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Case Report

A CHILD WITH PAROXYSMAL EXTREME PAIN DISORDER AND ERYTHROMELALGIA: CHALLENGES IN HYPERTENSION TREATMENT

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SUMMARY – Paroxysmal extreme pain disorder (PEPD) and inherited erythromelalgia (IEM) are two distinct syndromes caused by pathogenic mutations in the *SCN9A* gene. Still, they can be part of a clinical continuum manifesting in the same patient. The main clinical characteristics are painful attacks accompanied by various autonomic nervous system symptoms, the most severe being apnea, bradycardia and asystole. Arterial hypertension has also been reported, especially in secondary erythromelalgia, however, its pathomechanism is still not well understood. Some suggest that hypertension results from severe painful episodes that activate the sympathetic nervous system. Other hypotheses include autoimmune and inflammatory etiologies and dysfunctional nitrous oxide pathways causing non-apparent vasoconstriction. Currently, there are no specific guidelines for hypertension management in pediatric patients with IEM, making trial-and-error the most common therapeutic approach. Treatment is especially challenging in patients with PEPD who manifest with bradycardia and asystole and usually take several medications for controlling neuropathic pain. We report the clinical course of a patient with PEPD and IEM who was diagnosed with systolic-diastolic hypertension at the age of nine, which was successfully managed with low-dose doxazosin.

Keywords: *Paroxysmal extreme pain disorder; Erythromelalgia; Hypertension; Children*

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Introduction

Gain-of-function mutations in the *SCN9A* gene, coding for the α-subunit of $Na_V1.7$ channels, cause neuronal hyperexcitability and pain syndromes including inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD) and small fiber neuropathy[1].

Impaired fast inactivation of sodium channels and the production of a persistent current have been associated with PEPD: a rare autosomal dominant hereditary disease[1,2]. In the neonatal and infant periods, the main manifestations of PEPD are non-epileptic tonic attacks, unilateral skin flushing, harlequin color change (HCC) in areas of pain, hypersalivation, apnea, bradycardia and other symptoms of the autonomic nervous system[2,3]. Painful attacks often occur in the perineal or anorectal region, around the eyes, or in the lower face. Some attacks are accompanied by periods of extended asystole requiring resuscitation. Symptoms are often triggered by defecation, perineum cleaning, micturition, temperature changes, eating, or emotional stress[2,3].

Gain-of-function mutations that enhance channel activation by hyperpolarizing shifts cause IEM, which is characterized by episodic erythema, warmth and burning pain, typically located symmetrically on the extremities[1,4]. Symptoms are often aggravated by warm temperatures or exercise. Using fans, cooling the affected area and elevating the legs can relieve pain. Secondary skin infections are common[4]. Hypertension was also recognized as a complication in patients with *SCN9A*-related IEM[5].

We report a nine-year-old boy with PEPD and IEM, who was diagnosed with systolic-diastolic hypertension after successful treatment of cellulitis complicated by toxic shock syndrome.

Case report

A nine-year-old boy has been under multidisciplinary care since birth for PEPD and IEM caused by a pathogenic variant in the *SCN9A* gene. The patient was born at term after an uncomplicated pregnancy. On the first day of life, he had several apnea episodes with bradycardia and hypersalivation, and the next day developed non-epileptic tonic spasms followed by inconsolable crying and HCC (Figure 1).

