

Erythromelalgia: symptom or syndrome?

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Introduction

To "put your feet up" after a hard day's work is a most pleasant form of relaxation, but for the erythromelalgic patient the phrase has a more sinister meaning. Erythromelalgia (EM) is a disorder characterized by intense burning pain, increased temperature and redness of the skin, particularly of the lower limbs. The symptoms are precipitated by exposure to heat, dependency and exercise. Partial relief can be obtained by cooling and elevation. The disease can be debilitating and distressing

Nomenclature

Although the syndrome itself was described by Mitchell [1] in 1878, the first documented case was reported in 1834 by Graves.[2] Mitchell named it erythromelalgia (EM) based on three Greek words: erythros (red), melos (extremities) and algos (pain). Mitchell was not entirely certain, however, whether an increase in skin temperature should be part of the syndrome. Smith and Allen [3] in 1938 proposed that the syndrome be named erythermalgia (erythros, therm (heat), algos). However, although EM does not include the description of an elevation in skin temperature, the latter does not include reference to the involvement of the limbs which is one of the typical features of the disease. There is also a completely descriptive term, erythermomelalgia,[4] which is occasionally used in the literature. However, for obvious reasons, use of this tongue twister has not been widespread. For convenience we use EM in common with most other authors.

Symptoms of erythromelalgia

EM begins as an itching or prickling sensation which progresses to burning pain of a severe nature. The episodes are associated with redness, warmth and sometimes swelling of the involved part. EM is much more common in the legs than in the arms. The attacks last from minutes to days and are provoked by exercise, warmth and dependency of the limb. The symptoms can be induced by increasing the skin temperature into the critical range of 32 and 36°C.[5] Thus, attacks occur when the patients put their limbs under bedcovers at night, near heaters or into warm water, when they wear shoes or gloves or walk. Relief can be obtained by lowering the temperature of the skin, thus patients frequently expose their extremities or immerse them in cool or ice water. Cases have been reported whereby extreme measures have been undertaken to lower skin temperature, for example, sleeping with the feet out of a window, in the fridge or walking barefoot in the snow (personal communications and others).[6]

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Primary and secondary erythromelalgia

Erythromelalgia can take either a primary or secondary form. In primary EM there is no associated disorder, it exists in isolation. In contrast, secondary EM is associated with a number of disorders, particularly those with an increase in the platelet count, for example, thrombocythaemia,[7] in hyperviscosity syndromes, for example, polycythemia rubra vera[8] and where there is microvascular ischemia,[8-11] particularly when the ischemia is part of an inflammatory vascular disease such as occurs in diabetes[12] and systemic lupus erythematosus (SLE) [9] (Table 1). One should always attempt to differentiate between primary and secondary disease as the etiology, pathology and, therefore, treatment of primary and secondary EM are quite different. This is not always easy, but some specific clinical and laboratory features as delineated below may be helpful (Table 2).

Table 1 The associated conditions of erythromelalgia

| | |
|----------------------------------------------------------------|-------------------------------------------|
| Thrombocytosis | Microvascular ischaemia |
| Thrombocythaemia ⁷ | Systemic lupus erythematosus ⁹ |
| Polycythaemia rubra vera ⁸ | Rheumatoid arthritis ⁸ |
| | Diabetes ¹² |
| Hyperviscosity | Hypertension ¹¹ |
| Leukaemias particularly chronic myeloid leukaemia ⁷ | Syphilis ¹⁰ |
| | Mechanism unknown |
| | Familial nephritis ²⁹ |
| | Gout ³⁷ |

The five criteria for primary EM were defined by Browns in 1932. They are as follows:

- Attacks of bilateral or symmetrical burning pain in the hands and feet.
- Attacks initiated or aggravated by standing, exercise or exposure to heat.
- Relief is obtained by elevation and exposure to cold.
- During attacks the affected parts are flushed and congested and exhibit increased local heat.
- The condition is refractory to treatment.

