

Clinical features and management of erythromelalgia: long term follow-up of 46 cases

Louise K Parker* (1), Cristina Ponte* (2, 4), Kevin J Howell (3), Voon H Ong (1), Christopher P Denton (1), Benjamin E Schreiber (1)

(1) Centre for Rheumatology, Royal Free London NHS Foundation Trust, London, UK.

(2) Department of Rheumatology, Hospital de Santa Maria, Lisbon, Portugal.

(3) Microvascular Diagnostics, Institute of Immunity and Transplantation, Royal Free London NHS Foundation Trust, London, UK.

(4) Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon Academic Medical Centre, Lisbon, Portugal.

*equal contributors to this work

Corresponding Author

Professor Christopher P. Denton, Centre for Rheumatology and Connective Tissue Diseases, Division of Medicine, Royal Free Campus, London, Rowland Hill Street, NW3 2PF, UK.

E-mail: c.denton@ucl.ac.uk

Abstract

Objective: To review our clinical experience of this rare condition and describe the clinical features and response to therapy in a cohort of patients with erythromelalgia, a rare condition, characterised by paroxysmal hyperthermia of the extremities with erythema, pain and intense burning.

Methods: Review of the electronic and paper medical records of patients with the diagnosis of erythromelalgia, with a telephone interview to verify and complete clinical information relating treatment and outcome.

Results: 46 patients (41 females) were included in this study. Mean age was 57 years and mean duration of symptoms was 16 years. Raynaud's phenomenon was present in 36 patients (80%) and 4 patients (9%) had systemic sclerosis. Smoking (current or previous) was identified as a possible risk factor in 26 cases and exposure to chronic vibration in 3 cases. Overall, the effect on quality of life was mild in 15% of cases, moderate in 30% and severe in 48%. The most common symptoms were burning (96%), heat (93%), pain (87%), and redness (83%). Symptoms affected the lower limbs in 98% of cases, upper limbs in 76%, face in 20% and trunk in 11%. Triggers included heat (85%), exercise (78%) and time of day (76%). Various medications were tried, showing poor effect in most cases. Intravenous iloprost was given to 27 patients, with benefit in 17 patients (63%).

Conclusion: Erythromelalgia is a rare chronic debilitating condition. Exercise, heat and night time are common triggers. Current medical therapies are seldom effective and further research is sorely needed.

Key Words

Erythromelalgia; symptoms; therapy; iloprost; Raynaud's phenomenon

Introduction

Erythromelalgia was first described by the pioneering neurological physician Silas Weir Mitchell in 1878 [1] as a condition characterised by paroxysmal hyperthermia of the extremities resulting in erythema, pain and intense burning. The term *erythromelalgia* is derived from the Greek words – *erythros* (red), *melos* (extremities) and *algos* (pain). The lower limbs are more commonly involved than the upper ones and involvement is often bilateral and symmetrical. Cold exposure provides relief while warmth intensifies symptoms, which can be intermittent or, in rare cases, constant. Other potential triggers include exercise and dependency of the affected limb [2,3].

Population studies from the South of Sweden and from Olmsted County, Minnesota have estimated annual incidence at 0.36 and 1.3 per 100,000 of the population, respectively, and most published case series have showed a female predominance (ratio 1:2-3) with a wide age range [4,5,6,7].

A genetic association has been described with gain-of-function mutations in SCN9A encoding the sodium channel protein Nav1.7 subunit expressed in sympathetic and nociceptive small-diameter sensory neurons of the dorsal root ganglion [8]. Erythromelalgia can also be secondary to myeloproliferative diseases and blood disorders (especially polycythaemia), connective-tissue diseases, and drug reactions; however, inherited erythromelalgia is usually associated with onset in the first two decades of life [9]. De-novo mutations are common, therefore inherited cases cannot be distinguished from acquired erythromelalgia solely on the basis of age of onset or family history.

Despite the substantial clinical impact of erythromelalgia there are no agreed diagnostic criteria for the condition, no clinical guidelines of management or large randomised controlled trials of treatment.

To provide insight into clinical impact and current management we have reviewed our experience with erythromelalgia. Specifically we describe the clinical characteristics and response to treatment of patients with erythromelalgia in our centre over the last 13 years.

Methods

From our clinical records we identified patients with a diagnosis of erythromelalgia within our connective tissue disease cohort. Erythromelalgia was defined by symptoms and clinical assessment by an experienced connective tissue disease specialist. Demographic and clinical data were reviewed including telephone contact where data were incomplete using a structured simple proforma to standardise data collection. The study was performed with informed consent and local ethical committee approval.