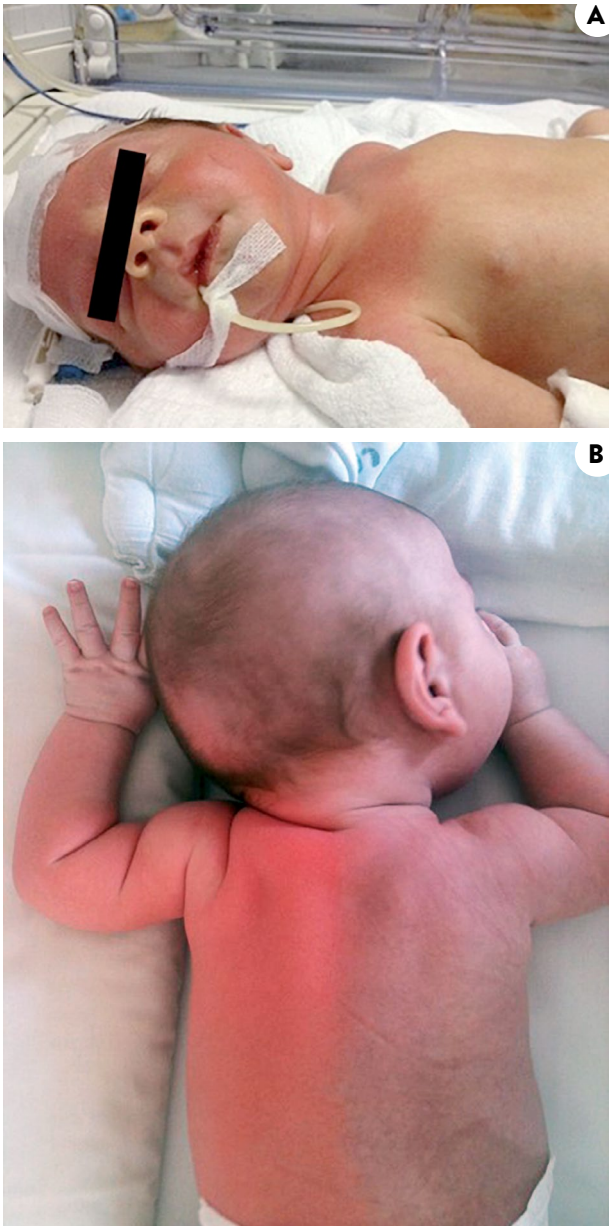

Figure 1. A) Sudden flushing of the face and neck in the newborn; B) Harlequin color change on the left side of the head and body

Due to suspected seizures, treatment with phenobarbitone was started. Laboratory work-up showed normal blood glucose, electrolytes, ammonia, lactate, hepatic, kidney and thyroid function, as well as normal metabolic tests and brain magnetic resonance imaging. Because of suspected focal changes on the right side in the electroencephalogram, phenytoin and a pyridoxine

trial were added, but had no effect. Several daily attacks with elevated blood pressure (113/73 mmHg, > 95th percentile) and sinus tachycardia were recorded in a Holter electrocardiogram (ECG). Due to the clinical presentation, PEPD was suspected and carbamazepine was administered instead of phenobarbitone, which resulted in a decrease in attack frequency and duration. Next-generation sequencing of the coding exons of *SCN9A* revealed a *de novo* heterozygous pathogenic variant c.4895C>A, p.Ala1632Glu, confirmed by Sanger sequencing.

In the following weeks, frequent episodes of apnea and bradycardia occurred. During hospitalization, an asystole of 15 seconds was recorded in the Holter ECG. The painful attacks, occasionally with Horner syndrome, were triggered by urination, defecation, solid food intake, sneezing and sudden external stimuli. The patient was treated with high-dose carbamazepine and gabapentin, but the response was incomplete. Episodes of apnea and asystole decreased over time, while symptoms of primary erythromelalgia developed at the age of seven. He suffered from a sudden onset of itching and pain in the distal parts of the extremities aggravated by clothing, sneezing and heat, mostly occurring at night. Repeated scratching and cooling of the extremities to achieve relief compromised the integrity of the skin and occasionally led to infections.

