Erythromelalgia in a young adolescent male

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Keywords

erythromelalgia, differential diagnosis, Fabry disease

Abstract

Erythromelalgia (EM) is a rare condition which is characterized by burning pain, warmth and redness of the limbs. Several cases of secondary EM have already been described. We report a 13-year-old boy who presented with burning pain in his hands and feet, which turned out to be secondary to Fabry disease. This case highlights the need for pediatricians and general practitioners to be aware of children who present with acute, unexplained pain episodes. When Fabry disease is diagnosed early and treated adequately this has a major impact on the associated morbidity and mortality.

Introduction

Erythromelalgia (EM), first described in 1878 by Weir Mitchell, is characterized by a triad of redness, warmth, and pain, usually of the extremities (1). Primary EM is a rare disease with an estimated incidence of 1,3/100.000 (2). In the largest retrospective study of EM, all 168 patients were white, the male-to-female ratio was 1 to 3, and the mean age was 55.8 years (3). The largest pediatric EM case series showed it to be more common in females and with a mean age of 14 years (4). During an attack of EM, the feet -or hands in 25%- become red, hot, and painful ('burning sensation') (5). The symptoms are intermittent in nearly all patients and episodes can last from minutes to hours and may be triggered by precipitating factors, usually by an increase in temperature of the affected acral area (e.g., increase in ambient temperature or exercise). Conversely, relief is achieved by the cooling of the affected extremity (5). EM is classified into primary and secondary disease. Primary EM (PE) is mainly caused by gain-of-function mutations in the *SCN9A* gene, encoding a voltage-gated sodium channel alpha subunit (Nav1.7) in sensory and sympathetic neurons (7). EM can be secondary in several diseases, such as hemorheological, metabolic, connective tissue, musculoskeletal, or infectious diseases, or it can be induced by drugs, or it can be a paraneoplastic phenomenon (8). Despite the fact that EM has been known for more than 140 years its pathophysiology and treatment remain elusive. And in children the demographic features, natural history, characteristics, prognosis, and pathogenesis of EM are even more poorly characterized. In this report, we present a case of secondary EM in a 13-year-old boy with burning pain in his hands and feet.

Case report

Approval from the Research Ethics Committee UZ/KU Leuven for this study was received (MP016948). A 13-year-old Syrian boy presented to his pediatrician with a 2-year history of intermittent severe pain in both feet and toes. The pain was accompanied by numbness, prickling sensation, erythema, and swelling of the affected extremities. Sometimes his hands and fingers could also be involved. An attack could be triggered by physical exercise. The pain was worst during the night, disturbing his sleep, with a pain score of 9 out of 10. The pain could be reduced by cold application and raising his feet. The symptoms had a major impact on his quality of life as he was unable to play sports for fear that the pain would increase. An episode passed spontaneously after a few hours. There was no medication intake and no relevant medical or surgical history. Immunizations were administered based on the standard schedule. There had been no recent trauma or illness before the first episode. His maternal grandmother was hard of hearing, his maternal grandfather had a stroke and died of an acute myocardial infarction, and one maternal uncle had a transient ischemic attack at the age of 48. His parents were distantly related. Clinical and neurological examinations were normal at the time of presentation. An initial blood test 'with full blood count, liver and kidney function and inflammatory markers) and an X-ray of both feet revealed no abnormalities. Musculoskeletal pains were first suspected. Therapeutic insoles were recommended, initially showing only a small improvement. Subsequently, Mediterranean fever was considered, but prophylactic analgesics proved ineffective. Consequently, he was referred to the University Hospitals Leuven, for further diagnostic work up in search for an etiology of his pain pattern as the pediatrician suspected a somatic origin.