The following data were collated: year of onset of symptoms, year of diagnosis, family history, smoking history, comorbidities, exposure to smoking or vibration, description of symptoms including distribution, triggers and relieving factors, complications, results of serological, neurophysiological and blood flow studies, therapies tried and clinical responses. Patients underwent thermographic assessment and nailfold capillaroscopy as part of routine assessment where co-existent connective tissue disease or Raynaud's phenomenon was suspected. Presence of Raynaud's phenomenon was defined by an experienced clinician based upon history and clinical assessment.

Given the biases involved in retrospective data collection and in a telephone patient survey, we have adopted a descriptive approach and focused on the clinical features, comorbidity ascertainment, especially Raynaud's phenomenon or defined connective tissue disease, and treatment approaches. The benefit or lack of impact of the treatments used was documented.

Results

Review of our clinical cohort identified 111 patients who had been clinically diagnosed with erythromelalgia. Of these 111 patients, 95 (86%) were female. The mean age of symptom onset was 41 years old. Sufficient clinical information was available and corroborated by telephone interview in 46 cases and these comprised the study cohort for this report.

From the final cohort of 46 patients, 41 (89%) were female and the mean age was 57 years at the time of the study. The average age for erythromelalgia onset was 41 ± 16.6 years (range 8-84) and on average patients had 10 years of symptoms before receiving the diagnosis of erythromelalgia.

Raynaud's phenomenon was present in 37 patients (80%), with an average age at the onset of symptoms of 34 years old, on average 7.4 years before the erythromelalgia symptom onset. Four patients (9%) were diagnosed with systemic sclerosis, all with limited distribution. Other connective tissue diseases were diagnosed in a further four patients: an overlap of Sjogren's and rheumatoid arthritis; undifferentiated connective tissue disease with small vessel vasculitis; undifferentiated connective tissue disease; small vessel vasculitis. Four patients had malignancies (three breast cancers and one ovarian cancer). The majority of patients (57%) were past or present smokers, with three current smokers and 23 previous smokers. Exposure to chronic vibration with industrial machinery was observed in three cases (7%).

With regard to family history, 12 patients had a first-degree relative with Raynaud's phenomenon (11 of these 12 patients also had Raynaud's phenomenon), six patients had a first-degree relative with a connective tissue disease (three rheumatoid arthritis, one vasculitis, one systemic lupus erythematosus and one limited cutaneous systemic sclerosis with discoid lupus) and three patients reported a family history of erythromelalgia (in a father, a mother and a son).

The most common symptoms were of burning (96%), heat (93%), pain (87%), redness (83%), swelling (65%) and numbness (54%). They were described as continuous in 22 cases (48%) and intermittent in 24 cases (52%). Symptoms affected the lower limbs in 45 patients (98%), upper limbs in 35 (76%), face in 9 (20%) and trunk in 5 (11%). Patients reported worsening with hot environments (85%), exercise (78%) and night-time (76%) and improvement with cooling (78%) and elevation (52%). Complications included infection in three patients (7%) and skin breakdown – including ulcers and fissures - in six patients (13%).

Overall, the effect on quality of life was self-rated as non-existent in three patients (7%), mild in seven (15%), moderate in 14 (30%), and severe in 22 (48%) with intolerance to any physical activity in six of these patients.

All cases had routine haematological assessment. Blood tests showed a mean haemoglobin of 13.6 g/dL, mean platelets of $285 \times 10^9/L$ and mean ESR of 10 mm/1st hour. No cases of polycythemia or thrombocytopenia were found.

Autoimmune serology, including antinuclear antibodies (ANA) and extractable nuclear antigen panel, was available for 45 patients. Of these, ANA was positive in seven patients. Of the four patients with limited cutaneous systemic sclerosis, the staining patterns were consistent with anti-centromere; anti-RNA polymerase; nucleolar and fine speckled and homogenous staining. No other antibodies to extractable nuclear antigens were detected. Anti-double stranded DNA was tested in 37 patients (all results negative), anti-neutrophil cytoplasmic antibody was tested in 18 patients (all results negative) and complement levels assessed in 34 patients (five patients with results below normal range; one had a background history of undifferentiated connective tissue disease).

Additional investigations were performed in selected patients. Infrared thermography with cold challenge of the extremities was performed in 20 cases (**Figure 1**). Thermography findings (“vasospastic” or “normal” rewarming after cold challenge) were concordant with the reported presence or absence of Raynaud’s phenomenon in 16 of 20 cases. Three patients without clinical Raynaud’s were nonetheless vasospastic on thermography, and one patient with Raynaud’s phenomenon exhibited a normal rewarming response. Formal neurophysiology testing of thermal thresholds was performed in seven patients and were diminished in four of them. Capillaroscopy was performed and graded in 20 cases and showed minor changes (dilatation or drop out) in those cases (n=8) with features of an associated connective tissue disease and no other consistent abnormal patterns were identified in this cohort.