At the age of nine, he was admitted to the intensive care unit for cellulitis of the left leg and toxic shock syndrome caused by group A β-hemolytic streptococcus and *Staphylococcus aureus*. Parenteral antibiotic and immunoglobulin therapy, and a correction of hypokalemia and hypoalbuminemia were commenced. The results of a lumbar puncture and head CT, which were performed due to impaired consciousness, were normal. He recovered completely, but arterial hypertension of up to 150/100 mmHg (> 95th percentile) persisted. Laboratory tests (complete blood count, electrolytes, kidney, hepatic, thyroid and adrenal function, lipid profile, cortisol, renin and aldosterone concentrations), fundoscopic exam, a kidney ultrasound, a Doppler ultrasound of the renal arteries and ECG were normal. Mild mitral insufficiency was observed on echocardiography without any indications of left ventricle hypertrophy. Systolic-diastolic hypertension during daytime and nighttime was recorded in 24-hour blood pressure monitoring (ABPM) (mean daytime and nighttime pressure > 95th percentile) with daily painful episodes despite chronic carbamazepine and oxcarbazepine therapy, with diazepam and tramadol as needed. He was prescribed doxazosin 1 mg per day. After three months, there were fewer episodes of erythromelalgia-related pain and 24-hour ABPM showed normal values. Meanwhile, pregabalin was also started for the control of neuropathic pain, with an initial improvement in pain relief. However, the patient developed blurred vision as a side effect and his parents reported hyperactivity and aggressive behavior. For this reason, the dose of the drug was reduced and discontinued after a few months, as the parents had the impression that it was no longer effective. Slightly better pain control was achieved with a higher dose of carbamazepine. During the last evaluation at the age of 10 years and 9 months, the patient still had elevated blood pressure and tachycardia, but only during painful episodes. Despite the daily attacks, he had normal somatic and psychological development.

Discussion

PEPD has been described in less than 500 patients, predominantly in the UK and the Netherlands, while IEM is estimated to affect 0.36-2/100,000 people per year in the USA and Europe[3,6-8]. Erythromelalgia was first named in 1878 by Mitchell and later categorized by Smith and Allen in 1938 as a primary, which may be sporadic or familial, and secondary form with different etiologies[9,10]. The more common type of erythromelalgia, especially in adults, is secondary erythromelalgia caused by hematological or neoplastic diseases, myeloproliferative disorders, infections, metabolic diseases and medications. In these cases, it is very important to treat the associated diseases[11].

Although PEPD and IEM are two distinct syndromes caused by mutations in the *SCN9A* gene, they can be part of a clinical continuum, as was the case in our patient. In fact, in 2008, Estacion et al. reported a patient who harbored the same pathogenic variant and also had a mixed clinical phenotype with characteristics of PEPD and IEM. Using a patch-clamp analysis, the authors also demonstrated that a c.4895C>A mutation in the *SCN9A* gene causes hyperpolarisation, impairs fast inactivation and prevents full inactivation of NaV1.7 sodium channels[12].

We present a patient with a rare combination of symptoms of PEPD and IEM, complicated by secondary arterial hypertension. The pathomechanism of hypertension in PEPD and/or IEM is not completely understood. It may be considered a consequence of severe pain rather than autonomic neuropathy, since other autonomic symptoms were not observed in reported patients[13]. However, our patient manifested Horner syndrome during facial pain episodes, indicating autonomic nervous system involvement. Furthermore, hypertension in a condition characterized by peripheral vasodilation suggests non-apparent vasoconstriction of resistance vessels due to continuous tissue hypoxia caused by skin damage and possible increased arteriovenous shunting in the microcirculatory bed[14,15]. Successful sodium nitroprusside treatment observed in IEM patients suggests a dysfunction of endothelial-dependent nitrous oxide pathways, while a positive effect of corticosteroid therapy indicates an inflammatory and autoimmune etiology[14,16]. To the best of our knowledge, no studies have been performed to evaluate the connection between altered $Na_V1.7$ and hypertension, but it has been reported that another sodium channel, Nax, acts as the first sensor of sodium increase and could induce hypertension[17]. Furthermore, new evidence indicates that blood pressure variability worsens the clinical outcome and correlates with cardiac, renal and vascular damage, regardless of elevated mean blood pressure[18,19].

