Rev Bras Anestesiol. 2018;68(5):531–534

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
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CLINICAL INFORMATION

Pain management in children with erythromelalgia: case report

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Received 13 February 2017; accepted 28 December 2017
Available online 11 March 2018

KEYWORDS
Erythromelalgia;
Neuropathic pain;
Children

Abstract Erythromelalgia is a neuropathic pain syndrome due to an autosomal dominant gene, characterized by erythema, increased skin temperature and burning pain in hands and feet, whose treatment is often unsatisfactory. In this paper, we report a case of a 9 years old female patient whose first episode of burning pain, erythema and edema of the hands, without triggering factors, had instant relief after immersion in cold water. She presented with systemic arterial hypertension and had seizures. The patient was treated with gabapentin (150 mg.8 h^{-1}) and amitriptyline (12.5 mg) orally, intravenous lidocaine infusion (120 mg), without relieving pain complaints. Due to the lack of response to the proposed treatment, it was decided to gradually reduce these medications and to introduce carbamazepine (200 mg) orally and, after 4 days of treatment, there was complete relief of the manifestations.

PALAVRAS-CHAVE
Eritromelalgia;
Dor neuropática;
Crianças

Tratamento da dor em criança com eritromelalgia: relato de caso

Resumo Eritromelalgia é uma síndrome dolorosa neuropática decorrente de gene autossômico dominante, caracterizada por eritema, aumento da temperatura da pele e dor em queimação, em mãos e pés, e o tratamento é muitas vezes insatisfatório. Neste caso, está o relato de uma paciente do sexo feminino, com nove anos e primeiro episódio de dor em queimação, eritema e edema em mãos, sem fatores desencadeantes, com alívio instantâneo após imersão em água fria. Apresentava hipertensão arterial sistêmica e teve crises convulsivas. Foi tratada com gabapentina (150 mg.8 h^{-1}) e amitriptilina (12,5 mg) via oral, lidocaína (120 mg) venosa em

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https://doi.org/10.1016/j.bjane.2017.12.005

infusão, sem alívio das queixas álgicas. Devido à ausência de resposta ao tratamento proposto, decidiu-se redução gradativa dessas medicações e introdução de carbamazepina (200 mg) via oral e após quatro dias de tratamento houve alívio completo das manifestações.

Introduction

Erythromelalgia is a chronic and debilitating disease characterized by burning pain and increased skin temperature, associated or not with edema. Usually affects upper and lower extremities, which worsens with heat and improves with low temperatures. It may be primary or idiopathic and is an autosomal dominant inherited disorder. Secondary erythromelalgia occurs in association with vasculopathies, collagen diseases, diabetes mellitus, peripheral neuropathy and use of some drugs,[1] in addition to hypertension, systemic lupus erythematosus, rheumatoid arthritis, HIV, gout, thrombocytopenia, myeloproliferative disorders, occurs mainly in a later phase. Approximately two thirds of cases are primary and one third is secondary.[2]

The clinical manifestations of primary erythromelalgia begin in childhood or adolescence and, with advanced age, it may progress and become constant.[3]

Although not well known, the pathophysiological mechanisms of erythromelalgia include increased blood flow, microvascular shunt, increased local metabolism and small fiber neuropathy. Erythromelalgia is linked to a mutation with an abnormality in ion channel.[4] Histopathological examination reveals reduced density of the autonomic nerve plexuses in the skin.[5]

There is no cure for erythromelalgia; thus, its treatment is focused on relieving the patient's manifestations, which may be done with topical, oral, and behavioral therapy. Erythromelalgia usually follows a chronic course, sometimes progressive and incapacitating.[6]

Erythromelalgia causes impaired quality of life, in addition to higher mortality.

Because it is a rare condition with a severe evolution, its early diagnosis and pain treatment are fundamental. The patients affected may evolve with ischemia and finger and toe gangrene by exposure to cold in an attempt to relieve the pain.

Case report

A nine-year-old girl, 28 kg, presented with a history of severe burning pain in the palmar region for 20 days, which showed instant improvement after immersion in cold water. Hospitalized for five days, the patient and her guardian reported that it was the first occurrence of the symptom.

On physical examination, the patient had good general condition, heart and lung auscultation without alterations, hypertension, present and symmetrical pulses in the upper (radial and ulnar 4+) and lower limbs (bilateral pedis and tibial 4+). In the palmar region, she had bilateral hyperemia, increased local temperature associated with mild edema, without limitation of joint movement angles, strength preserved, without trophic changes.

She denied concomitant diseases or previous hospitalizations and had already sought medical attention at another service seven days ago; prednisone (10 mg.8 h^{-1} for five days) was prescribed orally without symptom relief.

On the day of the evaluation the child received intravenous dipyrone (100 mg every 8 h) without pain relief.

Blood count was unchanged.

Erythromelalgia was diagnosed by the Pain Department team and gabapentin (150 mg.night^{-1}), amitriptyline (12.5 mg.night^{-1}), and dipyrone (750 mg.6 h^{-1}) were prescribed orally. Intravenous lidocaine (120 mg.h^{-1}) was also given once.

The child had three convulsive seizures the day after the medication introduction, with different characteristics. The first one, at 6 h, generalized tonic-clonic, lasted less than two minutes; the second one occurred after one hour, with a fixed stare, not responsive to calls and developed a reduction of oxygen saturation, lasting less than two minutes with spontaneous resolution, followed by drowsiness. The third one occurred after 12 h with horizontal nystagmus and hand tremor, and lasted less than 25 s. Diazepam and phenytoin (intravenous until seizure control) were administered, and the patient was sent to the Intensive Care Unit (ICU) with no need for tracheal intubation.