Using these five criteria as a clinical guide, primary EM can often be separated from secondary EM. In primary EM both arms and legs can be affected. In secondary EM, the attacks may be unilateral or otherwise asymmetrical usually affecting only the lower limbs. Furthermore, we and others[13] have found the secondary group more amenable to treatment. An additional differentiating feature is the age of the patient, with a younger age group affected by the primary form. The average age of onset of secondary EM is usually well over 40 years.[13] The primary form is also suggested by a family history of EM [14] and occurs more frequently in the male sex. The sex distribution appears equal, however, in the secondary form. Although the etiology may differ, trophic changes occur in both. In primary EM the symptoms can be so severe that excessive cooling is employed such as immersion in iced water, and cold injury may result. In secondary EM decreased tissue nutrition and trophic changes

Table 2 Primary and secondary erythromelalgia

| Primary | Secondary |
|----------------------------------------------|------------------------------------------------------------|
| Limbs affected symmetrically and bilaterally | Nonsymmetrical distribution, can affect single limb only |
| Often both arms and legs | Usually lower limbs |
| Trophic changes self-induced through cooling | Trophic changes reflect underlying ischaemia |
| Younger age group | Older age group |
| Men predominate | Men and women affected |
| Family history possible | Family history unlikely |
| Normal blood tests, e.g. ESR | Abnormal tests on occasion, e.g. ESR, FBC, immunopathology |

occur secondary to ischemia. The mechanisms by which cooling produces clinical relief may also differ in the two groups. Cold will induce anesthesia but, additionally, in the primary form it will produce vasoconstriction and in secondary EM a decreased tissue oxygen requirement.

Pathology

In primary EM where there is no associated disorder the classical concept of excessive vasodilatation and increased blood flow in the absence of ischemia is probably correct. It is of interest that primary EM and primary Raynaud's disease often co-exist.[15] Raynaud's disease is episodic digital ischemia secondary to vasospasm provoked by cold, and is thought in the primary form to be linked to some mechanism of vascular tone instability.[16] As with primary Raynaud's disease, primary EM is linked with migraine[17] and also possibly with pre-eclampsia in pregnancy, [18] though large epidemiological studies have not been possible in a disease as rare as EM.

The pathology of primary EM is not fully understood. It might be supposed that the generalized instability of vascular tone might cause distress by increased blood pressure in the minute skin vessels during an EM attack. However, although such increased blood flow might initiate the symptoms, it does not maintain them as shown by the fact that the distress is not alleviated by obstructing the blood flow using a proximal blood pressure cuffs.[8] Uno and Parker[19] demonstrated a reduction of nerve terminals in the periarterial and sweat gland plexi almost like a congenital 'sympathectomy'; however, this was only a single case study. A defective prostaglandin (PG) metabolism has also been postulated. Jorgensen and Sondergaard [20] reported two EM patients who produced grossly abnormal blistering reactions to intradermally injected PGs with a normal reaction to other inflammatory mediators such as serotonin, histamine and bradykinin. PGs are highly vasoactive in the human skin. When injected dermally the PGs of the 'E' family produce a prolonged erythema. PGs are also known to cause hyperalgesia and modulate pain sensation.[21] However, although an increased sensitivity to PGs could explain the symptoms of EM it does not explain what triggers the attack or why the patients can experience symptom-free intervals.

Of interest is a report from China suggesting that the development of EM may be connected with virus infections of the respiratory tract.[22] This report documents an outbreak of EM in five schools in one city where 12% of the students developed EM. Sixty-one per cent of the patients had symptoms of an upper respiratory tract infection just before the EM began and 91% of pharyngitis. A pox virus was later isolated from the sufferers but as human infection with pox virus is uncommon today the relevance of the above findings is uncertain.

