Primary Erythromelalgia in a 12-Year-Old Boy: Positive Response to Sodium Channel Blockers Despite Negative SCN9A Mutations

Primäre Erythromelalgie bei einem 12-jährigen Jungen: Positiver Effekt von Natriumkanalblockern trotz negativer SCN9A-Mutationsanalyse

Authors

A. Jakob[1], R. Creutzfeldt[1], O. Staszewski[2], A. Winterpacht[3], R. Berner[1], M. Hufnagel[1]

Affiliations

[1] Centre for Pediatrics and Adolescent Medicine, General Pediatrics , Germany
[2] Institute of Neuropathology, University Hospital Freiburg, Germany
[3] Institute of Human Genetics, University Hospital Erlangen, Germany

Key words
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Schlüsselwörter
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- Natriumkanalblocker
- Lidocain
- Mexiletin

Abstract

Erythromelalgia is a rare disorder characterized by recurrent pain attacks, swelling and redness in the distal extremities. The primary forms of the disorder are caused by mutations in voltage-gated sodium channels. Treatment is difficult and controlled therapeutic studies offer little to no guidance. We report on a 12-year-old boy and his first occurrence of primary erythromelalgia. Genetic findings for mutations in the SCN9A gene, which encodes for the α-subunit of sodium channel $Na_V1.7$, were negative. Although initial treatment with sodium nitroprusside was ineffective, subsequent medication with lidocaine and mexiletine, in combination with gabapentin, was successful. Despite negative findings for mutations in the sodium channels, the use of sodium channel blockers should be considered in these patients.

Zusammenfassung

Die Erythromelalgie ist eine seltene Erkrankung, die durch wiederkehrende Schmerzattacken, Schwellungen und Rötungen der distalen Extremitäten charakterisiert ist. Die primären Formen sind durch Mutationen in den spannungsabhängigen Natriumkanälen verursacht. Die Therapie ist schwierig und kontrollierte Therapiestudien fehlen. Wir berichten von einem 12-jährigen Jungen mit Erstmanifestation einer primären Erythromelalgie. Eine Mutationssuche im SCN9A-Gen, das für die α-Untereinheit des Natriumkanals $Na_V1.7$ kodiert, blieb negativ. Obwohl die initiale Therapie mit Natriumnitroprussid erfolglos blieb, zeigte die nachfolgende Therapie mit Lidocain und Mexiletin, in Kombination mit Gabapentin, einen guten klinischen Effekt. Trotz negativer Befunde für Mutationen in den Natriumkanälen sollte der Einsatz von Natriumkanalblockern bei Patienten mit primärer Erythromelalgie erwogen werden.

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Correspondence
PD Dr. Markus Hufnagel
University Hospital Freiburg
Centre for Pediatrics and Adolescent Medicine
Mathildenstraße 1
79106 Freiburg
Germany
Tel.: +49/761/2704 3000
Fax: +49/761/2704 4730
markus.hufnagel@uniklinik-freiburg.de

Introduction

Molecular genetic studies of familial pain syndromes have shown that voltage-gated sodium channels play a major role in the pathogenesis of painful neuropathies. Several channels have been able to be located throughout the nervous system and familial pain syndromes are associated with mutations in one of these channels [9]. Sodium channels are made up of a single α-subunit and multiple ß-subunits. Several mutations in the SCN9A gene, which encodes the α-subunit of sodium channel $Na_V1.7$, have been discovered in patients with primary erythromelalgia [10, 23]. It has been demonstrated that these mutations cause both a hyperpolarizing shift in activation and slowed deactivation [5]. This channel is expressed primarily in nociceptors of the dorsal root ganglion and sympathetic neurons [11]. This suggests that the biophysical alterations contribute to the pain.