A wide variety of medications were tried. **Figure 2** lists all therapies tried by at least five patients and the subjective report of efficacy. Overall, a marked response was reported in 5% of cases, a mild or moderate response in 23% and no response in 72%. Intravenous iloprost was the treatment that showed the best efficacy; it was administered to 27 patients with positive response reported by 17 patients (63%). A moderate or marked response to iloprost was reported in 12 patients (52%) with Raynaud's phenomenon and two patients (50%) without Raynaud's phenomenon. The treatment regimen was similar to that used for Raynaud's phenomenon with a starting dose of 2ng/kg per minute, increasing to a target dose of 2ng/kg per minute if tolerated and administered for 6 to 10 hours daily on 5 consecutive days.

Discussion

Our findings suggest that erythromelalgia is most common in women, with a large age spread and an average age of 57 years. Symptoms varied quite widely, but sensations of burning and heat were found in about 95% of patients. Most patients found their symptoms were worse in hot environments and relieved with cooling. These findings are consistent with those of other studies, which described attacks of erythromelalgia being precipitated by heat, exercise and standing [4,10,11,12,]. The Mayo Clinic published a description of 168 patients with erythromelalgia treated between 1970 and 1994 [6]. They reported an average age of 56 ± 18.9 years compared to 41 ± 16.6 in our cohort. In their cohort 73% were female compared to 89% in our cohort. They found myeloproliferative disease in 10% of patients (as opposed to none in our cohort).

Interestingly, in our series, 80% of patients described some features of Raynaud's phenomenon in addition to erythromelalgia, while 18% had associated connective tissue diseases. A further 7% of patients without clinical Raynaud's phenomenon were nonetheless shown to have a component of peripheral vasospasm by microvascular assessment [**Figure 1**]. The high incidence of vasospasm in

this group, combined with the regular use of cooling strategies for symptomatic relief, may have contributed to the risk of skin ulceration observed.

Our findings confirm the refractory nature of erythromelalgia and resistance to many treatment options with relatively little alleviation of symptoms using the majority of therapeutic interventions [Figure 2]. Overall, the best response appeared to be with intravenous prostacyclin therapy, described as somewhat or very helpful by 63% of patients. This approach may therefore be considered in severe or refractory cases. Interestingly, we found no association between presence of Raynaud's phenomenon and response to intravenous iloprost therapy. In one small pilot randomised double blind trial of iloprost (n=8) versus placebo (n=4), treatment with intravenous iloprost was associated with reduction in symptoms and in sympathetic dysfunction [12]. In the Mayo clinic series, they did not report any use of intravenous prostacyclin analogues, nor use of gabapentin or pregabalin (the latter drug was not available at the time). No treatments were found to be particularly effective, with 50-80% finding each treatment not helpful at all, and only 20% finding treatments very helpful.

In a follow up prospective study performed at the Mayo Clinic between 1999 and 2001, detailed vascular and neurological assessment in 57 patients showed frequent small fibre neuropathy, with 86% showing evidence of abnormal autonomic reflexes. During symptoms, blood flow increased ten-fold in the affected limb [10].

The association between Raynaud's phenomenon and erythromelalgia has been described and various hypotheses put forward as to the possible link between the two conditions [10]. Potential mechanisms of action of iloprost in erythromelalgia include alleviation of Raynaud's phenomenon as well as modulation of platelet function, endothelial cell homeostasis or other metabolic effects of intracellular upregulation of cyclic AMP. In our cohort of Raynaud's phenomenon associated erythromelalgia, Raynaud's phenomenon appears to precede the onset of erythromelalgia and most demonstrated vasospastic responses on thermography; this suggests that in a cohort of

erythromelalgia, the reactive hyperaemic phase may be triggered by the initial vasospasm. This is supported by other studies that showed basal skin perfusion is reduced in the extremities of patients with erythromelalgia [13,14]. It is possible that pathogenic processes may be shared including enhanced vascular tone with increased vasomotor reactivity, enhanced receptor hypersensitivity or increased vasoactive mediators.

Strengths of this study include a relatively large number of cases at a single centre, with a consistent approach to management, including investigation and treatment. In addition, the specialist nature of the service and links with rheumatology ensure that associated connective tissue disease is robustly diagnosed. To date, this is the largest reported cohort of patients with erythromelalgia treated with iloprost.

Our study had several limitations. Of the 111 patients with erythromelalgia whose case notes were reviewed, only 46 patients completed the questionnaire and information on the other 65 patients who had been treated at the unit was not available. The retrospective nature of the study inevitably left some gaps in data and relied on patient recall to answer our screening questions. However, the results reported in this study are broadly consistent with the experience of other centres. In addition, no cases of erythromelalgia associated with myeloproliferative disorder were included and so we cannot extrapolate our observations about treatment response into this group of patients where primary management generally focuses on the underlying haematological abnormality.