The current research into neuropeptides and their effects may, however, be relevant to EM. Calcitonin gene-related peptide (CGRP) is a marker for a class of sensory ganglion neurones in the superficial spinal and medullary dorsal horn.[23] Peripheral terminals with CGRP-like immuno-reactivity are found in tissues in which sensory stimulus is usually painful. This suggests a role for this peptide in nociceptor processing. CGRP is

also an important vasodilator. A report of a patient with the features of EM was recently published [24] showing increased staining for CGRP in the spinal cord at the point corresponding to the distribution of the perceived burning pain. As approximately 42% of our primary EM patients date their symptoms from a time of back injury (unpublished observations) the above hypothesis is attractive. Back injury is, however, common and further studies are required to investigate the occurrence of back injury in these patients and the CGRP hypothesis.

From the nature of the symptoms in primary EM it seems logical that the underlying cause must be some mechanism whereby blood flow is intermittently increased. Interestingly, however, the mechanism of this increased flow could be ischemic. Mandell et al [25] suggested that, due to the initial increase in blood pressure within the microcirculation, the precapillary arterioles constrict to protect the vulnerable capillaries. This increased tone diverts blood to the deep dermal and subdermal arteriovenous shunts. Blood flow, they theorize, may therefore be deficient distally and this ischemia may further stimulate blood flow.

An ischemic basis for secondary EM is more firmly established. We believe it can take two forms: (1) inappropriately increased blood flow through the arteriovenous (A/V) anastomoses and (2) reactive hyperemia. Core body temperature is maintained within a narrow range by thermal regulatory mechanisms that rely largely on variations in cutaneous blood flow. Several features make the cutaneous circulatory system well suited for its role in thermal regulation. One of these features is the arteriovenous anastomosis which are abundant in acral areas (Figure 2). In warm or hot environments (between 32 and 36°C) the A/V anastomoses open and heat exchange with the external environment takes place. In cool environments the nutritional flow is maintained whilst the AN anastomoses close to conserve heat. In 'ischemic' secondary EM some obstruction to nutritional flow might occur. This could be through various mechanisms such as platelet aggregation,[7] hyperviscosity of the blood[8] or endothelial cell swelling. Anaerobic respiration of the cells and tissue damage causes release of inflammatory chemicals which cause both pain and vasodilatation of the A/V anastomoses. The end result is a continuous surge of blood through the A/V shunt into the venous side of the circulation which completely bypasses the narrowed or occluded nutritional vessel. The decreased flow in the nutritional vessels, if prolonged, would result in the ischemia-related trophic changes sometimes seen with secondary EM. However, the increased flow in the A/V anastomoses would be manifest clinically as erythema and an objective increase in temperature of the affected area. This hypothesis is supported by objective measures such as the increase in Doppler detected flow and hot thermograms but low tissue pO₂ levels reflecting poor microcirculatory flow.[7]

Table 3 Investigation of erythromelalgia

| | |
|---|------------------------------------------------------------------------------------------------------------------------------------------------------|
| ● | History and examination |
| ● | Full blood count including platelet count and WBC differential |
| ● | ESR/plasma viscosity |
| ● | Immunopathology – antinuclear antibody and RA latex – ?anticardiolipin antibody |
| ● | Blood sugar |
| ● | Noninvasive vascular tests, e.g. – Doppler pressures – thermography – tissue pO ₂ monitoring – laser Doppler flow measurement |

A number of patients may have a reactive hyperemic basis for their symptoms. We have already noted the association of Raynaud's phenomenon with EM.[15] A significant number of EM-like patients in whom cold-induced vasoconstriction can be objectively demonstrated note no symptoms during the vasospasm but suffer dreadfully from

burning and warm extremities during the return of blood flow-the so called reactive hyperemic response. In these cases the ischemic stimulus is vasospasm rather than the platelets or other cellular elements described earlier and the treatment must reflect the underlying ischemic etiology.