During the initial assessment at our department the history was repeated and the absence of abnormal sweating, hearing and vision problems was also assessed. Clinical examination was normal, except for pressure pain of metacarpophalangeal joints 3 and 4 on the right and joint 1 on the left. No cutaneous lesions, especially no angiokeratomas, were observed. The additional laboratory work up included blood tests for thyroid function, immunity, and infection (Lyme borreliosis, Syphilis, Cytomegalovirus, Epstein Barr, and HIV), as well as a chest X-ray and a tuberculin skin test. The only abnormal result was the blood test for Fabry disease, which showed a significant decrease (<0.8 µmol/L/h, REF ≥15.3 µmol/L/h) in the enzyme activity of alpha-galactosidase A (alfa-gal A). A tentative diagnosis of secondary EM in the context of Fabry disease (FD) was made. Genetic testing was also done to exclude false low enzyme activity and showed a hemizygous mutation (c.1226C>T, p.Pro409Leu) of the galactosidase alfa (*GLA*) gene, coding for alfa-gal A. In addition, there was a significant increase (52.1 ng/ml, REF ≤1.8 ng/ml) in plasma globotriaosylsphingosine (lyso-Gb3), a storage product in this disease. Based on the presence of acroparesthesias, an undetectable low activity of alfa-gal A, the hemizygous mutation of the *GLA* gene, and a significantly elevated lyso-Gb3, secondary EM due to FD was definitively diagnosed.

Further follow-up and treatment was required in the context of this diagnosis. A 24-hour urine collection showed no proteinuria. His audiometry was normal. A cardiac ultrasound there was a mild thickening and hypertrophy

Table 1: Cases of Pediatric Erythromelalgia with Onset up to the age of 18 years (published since 1979 in chronological order)

First author, publication year	No	Sex (M/F)	Age at onset of symptoms vs. at diagnosis (y)	Major somatic symptoms	Dysautonomia signs	Illness, vaccination, a trauma in preceding weeks	Pathological confirmation of SFN	Autonomic function testing	Electrodiagnostic testing	Capillary microscopy	Blood test	Genetic testing	Outcome of immunotherapy	Diagnosis
Ozsoylu, 1979	1	F	9 vs. 9	Burning pain, warmth, swelling, and erythema in hands and feet	AHT	No data	No data	No data	No data	No data	Normal	No data	None administered	HAE
Cimaz, 2001	1	M	3 vs. 10	Burning pain, swelling, and ulceration in lower limbs and hands	AHT	No data	No (SB)	No data	No data	No data	Low GH, low IGF-1	No data	MR (systemic CS)	EM due to GH deficiency
Chan, 2002	1	M	no data vs. 11	Burning pain, warmth, and erythema with hyperkeratosis, maceration, and ulceration in hands and feet	AHT	No data	No data	No data	Abnormal NCS	Abnormal	No data	No data	None administered	HAE
Pfund, 2009	1	F	12 vs. 12	Burning pain, warmth, swelling, and erythema in hands and feet; muscle weakness in knees and feet	AHT	No data	Not performed	Abnormal QST	Abnormal ENG, NCS	Normal	Normal	No data	GR (systemic CS)	EM due to LFA
Firinci, 2010	1	F	11 vs. 11	Burning pain, warmth, and erythema in hands and right arm; arthralgia in hands and feet	No data	No data	No data	No data	Normal	No data	Hypocomplementia, high ESR, positive ANA, and positive dsDNA	No data	GR (systemic CS)	EM due to SLE
Morales, 2012	1	M	No data vs. 9	Burning pain, warmth, swelling, and erythema in hands and feet	AHT	No data	No (SB)	No data	Normal	No data	Normal	Normal	CR (systemic CS)	HAE
Wu, 2013	1	M	11 vs. 11	Burning pain, swelling, and erythema in the left medial thigh	No data	Trauma 8 weeks before	No (SB)	No data	No data	No data	Normal	No data	GR (systemic CS)	EM due to trauma
Duchatelet, 2014 (b)	2	M	4-9 vs. 11-14	Pain, swelling, and erythema in ears, hands, legs, and feet; plantar keratoderma	No data	No data	1/2 no (SB), 1/2 no data	No data	No data	No data	No data	2/2 TRPV3 mutations	No data	EM due to OS
Duchatelet, 2014 (a)	1	F	3 vs. 3	Pain, swelling, and erythema in ears, hands, and feet; plantar keratoderma	No data	No data	No (SB)	No data	No data	No data	No data	TRPV3 mutation	GR (systemic + topical CS)	EM due to OS
Huh, 2015	1	F	12 vs. 12	Burning pain and erythema in ears, hands, central body, and feet	No	No data	Not performed	No data	No data	No data	Normal	No testing	MR (systemic CS)	EM due to vasculitis
Hobson-Webb, 2015	1	M	7 vs. 7 (Pompe disease), 11 (SFN)	Burning pain and tingling in fingers and toes; muscle weakness	Bradycardia, gastrointestinal dysfunction, and urinary incontinence	No data	Yes (SB)	Abnormal QSART	Normal	No data	Normal	GAA mutations	None administered	EM due to SFN due to Pompe disease
Faignart, 2020	5	3M/2F	6-11 vs. 10-15	Burning pain in hands and feet	4/5 AHT, 3/5 tachycardia, 2/5 hyperthermia	3/5 preceding or concomitant infection	3/4 yes (SB)	1/1 abnormal ESC, 1/2 abnormal SSR	Normal	1/5 normal, 4/5 no data	2/5 positive ANA, 1/5 thrombocytosis, 1/5 low IgG	Normal	1/1 CR (CS), 1/1 CR (IVIg)	EM due to SFN
Fleitman, 2020	4	F	No data vs. 9-17	Burning pain, swelling, and erythema in lower limbs	No data	No data	Yes (SB)	No testing	Normal	No testing	1/4 low vitamin D, 1/4 low IgA and IgD, 1/4 positive ANA and HLA-B52	2/4 MEFV mutation (het), 1/4 MEFV mutation (hom)	1/1 GR (IVIg), 1/1 GR (anti-IL-1 agents + IVIg + CS), 1/1 MR (CS)	3/4 EM due to SFN, FMF; 1/4 EM due to SFN, Behçet's disease