The most common approach in the treatment of PEPD and IEM is a stepwise trial-and-error approach, due to the partially understood mechanisms of action in PEPD and IEM, treatment side-effects and the narrow therapeutic window[20]. The treatment of individuals with PEPD has been somewhat successful with carbamazepine that interacts with Nav1.7 in its inactivated state[21]. Some improvement in the symptoms of erythromelalgia, both primary and secondary, was reported with the administration of aspirin, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, antihistamines, vasodilators, β-blockers, opioids, gabapentin, corticosteroids, acetaminophen, sympathectomy and physical methods. Mexiletine, capsaicin, tetracycline and doxazosin were also used, but patients reported no symptom relief[4].

When considering the treatment for our patient's hypertension, there was a contraindication for β-blockers due to recorded asystole. ACE inhibitors and calcium channel blockers had possible interactions with other prescribed medications. Therefore, we opted for peripheral α-blocker doxazosin that causes blood pressure decrease and possibly has a favorable effect on the pathomechanism of erythromelalgia via peripheral vasodilatation. After three months of treatment, control 24-hour ABPM was normal with fewer pain attacks. The latter might be influenced by pregabalin treatment, which was started in the meantime. However, pregabalin was discontinued after six months due to an increase of pain attack frequency and reported side effects. After twelve months of doxasozin treatment, the patient experienced elevated blood pressure and tachycardia only during the attacks.

Most approaches to treat IEM-related symptoms were partially successful[4]. Hypertension in children with IEM was managed with nitroprusside, nifedipine, angiotensin-converting enzyme inhibitors, nitroglycerin and calcium channel blockers[5,14].

Conclusion

Due to variable treatment approaches and a lack of systematic drug efficacy, the management of IEM-related hypertension in children must be individualized. That is especially important in complex patients who suffer from both PEPD and IEM, considering the possibility of bradycardia and asystole. Further research is needed to provide clear recommendations for IEM-related hypertension treatment.

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Sažetak

DIJETE SA SINDROMOM EKSTREMNE PAROKSIZMALNE BOLI I ERITROMELALGIJOM: IZAZOVI U LIJEČENJU HIPERTENZIJE

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Poremećaj ekstremne paroksizmalne boli i nasljedna eritromelalgija dva su različita sindroma uzrokovana patogenim mutacijama gena *SCN9A*, ali oba mogu biti dio kliničkog kontinuuma u istog pacijenta. Vodeća klinička obilježja su napadaji boli praćeni simptomima autonomnog živčanog sustava, od kojih su najteži apneja, bradikardija i asistolija. Arterijska hipertenzija u literaturi je opisana kao dodatno kliničko obilježje, najčešće u pacijenata sa sekundarnim oblikom eritromelalgije. Patomehanizam hipertenzije u ovim sindromima još nije potpuno razjašnjen. Mogući uzrok je aktivacija simpatičkog sustava zbog epizoda jake boli, a ostale teorije porasta krvnog tlaka uključuju autoimunu i upalnu etiologiju te endotelnu disfunkciju uslijed smanjene raspoloživosti dušikova oksida što posljedično dovodi do vazokonstrikcije. Trenutno ne postoje jasne smjernice za liječenje hipertenzije u pedijatrijskih pacijenata s eritromelalgijom. Stoga je najčešći terapijski pristup „pokušaj-pogreška". Posebice je izazovno liječenje pacijenata sa sindromom ekstremne paroksizmalne boli jer oni mogu imati bradikardiju i asistoliju te često uzimaju nekoliko različitih lijekova za kontrolu neuropatske boli. U ovom radu prikazan je klinički tijek pacijenta sa sindromom ekstremne paroksizmalne boli i eritromelalgijom kod kojeg je dijagnosticirana sistoličko-dijastolička hipertenzija u dobi od devet godina, a koja je uspješno kontrolirana niskom dozom doksazosina.

Ključne riječi: *Poremećaj ekstremne paroksizmalne boli; Eritromelalgija; Hipertenzija; Djeca*