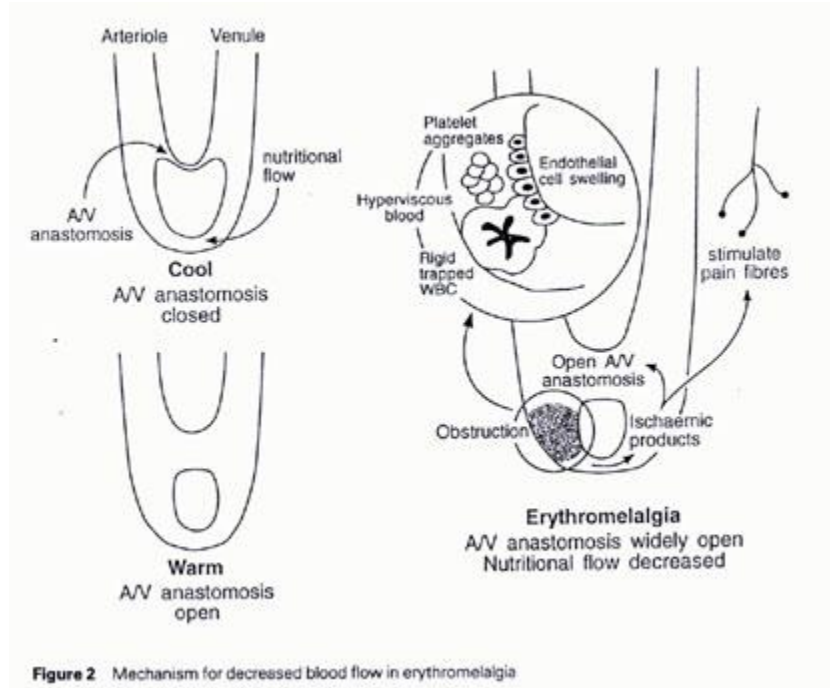


Figure 2 Mechanism for decreased blood flow in erythromelalgia

Incidence and prevalence

The number of primary cases of EM are far fewer than those of secondary EM, although the exact ratio is unknown. EM symptoms can predate the associated disease by 12 [8] to 16 [7] years so a number of patients initially documented as primary EM may in fact be early secondary EM. Some workers believe so strongly that the vast majority of primary EM patients will progress to secondary EM that they recommend continuous follow-up and blood tests.[13] The primary EM population is likely to decrease further as more sophisticated laboratory tests become available. Our own EM investigation unit is a tertiary referral center in which we see only cases where a previous hospital consultant has failed to determine a cause for the EM. Using a six-hour program (two three-hour sessions) we find an associated disease or underlying cause for the symptoms in approximately 60% of patients: thus, as we understand more about the mechanism of blood flow so the primary EM population diminishes.

Not only is it difficult to calculate the incidence of both primary and secondary EM but it is also impossible to document the true incidence of each associated disease in secondary EM. The reasons for this are two-fold. (1) The literature is inaccurate. One of the major criteria for the diagnosis of EM is an increased temperature of the affected part not just the sensation of heat. Even in 1972 a review of the literature [6] showed that only approximately half the published reports dealt with true EM. The others dealt with

erythralgia (red, pain), most probably having their origins in obstructive peripheral vascular disease. (2) The clinician referral patterns produce a marked bias, for example, Michiels and his colleagues in The Netherlands have published widely on EM. The majority of their patients have a myeloproliferative disease, usually thrombocythemia. Such has been the frequency of this relationship they suggest that "EM is a separate microvascular disorder that appears to be an expression of underlying thrombocythaemia." In contrast only 21 out of 51 (41%) of patients presenting to the Mayo clinic had secondary EM[8] and our own experience with 63 patients reveals only two with a myeloproliferative disease. We do not believe the incidence of associated diseases varies so widely with geography and remain convinced that the above merely reflects referral patterns. Support for this comes from our own hematologists who have a number of patients with EM and myeloproliferative disorders which they manage satisfactorily without referral to our group.