Abbreviations: AHT = arterial hypertension, ANA = antinuclear antibodies , CR = complete remission, CS = corticosteroids, dsDNA = double-stranded DNA, EM = erythromelalgia, EMG = electromyography, ESC = electrochemical skin conductance, ESR = erythrocyte sedimentation rate, F = female, FMF = familial Mediterranean fever, GBS = Guillain-Barré syndrome, GH = growth hormone, GR = good response, HAE = hypertension-associated erythromelalgia, het = heterozygote, HLA = human leukocyte antigen, hom =homozygote, Ig = immunoglobulin, IGF-1 = insulin-like growth factor-1, IL = interleukin, IV = intravenous, LFA = large-fiber axonopathy, M = male, MR = mild response, NCS = nerve conduction studies, OS = Olmsted syndrome, PR = poor response, QSART = quantitative sudomotor axon reflex test, QST = quantitative sensory testing, SB = skin biopsy, SFN = small-fiber neuropathy, SLE = systemic lupus erythematosus, SSR = sympathetic skin response, TST = thermoregulatory sweat test, y = years

of the papillary muscles and the mitral valve. Electrocardiogram revealed the presence of rare isolated ventricular extrasystoles, which appeared benign on further assessment using a 24-hour Holter registration and ergospirometry. Magnetic resonance imaging of the brain showed a few nonspecific, subcentimetric lesions (para)median in the vermis, common to this disease. There were no white matter lesions. In addition, the ophthalmological examination showed normal vision and absence of cornea verticillata, but a mild tortuous retinal vasculature was seen.

Enzyme replacement therapy (ERT), using agalsidase beta (Fabrazyme°), a recombinant human alfa-gal A, was started every two weeks on the basis of the cardiac signs of end-organ damage and the neuropathic pain with important impact on quality of life. His neuropathic pain proved hard to treat and needed a multidisciplinary approach with specialists from the pain clinic. He is treated with a combination of morphine analogues and several pain modulators. Preventive measures, such as avoiding triggering factors, were also advised. With this combination moderate physical exercise is possible without invoking severe pain episodes.

Because FD is an X-linked inherited disease, further genetic screening was performed in other family members. This revealed that his mother and sister were heterozygous, and one younger brother was hemizygous for the familial mutation. The other family members were not affected.