Clinically, erythromelalgia presents with 3 characteristics: intense redness (erythros – Greek), severe pain (algia – Greek) in the extremities (melos – Greek), and localized warmth. It is suspected that the sodium channel mutation is also responsible for a dysfunction in the vasomotor regulation, which leads to arteriovenous shunts [7]. The subsequent inadequate perfusion results in hypoxia in the affected tissue and may enhance the pain experienced by these patients. The lower extremities are more frequently affected than the upper extremities and distribution is usually symmetrical [4, 6]. The pain is described as a deep aching of the soft tissue combined with a painful burning sensation. Pharma-

cological treatment of the pain disorder is often difficult. Controlled studies offering treatment recommendations are lacking. The 2 most commonly used classes of drugs for this purpose are sodium channel blockers (e.g., lidocaine, mexiletine or carbamazepine) and vasodilators such as sodium nitroprusside. Alleviation of pain without drugs is usually achieved only by continuously cooling the affected extremities with freezing water or ice.

We report on a 12-year-old boy who suffered from excruciating pain in his distal extremities due to primary erythromelalgia. Key to the patient's diagnosis was the observation that, at least in the early stages, symptoms were alleviated only by immersion of his hands and feet in ice water. Vasodilators showed no effect, but treatment with sodium channel blockers was successful, even though no mutations were found in the SCN9A gene.

Case report

A 12-year-old boy in our outpatient clinic presented with a 1-month history of intermittent pain located in the interphalangeal joints of both feet – a pain he experienced for the first time after playing soccer on a hot summer day. During the 5 days prior to presentation, this pain slowly increased, associated swelling developed, and the affected areas spread to involve fingers as well as feet. The patient reported neither redness nor warmth in the affected areas and had no other symptoms or complaints. His past medical history, apart from an upper respiratory infection 4 weeks prior to commencement of the pain, was unremarkable. Upon physical examination, he presented with excruciating pain when touched on the phalanges of both hands and feet. However, no swelling, redness or warmth was apparent. Although his blood pressure was elevated (i.e., 140/60 mmHg), further examination of the patient was without pathological findings and initial laboratory work-up did not show any pathological changes. The patient was sent home with presumptive post-infectious arthritis and treated with ibuprofen and paracetamol.

Three days later, he returned due to aggravated paroxysmal pain without paresthesias. The patient was no longer able to walk due to excruciating pain. Physical findings were unchanged. Apart from arterial hypertension, no other signs of autonomous dysfunctions were present, (no dysrhythmia, orthostatic hypotension, paralytic ileus, bladder dysfunction or abnormal sweating). Differential work-up revealed normal results for blood count and glucose, as well as negative findings for rheumatoid factors, antinuclear antibodies, HLA-B27, anti-streptolysin O, antiphospholipid antibodies, antineutrophil cytoplasmic antibodies, and borrelia antibodies. No evidence of complement system activation was detected. MRI studies were normal without signs of arthritis, tendovaginitis, myositis or osteomyelitis. Treatment with peripheral analgesics, including acetylsalicylic acid and high-dose piritramide, did not alleviate any pain. The only therapy that succeeded in reducing the pain was immersing the affected extremities in freezing water. Based on this finding, a clinical diagnosis of primary erythromelalgia was made. Direct sequencing of exons 1 to 26 and the flanking intron sequences revealed no mutation in the coding region of the SCN9A gene. A skin punch biopsy showed no inflammatory changes. Normal density of intraepidermal nerve fibers by fluorescence immunohistochemistry, using the antibody PGP9.5, excluded a small-fiber axonopathy, The clinical features of allodynia and hyperalgesia in our patient might be explained by an acute small-fiber neuropathy, which is often associated with erythromelalgia in children [4], but other common clinical findings such as a burning pain character, numbness, tickling paresthesias and reduced pinprick and thermal sensation were absent in our patient. Additionally, small-fiber neuropathy usually has a chronic course and lasts many years. A sensory variant of a Guillain-Barré syndrome was determined to be unlikely, due to the absence of paresthesias, the lack of diminished or absent ankle reflexes, and the involvement of the hands without ascension of the sensory defects beyond the feet. Fabry's disease was ruled out by normal activity of L-D-galactosidase in serum and in polymorphonuclear leukocytes. The patient's elevated blood pressure did not respond to nifedipine.

