RP, acrocyanosis and Fabry disease.[20] Strict application of the criteria proposed by Thompson *et al.* (Table 2) has been strongly advised.[14,21] Heat intolerance and relief with cooling are described as hallmarks of the condition, and are very strong indicators.[13] Given that symptoms are intermittent, clinicians may attempt to provoke signs and symptoms by immersing the affected areas in hot water to help aid diagnosis.[13] Raised temperature of affected areas has been seen on thermography, but this is a research tool and is not required to establish a diagnosis.[1,18] Biopsy is not routinely performed and is not considered useful for diagnosis or treatment decisions; however, subtle nonspecific findings of decreased epidermal and perivascular nerve density have been seen in primary erythromelalgia with no evidence of thrombi, as opposed to thrombi in secondary erythromelalgia associated with myeloproliferative disease.[12,22,23] Once erythromelalgia is confirmed to be likely, it can be differentiated into either primary or secondary erythromelalgia.

Types of erythromelalgia

Primary erythromelalgia

A diagnosis of primary erythromelalgia requires exclusion of underlying causes (see 'Secondary erythromelalgia'), it is confirmed by presence of the *SCN9A* mutation and can be inherited or sporadic. Genetic testing is available, with over 20 mutations in the *SCN9A* gene now characterized. This consideration is important because primary erythromelalgia is caused by an autosomal dominant mutation, and therefore an affected individual will have 50% chance of passing on the mutation to each offspring. The NHS offers genetic testing for £625, which is carried out by the East Anglian Genetics Service in Cambridge.[24]

Table 2 Clinical diagnostic criteria proposed by Thompson *et al.*[21]

Burning extremity pain
Pain aggravated by warming
Pain relieved by cooling
Erythema of affected skin
Increased temperature of affected skin

Secondary erythromelalgia

Secondary erythromelalgia has been linked with a variety of underlying associations including myeloproliferative, vascular, connective tissue, musculoskeletal, neurological disorders and certain drugs[1,2] (see

Table 3 Causes of secondary erythromelalgia.[3,13]

Haematological disease
Polycythaemia vera
Idiopathic thrombocytopenia
Leukaemia
Systemic macrocytosis
Drug eruptions
Iodine contrast
Calcium channel blockers
Bromocriptine
Connective tissue disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Sjögren syndrome
Vasculitis
Neoplasia
Primary colon or breast carcinoma
Paraneoplastic
Subcutaneous panniculitis-like T-cell lymphoma
Astrocytoma
Thymoma
Metabolic
Diabetes mellitus (types 1 and 2)
Hypercholesterolaemia
Gout
Infective
Influenza
Acquired immunodefiency syndrome
Recurrent bacterial infections
Syphilis
Musculoskeletal disorders
Sciatica
Carpal tunnel syndrome
Neck and other trauma, including surgery
Burns and frostbite
Neuropathies
Neurofibromatosis
Multiple sclerosis
Small fibre neuropathies
Other
Atherosclerosis
Thromboembolism and cholesterol emboli
Mushroom intoxication and mercury poisoning
Lichen sclerosis

Table 3). Further investigations should be aimed at ruling out these associations and depend on the presentation. Myeloproliferative disorders are often found as an underlying association, but importantly can have a median onset of 2.5 years after the onset of clinical symptoms and therefore it is recommended to screen patients with periodic full blood counts.[2]

Specialist centres in the UK include Great Ormond Street Hospital for Children, and the Pain Control Service and National Hospital for neurology and neurosurgery, pain management centre.[25] The Erythromelalgia Association is an international, all volunteer, nonprofit organization, which provides education, awareness and community support for erythromelalgia, as well as supporting research in this field.[26]

Treatment

The approach to treating primary and secondary erythromelalgia differs. Treating secondary erythromelalgia involves treating any underlying disease, which can be helpful in controlling symptoms in some patients, but has not shown consistent results. Aspirin can be very effective for cases associated with thrombocythaemia, polycythaemia and other blood dyscrasias, but has shown disappointing results when used for symptoms associated with other underlying causes.[1,2,13]

