

Erythromelalgia

Erythromelalgia: two case reports and literature review

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Abstract: Erythromelalgia is a rare disease of unclear etiology characterized by recurrent erythema, burning pain and warmth of the affected extremities. In this paper we reported 2 cases of primary familial erythromelalgia and difficulties with achieving a significant improvement with the currently available treatment. Moreover, this paper provides a brief update on pathophysiology, prognosis and treatment of erythromelalgia.

Key words: erythema, erythromelalgia, limb pain, microcirculation, sodium channel mutation

INTRODUCTION

Erythromelalgia (EM) is a rare disorder (2.5–3.3/1 million/year), characterized by 3 major symptoms: redness, warmth and burning pain of the extremities. The first case of EM was described by Graves in 1834. In 1878 Mitchel coined the term “erythromelalgia” (*erythros* – red, *melos* – limbs, *algos* – pain). In 1938 Michiels suggested to reserve the term “erythromelalgia” to cases secondary to myeloproliferative disorders and to apply the term “erythralgia” (therme-warmth) for idiopathic disease, unresponsive to aspirin therapy. Initially 3 diagnostic criteria were identified: red, hot and painful extremities. Thereafter the diagnostic criteria were expanded to include 3 other symptoms: aggravation of symptoms in response to warmth, relief by cold and unresponsiveness to therapy [1–3]. In primary EM there are no characteristic histopathologic changes [4] nor are there changes in laboratory tests; thus the diagnosis is still based upon clinical symptoms. Presently Thompson’s criteria are most commonly used: 1) burning pain of the extremities, 2) aggravation of pain by warmth, 3) pain relieved by cold, 4) erythema of affected skin, and 5) increased temperature of affected skin [1,2].

In EM symptoms are usually symmetrical, and more often involve lower (88%), than upper extremities (26%); women (73%) are more often affected than men (27%). In most cases symptoms are not persistent, but recurrent (97%) and onsets can last from minutes to several hours. Symptoms may be worse at night or after alcohol consumption and are aggravated by high temperature of the environment, warmth, and

physical exercise. The pain can be relieved only by cold. The symptoms are so strong and annoying, that patients often act in a way considered bizarre. Peculiar behaviors have been described, including immersing limbs in ice water, sleeping with feet extended through an open window in the winter time, walking barefoot in the snow or even placing extremities inside a refrigerator every time a “burning hot” pain appears. Tissue damage (ulcers, necrosis) occurs, but is probably not associated with the disease or with atrophic changes but results from frostbite caused by excessive cooling [3].

It is important to distinguish primary, idiopathic, familial EM with early onset of symptoms, from EM that is secondary to other disorders and responds to therapy of such causational disorders. Most often secondary EM is associated with myeloproliferative disorders such as essential thrombocythemia, polycythemia vera and leukemia [5,6]. There are cases of paraneoplastic EM [7] and EM as a part of autoimmune neuropathy [8,9]. The typical symptoms of EM appear also in other diseases such as: diabetes, rheumatologic diseases (rheumatoid arthritis, systemic lupus erythematosus), multiple sclerosis, AIDS and other infectious diseases [2,3,10]. In those cases of secondary EM symptoms were tied to underlying conditions: increase number of blood cells in myeloproliferative diseases, pathologic angiogenesis in neoplastic disorders, polyneuropathy in diabetes. EM was observed after use of certain drugs, for example verapamil, nifedipine, bromocriptine, as well as after mushroom poisoning with *Clitocybe acromelalga* and *C. amoenolens* [11].

The reason of coexistence of primary EM and hypertension in some cases is not well understood. The numbers of hypothesis about EM etiology have been raised. Many mechanisms have been considered: vasculopathy, neuropathy, local tissue hypoxemia and increased cellular metabolism. One of these hypotheses proposes that symptoms result from tissue hypoxemia, which is caused by maldistribution of skin microvascular blood flow. The contraction of pre-capillary sphincters and the opening of anatomical arteriovenous shunts (pathological

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CASE REPORTS

thermoregulatory reaction) result in skin hypoxemia and hypotrophy. Thus cooling would decrease oxygen consumption. During symptoms the following observations were made: increased skin temperature of affected limbs, increased blood flow in the microcirculation measured by laser Doppler and decreased tissue oxygenation measured by transcutaneous oximetry. Mitochondrial dysfunction has also been speculated, although involvement limited to the extremities is hard to explain [12,13].