Investigation

Once the diagnosis of EM has been made on clinical grounds it is important to differentiate between primary and secondary EM (Table 3). Often the history itself will provide pointers to the associated disorder, for example, polyuria and polydipsia in diabetes and photosensitivity in SLE. Similarly, clinical examination may be helpful and should be detailed, with particular attention being paid to the blood pressure, peripheral circulation and nerve supply.

A simple full blood count, including platelet count, may point to some myeloproliferative disorder and a bone marrow aspirate may be required. A plasma viscosity measurement can be helpful if available. If not, an ESR should be measured. This is usually low in primary EM. An elevated blood sugar may point to diabetes and a positive antinuclear antibody test to SLE. A rheumatoid factor should also be part of the immunopathology screen and we have seen two patients with EM whose blood was positive for anticardiolipin antibody (Antiphospholipid Syndrome).

Although the equipment in various vascular laboratories tends to differ throughout the country, 'noninvasive' vascular tests can be helpful. Essentially a measure of both the macro- and microcirculation is required with some device to differentiate microcirculatory nutritional flow and flow in the A/V anastomosis. For example, thermography will show the increase in heat, although a tissue oxygen monitor will show decreased tissue pO_2 . The microcirculation should be assessed in both a warm and cold environment and the effect of posture will give some insight into autonomic nervous control, for example, failure of vasoconstriction on standing will occur in some diabetics. We have our own program of tests devised from a six-hour testing program and are currently investigating these prospectively. If validated we hope these will be generally useful to others faced with the clinical problem of EM.

Differential diagnoses

Erythema and burning pain may be seen in obstructive vascular disease, particularly

Buerger's disease.[6] However, the presence of cold extremities differentiates it from EM. Fabry's disease in children can present with episodes of burning pain in the feet and palms of the hands.[26] These symptoms may predate the cutaneous angiokeratomas diagnostic of this disorder, however it can be easily diagnosed by demonstrating deficient alpha-galactosidase A activity in the blood.

There are a number of syndromes that can closely mimic EM, in particular the posttraumatic reflex dystrophies. These include causalgia, reflex sympathetic dystrophy and shoulder-hand syndrome.[27] Burning pain and hyperalgesia are features of these conditions, although skin temperature and color vary. The extremity is usually cold and painful but can be warm and erythematous. However, virtually all cases of post-traumatic reflex dystrophy are associated with trauma, for example, physical trauma in the case of reflex sympathetic dystrophy and cerebrovascular accident or myocardial infarction in the case of shoulder-hand syndrome.

Infection in the form of bacterial cellulitis should also be considered as a differential diagnosis of a warm painful leg. In reality, however, confusion between EM and bacterial cellulitis is not common.

Management of erythromelalgia

The choice of therapy for each EM patient depends on its respective etiology. Poorly defined patient groups have led to widespread controversies in the literature. Obviously, if microvascular ischemia contributes to EM, vasodilators may be of use, however, their use in a vasodilatory EM is contra-indicated, and may worsen the situation.[28] Conversely, beta-blockade may worsen ischemic EM but help vasodilatory EM. [14,29] Those workers who study predominantly EM secondary to thrombocythemia, can actually use a response to aspirin as a diagnostic test,[7] whereas other forms of EM referred elsewhere will receive no benefit from such treatment.[30] We, therefore, divide the treatment of EM into four broad groups:

- 1) aspirin (and possibly other cyclo-oxygenase inhibitors);
- 2) vasodilator therapy;
- 3) vasoconstrictor therapy;
- 4) symptomatic treatment.