For both primary and secondary erythromelalgia, avoidance of trigger factors is helpful in preventing flares.[2,18] There is great heterogeneity in response to treatment, and many pharmacological agents have been used alone or in combination. Topical capsaicin cream has been reported to help, but may increase pain and redness. Oral treatments include selective serotonin reuptake inhibitors, anticonvulsants, calcium channel blockers and tricyclic antidepressants such as amitriptyline. Infusions of nitroprusside, lidocaine and prostaglandins have also been utilized. More invasive approaches include sympathetic blocks, epidurals and sympathectomy, which have had varying success.[8,13,27,28] Treatment aims are to reduce symptom burden; however, in some case reports remission has been achieved.

Since the gene mutation discovery for primary erythromelalgia, treatments have targeted the mutated sodium channel. Mexiletine, which is a nonselective sodium channel inhibitor (class 1B antiarrhythmic), has been found to have a normalizing effect of the biophysical properties of mutated $Na_v1.7$ sodium channels, and has been found to be very effective in some cases of primary erythromelalgia.[6] Ranolazine, a drug licensed for angina, which has been shown to block $Na_v1.7$ channels *in vitro*, has been successful in treating pain in a patient with primary erythromelalgia according to a recent case report.[29] Oral and topical novel selective $Na_v1.7$ channel modulators are currently undergoing trials.[8] However, given that $Na_v1.7$ is also found on sympathetic neurons, this has the potential to lead to adverse effects.[8,18]

Learning points

- Diagnosis of erythromelalgia is clinical, with investigations aimed at exclusion of differentials and associations.
- Erythromelalgia presents with redness, pain and heat of the extremities, which is exacerbated by warming and relieved by cooling.
- Symptoms are intermittent, which can add diagnostic challenges.
- Primary erythromelalgia is caused by the *SCN9A* gene mutation, which codes for voltage-gated sodium channels ($Na_v1.7$).
- Secondary erythromelalgia may present prior to an associated myeloproliferative disorder and, therefore, serial blood tests should be measured if a secondary association has not yet been found.
- Treatment of pain in erythromelalgia can be difficult, and often polypharmacy is utilized.

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CPD questions

Learning objective

To answer questions based on the diagnostic work-up, and treatments of primary and secondary erythromelalgia.

Question 1

Diagnosis of erythromelalgia is confirmed by which of the following techniques?

(a) Thermography.
(b) Skin biopsy.
(c) Genetic testing for the *SCN9A* gene mutation.
(d) Application of clinical criteria after ruling out alternative diagnoses.
(e) Provoking signs with cold water immersion.

Question 2

If counselling a male patient with confirmed primary erythromelalgia, which is the most accurate advice?

(a) Each child has a 50% chance of inheriting the condition.
(b) Each child has a 25% chance of inheriting the condition if his partner is a carrier of the mutation.
(c) The patient must have inherited the condition from one of his parents.
(d) Both of the patient's parents must be carriers of the mutation.
(e) The patient cannot pass the mutation on to his male offspring.

Question 3

Secondary erythromelalgia is commonly associated with which of the following?

(a) Inflammatory bowel diseases.
(b) Asthma.
(c) Haematological disorders.
(d) Thyroid diseases.
(e) Antibiotics.

Question 4

Which of the following genes is mutated in primary erythromelalgia?

(a) *CDKN2A*.
(b) *SPINK5*.
(c) *FLCN*.
(d) *SCN9A*.
(e) *CYLD*.

Question 5

Which of the following is the best advice for treatment of erythromelalgia?

(a) Ice-cold water immersion is recommended for symptomatic benefit.
(b) Aspirin is particularly useful in cases of secondary erythromelalgia.
(c) Calcium channel antagonists such as mexiletine are particularly useful in cases of primary erythromelalgia.
(d) Nav1.7 could a target for potential new novel therapies for primary erythromelalgia.
(e) First-line treatment strategies could include tricyclic antidepressants, calcium channel antagonists, anticonvulsants or sympathectomy.

Instructions for answering questions

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Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
- Complete the required evaluation component of the activity

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