In neurological studies dysfunction of peripheral adrenergic neurons was observed without systemic autonomic dysfunction [12,14,15].

Since there are familial cases of EM, genetic factors were also taken under consideration. Primary EM is inherited in an autosomal dominant manner. In 2004 Yang et al. from University of Beijing examined patients with familial and sporadic EM and identified 2 mutations in SCN9A, the gene encoding the alpha subunit of the voltage-gated channel Nav 1.7, that is selectively expressed in nociceptive dorsal root ganglion cells and sympathetic ganglion neurons [16]. Later Dib-Hajj et al from Yale University described novel mutation in the same gene responsible for familial EM in 16 patients [17]. In both papers, patch-clamp was used to describe effects of EM mutation on biophysical properties of Nav 1.7 channel. Nav 1.7 channel generate threshold currents close to the rest potential. The mutation causes a hyperpolarization shift during activation, and decreases the threshold for single impulses and for opening the channel. By slowing down inactivation, channels are kept open for a longer time even after the activating stimulus is removed. Force and intensity of stimulus in sensory receptors is coded by frequency of action potentials. In EM there is decreased threshold for single impulses and high-frequency trains of impulses in pain-sensing neurons. That explained why the pain is experienced by EM patients with such intensity and for long period of time, non-proportionally to the small stimulus. [18]. It was recently described that by cooling Nav1.7 mutant channel gain biophysical properties of the wild-type sodium channel [19]. There were also cases of familial EM without SCN9A gene mutation, which suggests the involvement of other genes [20]. To summarize, mutations described in SCN9A explain the molecular basis of impaired pain perception. However, to elucidate mechanisms of vasculature findings in EM we need to understand the influence of mutation on sympathetic ganglion neurons.

CASE REPORTS

A 18-year-old man was admitted to the Clinic of Internal Medicine, Hypertension and Angiology in Warsaw in August 2004 because of erythema and severe burning pain and warmth in his feet and calves. These symptoms were relieved with cooling of the lower limbs (cooling by fresh air, iced water immersion of the lower limbs, walking barefoot in the snow). Exercise did not provoke the symptoms.

The patient experienced the above signs for the preceding 5 years with variable intensity. He was admitted twice to the dermatology department of regional hospital where a diagnosis of erythromelalgia was made by way of the clinical presentation. Medications included nonsteroid anti-inflammatory drugs, pentoxifylline, vitamin B3 preparation with rutin and Aesculus hippocastanum (horse chestnut) extract and were ineffective.

Family history showed that one of six brothers and sisters had the same symptoms. The others were healthy.

The following characteristics were observed during physical examination on admission of the patient to the Clinic: height 156 cm, weight 47 kg, BMI 19 kg/m², body temperature 36.8°C, blood pressure 150/100 mmHg, heart rate 80/min. He demonstrated erythema of feet and distal part of the calves and dry necrosis of the right hallux (Fig. 1). The pulse on peripheral arteries was symmetric and well palpable. There were no other abnormalities on physical examination.

The brother of the patient (25 years old) who shared similar symptoms was admitted to the Clinic to extend the diagnostic investigation. Physical examination revealed the following characteristics: height 163 cm, weight 64 kg, BMI 24 kg/m², body temperature 36.6°C, blood pressure 140/90 mmHg, and heart rate 100/min. Bilateral erythema of the feet was observed. The age of initial occurrence of erythema was 6-7 years. He reported first feeling a burning sensation inside the lower limbs and subsequently noticed erythema and pain that were relieved only with cold water or fresh air. Severity of symptoms gradually progressed and after 8 years ulcerations, congelations and deformations of the feet were observed (Fig. 2). Analgesic treatment was ineffective.

In addition to EM, both brothers had a history of hypertension, growth and weight deficiency, but had not received anti-hypertensive medication. The younger brother increasingly neglected classes due to illness. The older brother was unable to work due to the same symptoms.