Given the observed ineffectiveness of nifedipine, and based upon reports of successful pain control through use of vasodilators, therapy was begun with sodium nitroprusside. A normal heart function and a regular ECG were confirmed in advance. While closely monitoring vital signs, in particular cardiovascular parameters, infusion was titrated to a maximal dosage of 6 mcg/kg/min. Since no change in symptoms could be documented after 5 days of therapy, we replaced nitroprusside with lidocaine, a sodium channel blocker. We started with 16.5 mcg/kg/min and titrated it to a maximum dose of 60 mcg/kg/min. Lidocaine levels under this dosage were within the recommended therapeutic range of 2–5 mg/l. Reduction of overall pain levels was achieved and ice water treatment for breakthrough pain could be reduced from an initial 20 h per day to 1 h per day. Therapy with mexiletine, an oral sodium channel stabilizer, was commenced with 2 mg/kg per day and increased to 10 mg/kg/day over a 3-week period, while reducing lidocaine in parallel. As a supportive drug for treatment of neuropathic pain, gabapentin, at a dose of 15 mg/kg per day, was started the same day as mexiletine. Intravenous lidocaine was stopped after 5 weeks. Prolonged pain experience led to a secondary pain syndrome. Psychological interventions reduced the conditioned anxiety response to pain.

Our patient was noted to be hypertensive for his age. Urine catecholamine metabolites were within normal range. Aside from the period of sodium nitroprusside therapy, blood pressure stabilization – without complete normalization – was achieved only through a combination of amlodipine, ramipril and prazosine. After 6 weeks of hospital treatment, the patient was able to be discharged on mexiletine, gabapentin and antihypertensive triple medication. At this stage, however, he was not completely free of pain. Only over the course of the following 6 weeks did the patient become symptom-free. His medication was tapered down accordingly. The absence of pain was accompanied by a normalization of his blood pressure. Gabapentin was discontinued after a total of 6 weeks of treatment, and mexiletine after 4 months of therapy. 8 months after stopping all his medications, the patient remained asymptomatic and was able to lead a normal life.

Discussion

Erythromelalgia is commonly characterized by episodic erythema, warmth and burning pain in the extremities. We report on a 12-year-old boy who initially did not show this classical triad of symptoms — a fact that initially mistakenly lead us to arthritis as the primary differential diagnosis. In a retrospective case series of 168 patients, 34 % of patients were found to present

with normal physical examination of the limbs [6]. The authors did not clarify the symptoms of the affected abnormal limb. Approximately 67% of patients experienced pain relief with cold water, which in our case was the critical key to diagnosis. In children, a quarter of erythromelalgia patients present with normal clinical findings upon examination and a monophasic course with full recovery is possible [4]. The pathophysiological mechanisms in erythromelalgia may be explained by a sensitization of polymodal C nociceptors — a state that could lower the temperature threshold for activation of C fibers from a normal value to the lower level encountered by erythromelalgia patients. Thus, skin temperatures above threshold could trigger both the burning pain (from activated C fibers) and vasodilation (via the axon reflex mechanism). Vasodilation would keep the skin temperature elevated and sustain the symptoms until external cooling is applied. This said, cooling, especially via use of ice and ice water, should be used with caution, in order to avoid skin necrosis and ulcerations [6,16]. Additional management strategies therefore should include avoiding triggers of symptoms – i.e., extreme heat, dramatic changes in temperature, and over-exertion during exercise [17].

Pharmacological approaches to relieve pain or – even more difficult to achieve – freedom from pain are challenging, especially in the pediatric population. Despite progress in understanding the molecular and genetic cause of the disease, the complete pathophysiological sequence leading to pain is not yet fully understood.