Discussion

A patient with episodes of extremity pain, accompanied by erythema and warmth, should be suspected of EM. The five Thompson criteria are often used to make the clinical diagnosis: (a) burning extremity pain, pain (b) triggered by warming and (c) relieved by cooling, (d) erythema of the affected limb and (e) increase in temperature of the affected skin (10). All of these were observed in this 13-year-old boy, which led us to the diagnosis of EM. As this disease can be primary or secondary, we considered a broad array of underlying diseases. We performed a literature search that revealed 13 articles of secondary EM cases in children up to 18 years (Table 1). In these case reports, 11 girls and 10 boys aged from 3-17 years are described. A combination of the history, clinical examination and technical investigations led to the primary disease underlying EM in these 21 patients. These included diseases such as arterial hypertension (14.3%), growth hormone deficiency (4.8%), long-fiber axonopathy (4.8%), systemic lupus erythematosus (4.8%), trauma (4.8%), genetic diseases (33.3%), vasculitis (4.8%), small-fiber neuropathy (23.8%), and Behçet's disease (4.8%). No Fabry disease has been described in children, except in a genetic screening of three generations of a Chinese family (boy of 16yrs) (9).

Reported causes of secondary EM are presented in Table 2 (3). In our patient, secondary EM was mainly considered due to the absence of similar symptoms in other family members (as primary EM is an autosomal dominant condition). The investigations revealed that his condition was due to Fabry disease.

Fabry disease is an X - linked inherited disorder of glycosphingolipid metabolism caused by mutations of the gene encoding alfa-gal A (11, 12). Absent or deficient alfa-gal A results in an accumulation of lyso-Gb3 in a variety of different cell types (13). Therefore, this lysosomal storage disorder can cause multi-organ failure and premature death (14). Reported incidences, ranging from 1 in 476.000 to 1 in 117.000 may probably underestimate the true prevalence (15,16). A higher prevalence of the disease, about 1 in 3000, has recently been indicated with a newborn screening study (17). The clinical severity varies dependent on alpha-gal A activity and genotype (18, 19). Nevertheless, FD usually appears in childhood, and occurs in a predictable order in typically affected males. Early-onset signs include neuropathic pain, gastrointestinal symptoms, hypohidrosis, angiokeratoma, and corneal changes. Renal, cardiac, and cerebrovascular involvement increases with age (14). It is the neuropathic pain, sometimes in combination with the erythema, which leads to the clinical presentation of secondary EM. Treatment options for patients with FD include enzyme replacement therapy (ERT) and additional chaperone therapy (20, 21). Reimbursement criteria for ERT in FD in Belgium are a diagnosis of Fabry disease (both enzymatic and genetic) and a clinical presentation with either: kidney disease (decrease in glomerular filtration rate or microalbuminuria >30mg/24h); cardiac involvement (hypertrophic cardiomyopathy or valvulopathy); vascular disease (peripheral lymphoedema or CVA/TIA) or severe neuronopathic pain with impact on the quality of life, refractory to other treatments. Of note, current treatment guidelines advocate considering ERT even for asymptomatic boys from the age of 7 (22).

It may thus be able to halt the progression of this multisystemic disease before irreversible organ damage occurs, making it crucial to suspect FD as early as possible.

Conclusion

Even though EM is a very rare presentation in pediatrics, a thorough differential diagnosis is indicated. In our patient we diagnosed a disease with significant morbidity and mortality where appropriate treatment is available and were able to facilitate the diagnosis in other family members.

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Table 2: Reported Causes of "Secondary Erythromelalgia"

Myeloproliferative diseases and blood disorders	
	Myeloproliferative disorders
	Essential thrombocythemia
	Polycythemia vera
	Myelodysplastic syndrome
	Pernicious anemia
	Thrombotic and immunologic thrombocytopenic purpura
Drugs	
	Cyclosporine
	Norephedrine
	Verapamil
	Nicardipine
	Nifedipine
	Pergolide
	Bromocriptine
Infectious diseases	
	Human immunodeficiency virus
	Hepatitis B vaccine
	Influenza vaccine
	Infectious mononucleosis
	Poxvirus
Neoplastic	
	Paraneoplastic
	Astrocytoma
	Malignant thymoma
	Abdominal cancer
Connective tissue diseases	
	Systemic lupus erythematosus
	Vasculitis
Physiologic	
	Pregnancy
Neuropathic	
	Hereditary sensory neuropathy
	Neuropathy
	Polyneuropathy
	Riley-Day syndrome
	Multiple sclerosis
	Acute diabetic neuropathy
	Neurofibromatosis Fabry disease
Others	
	Mushroom ingestion (*Clitocybe acromelalga and Clitocybe amoenolens*) Mercury poisoning

(adapted from Davis *et al*, 2006)