In summary, erythromelalgia remains rare and poorly understood, although recent advances have been made, particularly with identification of a genetic basis in some patients, and new impetus for exploring targeted therapies. There remains an important unmet need for effective therapy in this patient group. The present study adds to the literature of case series in this condition, but clearly leaves room for well-designed prospective study of patients with erythromelalgia. There has been little research on the clinical relevance of recently described genetic abnormalities [8,12]. However,

a clinical trial of carbamazepine (NCT02214615) is ongoing, as are phase II trials of selective blockers of Nav1.7 sodium channels. Very small pilot studies have indicated that agents which antagonise this voltage gated sodium channel have been associated with a reduction in symptoms [15].

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Figure legends

Figure 1. Assessment of erythromelalgia by infrared thermography with cold challenge of the extremities

Digit temperature responses in erythromelalgia to cold challenge of the extremities for one minute in water at 15°C. Left panel – “normal” response curve to foot cooling, along with an infrared thermogram recorded ten minutes after cold stress. Right panel – “vasospastic” response curve to hand cooling from another patient, plus thermogram from ten minutes post cold challenge.

Figure 2. Medications used for erythromelalgia symptoms and their reported efficacy

The range of treatments that were used in this cohort is indicated together with the patient reported benefit from each agent. The largest proportion of cases reporting benefit was for iloprost followed by potential neuromodulator agents including gabapentin, pregabalin or tricyclic anti-depressant drugs. More detail is provided in the text.

Figure 1. Assessment of erythromelalgia by infrared thermography with cold challenge of the extremities.

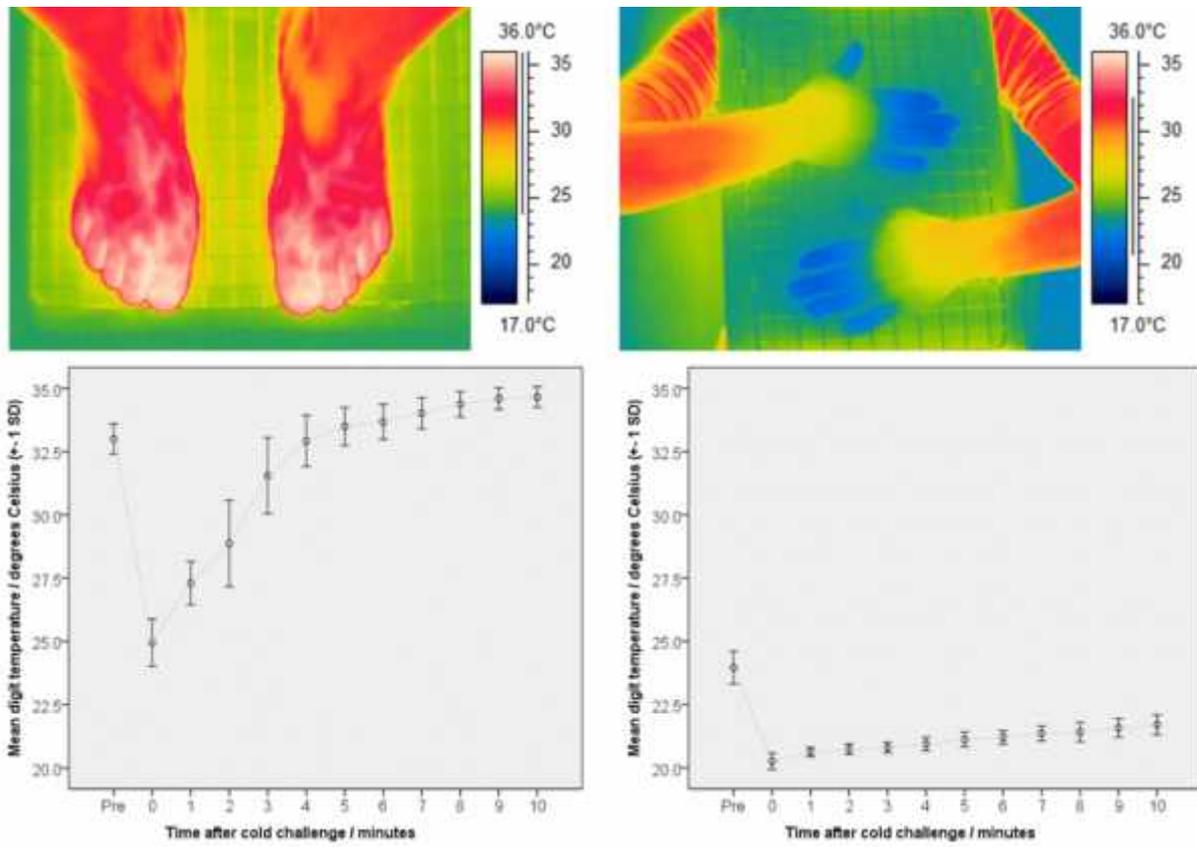


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