Routine laboratory tests included blood cell count, erythrocyte sedimentation rate, concentration of C-reactive protein, coagulogram, serum electrolytes, creatinine, glucose, transaminases, lipids, proteinogram, concentration of thyrotropin, iron, folic acid, vitamin B12, ferritin, transferrin and urine analysis. Complementary laboratory blood tests included rheumatoid factor and anti-nuclear antibodies. Electrocardiogram, echocardiography and ophthalmoscopy were performed. Subsequently a more detailed investigation to identify causes of hypertension was performed (abdominal ultrasonography, 24-hour urinary metanephrine, normetanephrine, Na, K and creatinine) but no significant abnormalities were noted.

The both brothers had ankle-arm index of the first Doppler ultrasound examination results of the popliteal and femoral veins were normal in the younger brother, but the older showed the insufficiency of left popliteal vein valve. Radiography of older brother's feet showed subluxation of metatarsophalangeal joint of the second left toe and acro-osteolysis all the distal phalanges. Radiography of the younger brother

showed osteolysis distal phalanx of the fourth left toe. Both had general osteoporosis of the bones of the feet.

A diagnosis of primary erythromelalgia was made after these complementary exams and then drug treatment were provided.

Both patients had continuous nitroprusside infusion with observation of ECG and blood pressure for 10 days, comencing with an initial dose of 0,1 pg/kg/min increasing to effective dose 2. pg/kg/min resulting in improvement of symptoms. Propranolol was given due to higher blood pressure and tachycardia. Chronic dihydralazin treatment was started at the conclusion of nitroprusside infusion. The patients returned home without pain in the lower extremities, with good control of blood pressure. The following treatments were prescribed: dihydralazine (the younger brother 50 mg three times daily, the older 40 mg three times daily) and propranolol (the younger brother 25 mg three times daily, the older 10 mg three times daily).

Two weeks after discharge from hospital the younger brother came back due to return of the symptoms. Nitroprusside infusion was used one more time, at the beginning in a continual infusion, and then only by nights. Dihydralazine was discontinued due to inefficacy; sildenafil was started 50mg twice daily with good response. A test of sildenafil therapy was provided because of its vasodilatory action. Sildenafil inhibits phosphodiesterase by blocking transformation cGMP to GMP producing vasodilatation of smooth muscles of blood vessels in the skin and skeletal muscles.

After 3 months the proband was re-admitted to the Clinic for the third time. Ten days after nitroprusside infusion was started, the patient received isosorbide mononitrate 100mg daily with continuation of propranolol. At this time the pain had relented, but periodically warmth had appeared.

After 3 further months the patient was admitted to the Clinic again due to a recurrence of symptoms that were relieved only by continual cooling. On physical examination advanced trophic lesions such as congelation, orthostatic oedema, and infected necrosis of the skin were observed. Treatment with nitroprusside infusion did not diminish pain. Amoxicillin and clavulanic acid were given parenterally. For two weeks the patient received epidural infusion of bupivacaine 0.1% and phentanyl 2 ng/ml resulting in pain control. That enabled regression of oedema and healing ulcerations resulting from elevation lower extremities. After a psychiatric consultation due to mood depression (reactive depression) fluoxetine therapy was started (20 mg daily). Treatment with diltiazem 120 mg three times daily was started after removal the epidural catheter. Symptoms diminished appreciably, but did not disappear.

The older brother did not experience aggravation of the disease. He developed symptoms after he had discontinued using dihydralazin and propranolol. In October 2005 he started taking diltiazem. At the beginning of this therapy itching erythema on the left thigh and abdomen were observed. This disappeared after initiation of antihistaminic treatment and reduction in dose of medicine. Finally the symptoms in the



Fig. 1. The erythema of feet and distal part of the calves and dry necrosis of the right hallux at the first time of admission to the Clinic.



Fig. 2. The ulcerations, congelations and deformations of toes at the first time of admission to the Clinic.

lower limbs subsided when he took diltiazem 60 mg three times daily.

In February 2006 the patients were admitted to the hospital to modify therapy. They got mexiletine 200 mg three times daily. One week later subjective reduction of lower limb pain was observed. Two weeks later the older brother stopped taking medication due to palpitation. He felt minor symptoms, especially in the night.