Primary erythromelalgia is the inherited form of erythromelalgia and represents a "channelopathy". It often runs in families, with an autosomal-dominant pattern of inheritance. Although the SCN9A gene, which codes for the α-subunit of sodium channel $Na_V1.7$, seems to be most commonly affected, other reports clearly exclude this gene locus [2]. Further potential candidate genes affected in the pathogenesis include additional sodium channel genes, such as SCN10A and SCN11A. Spontaneous mutations are most likely responsible for the sporadic cases that occur without family history; nevertheless, treatment strategies should not be dependent upon positive genetic findings.

Secondary erythromelalgia is defined as erythromelalgia that is related to another underlying disease. The most common diseases associated with erythromelalgia are essential thrombocytopenia, polycythemia vera, myeloproliferative disorders, various rheumatic diseases (such as systemic lupus erythematodes), diabetes and medications. All of the above were able to be excluded in our patient.

It is hypothesized that sodium nitroprusside is effective because erythromelalgia symptoms may be caused by tissue hypoxia that has been induced by impairment of microvascular blood flow through arteriovenous shunting. Nitroprusside has a potent vasodilating effect, in arterioles more so than in venules, which may redistribute the reduced blood flow. Reports of nitroprusside's successful use have been documented, including in relation to the pediatric population [3,14,21]. However, nitroprusside's clinical benefit has been controversial and our patient did not show any pain alleviation with the use of it. An explanation for the failure of nitroprusside may be deduced from the fact that our patient presented with severe pain but no swelling or redness of the affected extremities, indicating only a minor degree of arteriovenous shunting. The disturbed microvascular blood flow pattern, secondary to biophysical sodium channel alterations, may not contribute to pain in all patients. It is probable that such patients do not respond to nitroprusside.

The literature includes several promising reports regarding the benefits provided by sodium channel blockers in the treatment of erythromelalgia [16,18,20]. By stabilizing the membrane in neurons, depolarization and permeability are inhibited, slowing down the peripheral nerve conduction. Lidocaine, applied intravenously, and oral mexiletine, both class IB antiarrhythmia drugs and from the same substance class, have been used successfully for the treatment of neuropathic pain [1,8,22]. Most case reports of successful pain reduction in erythromelalgia patients began treatment with intravenous lidocaine and subsequently switched to oral mexiletine [16,18,20]. The effectiveness of intravenous lidocaine in producing analgesia in neuropathic pain seems to be a predictor of the following efficacy of oral mexiletine [12]. In a recent report by Iqbal et al. regarding 2 adult patients, mexiletine was initiated without prior use of lidocaine and both patients showed significant improvement of symptoms [15]. This strategy may be successful in shortening the duration of hospitalization.

Nevertheless, pain relief is not predictable with the use of sodium channel blockers. It should be emphasized that erythromelalgia patients suffer from severe pain with substantial morbidity and even mortality [4]. Therefore, despite pain alleviation in our patient under lidocaine treatment, we started oral gabapentin in parallel with oral mexiletine. McGraw et al. report gabapentin's effectiveness in pain relief in 2 erythromelalgia patients [19]. Additional therapeutic interventions, such as regional anesthetic blockade [13], were not necessary in our patient.

In summary, we report on a 12-year-old boy with new-onset primary non-inherited erythromelalgia, which may have been associated with small-fiber neuropathy. Standard analgetic therapy with peripherally acting analgesics and opioids in addition to sodium nitroprusside had no effect on pain. Sodium channel blockers – lidocaine and mexiletine – combined with gabapentin and additional psychological support, led to resolution of all symptoms. Despite improved understanding of the molecular aspect of this disease, pain management in these patients is challenging – particularly in children – given the absence of controlled therapeutic studies. Due to the rare occurrence of the disease in children, such studies should be performed collaboratively.

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