1) Aspirin

Even in low dose (75mg) aspirin can provide relief for two to four days in some patients, particularly those with a myeloproliferative disease, especially thrombocythaemia[7] and those with some forms of microvascular obstruction, e.g. diabetes.[12] The mechanism whereby benefit is obtained is not entirely clear. Although the duration of benefit might suggest an antiplatelet effect, other antiplatelet drugs do not control EM.[7,13] Furthermore, it is known that aspirin's antipyretic effects are not long-lived enough to produce the above benefit. Inhibition of prostaglandin synthesis via its cyclooxygenase inhibiting activity may be relevant,[21] as may its free radical scavenging properties.[31] Reperfusion generated free radicals are thought to contribute

to the reactive hyperemic response and microvascular thrombosis.[32]

2) Vasodilators

Patients with poor microcirculatory flow as a basis for their EM may benefit from such therapy. We have obtained benefit with naftidrofuryl. This is not a strong vasodilator and part of its mechanism of action may be to decrease tissue oxygen requirement and serotonin antagonism.[33] Nifedipine may also be used in the retard formulation but its potent vasodilatory effects can, by themselves, cause EM[34] so great care must be taken with patient selection. Some authors report success with nitroprusside[35] and methysergide,[12,17,36] the serotonin antagonist. Others have not found these to be helpful, although patient selection has not been clearly defined in these studies.[11,14,37] We[38] and others[39] have used prostacyclin and prostacyclin analogues, but as intravenous administration is required, this should be reserved for very severely affected patients. Sympathectomy will, theoretically, improve ischemia but worsen or, indeed, cause vasodilatory EM. Reports of both favorable and unfavorable responses are published in the literature.[40,41] If considering this treatment then a temporary sympathectomy using a local anesthetic should first be tried.

Interestingly, it has been suggested[11] that vasodilatation can be used as a treatment even in cases where there is a documented increase in flow. The mechanism of benefit is thought to be through the steal phenomenon seen in patients receiving vasodilators for obstructive peripheral vascular disease where the widespread systemic vasodilatation steals blood away from the affected area.[42] Such a steal phenomenon may also explain an apparent lack of benefit in some ischemic EM patients where the microvascular obstruction is severe. Response to vasodilator therapy is unpredictable and patients should be warned about a possible aggravation of symptoms. Such an aggravation, however, should disappear on cessation of the vasodilator.

3) Vasoconstrictors

Beta-blockade is anecdotally the most promising form of vasoconstrictor treatment for EM and reports of its success can be found in the literature.[9,30] Unfortunately, as with the vasodilators, if inappropriately given the EM can worsen. If their use is considered appropriate the unselective beta-blockers have the most potent peripheral vasoconstricting effects.

Ephedrine has been used in the past, though its side effect profile is high in the doses required to relieve the EM symptoms.[43]

4) Symptomatic treatment

We have achieved our best responses by combining the above with symptomatic treatment. 'Comfort shoes' to relieve pressure over the soles of the feet can help and are available on prescription. Patients should be instructed to avoid extremes of temperature, for example, direct heat such as from a car heater onto the feet and they should be

advised against cooling below approximately 20°C as ice emersion can cause tissue damage and less severe temperature drops will provoke a reactive hyperemia response.

Usually we employ one of the drugs used in the management of chronic pain.[34] Both amitriptyline and carbamazepine have proven very valuable to us by controlling the burning sensation/pain.[44] On occasions, transcutaneous electrical nerve stimulation (TENS) has provided benefit.

No one treatment is superior to another and the choice of drug must be made after careful consideration of the clinical and laboratory findings. In general, combinations have proven more useful to us than a single drug. It should also be noted that the treatment of the associated disease can induce remission of the EM symptoms, for example, venesection in polycythaemia rubra vera[45] and prednisolone in SLE.[9]

Conclusion

Erythromelalgia can produce severe and intractable symptoms. Investigations should be aimed at detecting the underlying or associated pathology otherwise treatment will be haphazard and even detrimental. The true incidence of EM has yet to be determined as has the frequency of associated disorders. Literature reports are biased by referral patterns and advice given should only be employed after careful assessment of each individual patient.

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