Ten days after discharge from hospital the younger brother had a recurrence of severe pain relieved only by strong cooling in spite of mexiletine application. He was hospitalized once more in April 2006 due to rapidly increasing trophic lesions of the skin. Ulcerations were treated by parenteral infusion of antibiotic and epidural infusion of bupivacaine for two weeks. Subsequently the patient reduced cooling. During this hospitalization he had a pharmacological lumbar sympathectomy.

CASE REPORTS

After this therapy and taking of dihydralazine he felt warmth without pain in his feet and calves.

In November 2006 brothers underwent bilateral pharmacological lumbar sympathectomy. Gabapentin (300 mg three times daily) and fluoxetine (20 mg daily) were administered. Both obtained substantial improvement in pain without effect on erythema, oedema and warmth. The younger brother received diltiazem and dihydralazine in addition. Good control of blood pressure was confirmed by ABP.

The described cases provide excellent illustrations of primary EM. The presence of a characteristic family history and physical examination make diagnosis of this rare condition easier.

DISCUSSION

In the above report two cases of erythromelalgia were described, both with typical symptomatology. Numerous medications were prescribed with various effects.

In patients with secondary EM causative treatment is used, therefore it is possible to reduce the symptoms in case of remission of the underlying disorder.

In primary EM there is no single effective therapy and the variety of methods that have been tried corresponds with abundance of hypotheses about the etiology of erythromelalgia. Most papers report cases with significant variation in response to therapy. There is only one double-blind, crossover, placebo-controlled study with misoprostol in a group of 21 patients [21]. The treatment approaches reported so far include: aspirin (probably cases of secondary EM with thrombocytemia), antidepressive therapy: selective serotonin reuptake inhibitors [22], venlafaxine [23,24], tricyclic antidepressants and also gabapentine, calcium channel antagonists (nifedipine, diltiazem), beta-adrenergic drugs, opioids, mexiletine and lidocaine. The combinations of above medications have been tried as well [1]. In cases of severe EM intravenous infusion of sodium nitroprusside [25], adenosine [8] or epidural infusion of bupivacaine and lidocaine [26] result in remission of symptoms. The results of sympathectomy are ambiguous: resolution and aggravation of symptoms were described [27]. There are single papers describing the use of dorsal column stimulators and neurosurgical procedures [1]. Since the mutation of Nav1.7 channel is known, the use of mexiletine and lidocaine, non-selective blockers of sodium channels, seems reasonable [28-30]. Unfortunately these drugs do not resolve symptoms completely. It is possible that use of substances which selectively block Nav1.7 receptor would be more efficacious and much safer, since they would act only in sensory neurons and sympathetic ganglions. There is an interesting paper describing a different response to therapy of lidocaine in patients with different location of mutation in the SCN9A gene [31]. There are experimental studies of gene therapy in animal models of neuropathic pain [18]. Maybe in the far future, gene therapy will become effective method of treatment in primary EM.

The retrospective medical record review of 168 patients with EM diagnosed in Mayo Clinic between 1970 and 1994 showed increased mortality in patients with EM compared with matched control subjects [3]. Increased mortality in secondary EM was connected with underlying disorders (neoplastic, rheumatologic diseases), but it is also important to mention deaths in primary EM group: suicides and fatal hypothermia. EM definitely decreases quality of life, makes impossible normal social function, work, and family life. It can cause depression. The aggressive cooling of extremities leads to ulcers, trophic changes, proceeding on to necrosis and amputations [32].

Both brothers have tried many medications described in the literature. It is hard to say with certainty if the observed transient improvement resulted from therapy or natural history of the disease. Perhaps only spontaneous aggravations and remissions of the disease were observed. There is no effective therapy that addresses the cause of EM. We do not know if the phenotype of EM can be caused by a mutation in additional genes or which genetic and environmental factors influence the time of onset and intensity of the disease.

Primary EM is a rare disorder caused by single gene mutation, characterized by paroxysmal, usually symmetrical burning pain, redness and increased temperature in affected limbs. It has to be emphasized that in all cases, even with early childhood onset of symptoms, secondary causes of EM must be excluded, so that causative therapy can be applied in time. Although an abundance of therapies have been described, currently none of these is fully effective. Primary EM is a chronic, sometimes progressive, disease, that considerably decreases quality of life. The discovery of the etiology and mechanism of a rare disease such as EM allows us to better understand other pain and microcirculation disorders in more common diseases and opens the way to new therapies.

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