A magnetic resonance imaging scan of the brain was performed, which showed images suggestive of reversible posterior encephalopathy syndrome, with evidence of areas with cortical and subcortical signal alterations in both brainstems of parieto-occipital predominance, larger on the left, with characteristic distribution favoring the possibility of an erythromelalgia diagnosis.

Gabapentin was maintained and amitriptyline and intravenous lidocaine were discontinued. The child was discharged from the ICU after five days, normotensive and without convulsive seizures, under prazosin (2 mg.12 h^{-1}), propranolol (40 mg.12 h^{-1}), and phenytoin (100 mg.12 h^{-1}).

The gabapentin dose was increased to 150 mg.8 h^{-1} (5 mg.kg^{-1}.$dose^{-1}$), but the patient remained with severe pain (NPRS 8). After discussing with the neurology team, carbamazepine (200 mg.8 h^{-1}) was introduced, with gradual reduction (one-third of the initial dose every 24 h) of other anticonvulsants (phenytoin and gabapentin), up to discontinuation after 72 h.

After 4 days, the patient evolved with complete pain relief (NPRS 0), without cryotherapy, when she was discharged with carbamazepine (200 mg.8 h^{-1}).

Discussion

Erythromelalgia evolves with burning pain in the extremities, especially hands and feet, and can affect any part of the body, in addition to erythema and increased temperature triggered by exposure to heat or physical activity. The events are generally bilateral and symmetrical.[7] In the present case, the reported events occurred in addition to worsening with physical activity and exposure to heat and improving with local cooling; a diagnosis of erythromelalgia was made. The episodes are intermittent and usually last from minutes to hours, as was the case with our patient. In this case, the events occurred in the hands, but in the literature the feet are more commonly affected (90% of cases).[8] The patient may present with arterial hypertension and seizures as observed.

Considering the absence of concomitant disease, the patient was classified as having primary or idiopathic erythromelalgia. It is an autosomal dominant genetic disease caused by the SCN9A gene, which encodes the alpha subunit of voltage-dependent sodium channels, particularly Nav1.7 subtype.[9] Mutant channels provoke hyperexcitability in peripheral sensory and sympathetic neurons, causing pain associated with erythromelalgia.[10] Secondary erythromelalgia (most commonly associated with myeloproliferative diseases) occurs in less than 10% of cases[8] and usually late.[11]

Epidemiological data on erythromelalgia are scarce. In a population study, the incidence was less than 2:100,000 inhabitants per year.[12] Erythromelalgia is more common in women, which corresponds to the gender of the patient in this case. In one study the incidence rates adjusted for age were 2 per 100,000 women and 0.6 per 100,000 men.[13] In the largest series reported, which included 32 patients (22 females), the mean age was 14 years (between 5 and 18), greater than the age of the patient in this case. The time for diagnosis was shorter (in the first event) than in the literature: 5.2 years.[14]

The pathogenesis of erythromelalgia is not fully understood despite the involvement of vascular, neural, and genetic factors. There is an increased blood flow and temperature in the affected area up to 10-fold, detected by Doppler, and the presence of microvascular arteriovenous shunts is the mechanism proposed to justify perfusion and skin nutrition deficits.[15] It is suggested that there is involvement of small and large nerve fibers in the development of events and change in electroneuromyography in 60% of patients.[16] Small fiber neuropathy can be proven with alteration in the quantitative sudomotor axonal reflex test in 80% of patients.[17] Skin biopsies show decreased density of epidermal nerve fibers in only 10% of cases, suggesting that small fiber neuropathy is functional and not structural or anatomical.[18] Skin biopsies are indicated to exclude other conditions as they do not aid diagnosis.[19]

The diagnosis for this reported case was clinical with the recognition of the classic signs and symptoms of erythromelalgia, but other semiological options are available although not recommended. The use of complementary exams does not influence the management of erythromelalgia. There is no serological test for erythromelalgia. Other tests such as electroneuromyography, nerve conduction studies, and autonomic reflex exams may be abnormal but are not routinely indicated.[16,17]

As it was a neuropathic pain, gabapentin was chosen,[20] which may be initiated with 300 mg.day^{-1} orally with an increase every three days up to 2400 mg.day^{-1}, divided into three times. Other drugs indicated are pregabalin, starting at a dose of 75 mg.day^{-1}, increasing every three days up to 300 mg twice,[21] amitriptyline (starting with 12.5–25 mg at night, increased to 100 mg at night), and venlafaxine (starting at 37.5–75 mg in the morning), increasing to 225 mg.day^{-1} twice daily.[22] Other less effective drugs include selective serotonin reuptake inhibitors (sertraline), sodium channel blockers (oral mexiletine and venous lidocaine),[23] and anticonvulsant drugs (carbamazepine),[24] outpatient treatment proposed to the patient in this case.

Despite the good outcome of our patient after hospital discharge, without recurrence of symptoms after three months, in a review of 168 patients with erythromelalgia, of the 94 patients available for follow-up questionnaire (medical follow-up of 8.7 years), 32 reported worsening of symptoms, 25 reported stability, 29 reported reduced symptoms, and only 10 reported the disappearance of complaints.[16] These data show the possibility of the event reoccurring in our patient in the future.

Conflicts of interest

The authors declare no conflicts of interest.

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