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ADVANCES IN PEDIATRIC RESEARCH

Novel mutation of *SCN9A* gene in a family with Paroxysmal Extreme Pain Disorder (PEPD): Considerations of paediatric interest

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Abstract

Introduction: Paroxysmal Extreme Pain Disorder (PEPD) is a rare autosomal dominant disease, caused by mutations in the *SCN9A* gene, which encodes the NaV1.7 voltage-gated sodium channel alpha subunit. Symptoms generally begin in early infancy with episodes of excruciating, burning and spreading pain in the lower part of the body, typically in the anorectal area, which can last from seconds to hours.

Case description: We describe the case of a 5-year-old male with PEPD and a novel heterozygous mutation c.5825c>T (p. Thr1942ile) in the *SCN9A* gene. This is a novel mutation that has not previously been reported.

Discussion: According to the available information, the clinical significance of the variant c.5825c>T (p. Thr1942ile) is unknown. However, its presence in the patient and in others affected family members, reinforces its possible pathogenicity and is suggestive of mutation segregation with the disease in this family.

Conclusion: We consider that it is a family case of interest to the pediatrician, for allowing: 1) To be able to intuit it by the clinic early and 2) To be able to confirm it by means of the corresponding genetic study.

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Introduction

Paroxysmal Extreme Pain Disorder (PEPD) – previously known as Familial Rectal Pain Syndrome [1] – is a rare autosomal dominant disease with fewer than 500 patients documented [2].

PEPD is caused by mutations in the *SCN9A* gene, which encodes the NaV1.7 voltage-gated sodium channel α-subunit [1]. The NaV1.7 is especially expressed in nociceptive neurons at the dorsal root ganglion and sympathetic ganglia neurons [2,3], but it is also present in the nerves innervating arterioles and arterio-venous shunts in the glabrous skin, the vascular myocytes and the vascular endothelium in human skin [1]. *SCN9A* mutations are causally associated with two phenotypic presentations: painful conditions (inherited erythromelalgia, small-fibre neuropathy and PEPD) and loss-of-pain-sensation conditions (congenital insensitivity to pain) [1,4].

PEPD-related NaV1.7 mutations impair channel inactivation and prolong action potentials and repetitive nociceptor firing in the areas where it is expressed, in response to provoking stimuli, which produces a hyperexcitable and persistently activated sodium channel, increasing the excitability of sensory neurons [4,5].

Symptoms generally begin in early infancy with episodes of excruciating,burning and spreading pain in the lower part of the body, typically in the

anorectal area, which can last from seconds to hours [2,5]. This pain is oftenaccompanied byerythema(harlequin colour change) [6]. PEPD is usually triggered by mechanical stimuli [1]. Pain episodes can also affect the ocular and mandibular regions [5].

Other clinical manifestations are tonic non epileptic seizures with normal electroencephalogram (EEG) [6], flushing, lacrimation, rhinorrhoea, hypersalivation, bradycardia, syncope and asystole [1,2]. Carbamazepine is the treatment of choice for PEPD, but in some patients this may not alleviate the pain [5,7].

We describe the case of a 5-year-old male with PEPD anda novel heterozygous mutation c. 5825c>T (p. Thr1942ile) in the *SCN9A* gene. This is a novel mutation that has not previously been reported.

Case Description

The index patient was a 5-year-old male, the second child of healthy non-consanguineous parents. He had an older brother who was unaffected. Personal history was unremarkable, and pregnancy and birth were normal, as was psychomotor development.

Inquiry into the family history revealed lower limb paraesthesia in the patient's father, who was 38-years-old, since childhood, similar facial and mandibular pain episodes in the paternal grandmother and pain attacks with profuse sweating in a paternal great-grandfather.

The child was first brought for consultation at the age of two, for episodes of parieto-occipital headache and severe sweating. The symptoms worsened at the age of three; in the evenings, there were episodes of excruciating pain and intense muscular contraction in the lower limbs, especially in the knees and ankles and in the right half of the body, lasting from one to forty minutes, one to three times a week. During the attacks, he cried with pain and tended to stay still, unable to walk, and even light touches were painful. In more recent episodes, he suffered from sweating and erythema after the pain attacks. He defecated or urinated after all the attacks, and then slept deeply. Subsequently, he sometimes limped for a few days.

Examination between crises revealed the patient to be in apparent good health; he was good natured and presented normal psychomotor development. A parapatellar autonomic vascular phenomenon was observed in both knees, lasting a few minutes, after which it disappeared completely. Examination of the joints showed them to be totally normal.

Further tests were then made. Biochemical analyses, blood count and hormonal study were all normal, apart from a slight increase in neuron specific enolase (22.8 ng/ml), creatinkinase (10^5 U/L) and S100B protein (0.27 ug/L). Doppler scan of the lower limbs, ultrasound examination of the knees, CT and nuclear magnetic resonance (NMR) were all completely normal. Electrophysiological study revealed no nerve or muscle dysfunctions. EEG did not show significant changes in electrical activity of the brain. A muscle biopsy was performed, but no dystrophy or inflammatory dysfunctions were evidenced.

Results

Gives the patient's clinical manifestations and the unremarkable results of the tests, genetic study was requested, after obtaining informed consent from the parents.

PCR sequencing

Genomic DNA was extracted from blood samples, followed by PCR amplification of the region of the *SCN9A* gene that includes the family variant c. 5825C>T (p. Thr1942I1e). Sequencing and analysis of the results obtained by comparison with the reference sequence NM_002977.3. This study revealed a novel heterozygous mutation c.5825c>T (p. Thr1942ile) in the *SCN9A* gene in the index patient. This analysis does not include information on mutations outside the regions analyzed or not detectable by the method used. A genetic study was then made of the parents and the patient's older brother. The same mutation was detected in the father, who mentioned having suffered lower limb paraesthesia since childhood, and the brother, who was apparently unaffected. The maternal genetic test results were normal. The paternal grandmother, who suffered from ocular and mandibular pain episodes, refused a genetic study. Treatment with oxcarbazepine was then started. Appreciating a considerable improvement of symptoms, after two years of treatment has only presented two episodes of pain of short duration.

Discussion

PEPD is a rare autosomal dominant disease that is characterised by episodes of intense burning pain and erythema in the anorectal, ocular and mandibular areas [1,2]. It is related to mutations of the *SCN9A* gene, which cause profound changes in the amino acid connectivity of the NaV1.7 channel. Such modifications may account for the gain-of-function effects measurable in dorsal root ganglion nociceptors by electrophysiological assays [4].

As the NaV1.7 channel is expressed in multiple structures, such as nociceptive neurons at the dorsal root ganglion, sympathetic ganglia neurons, the nerves innervating arterioles and arterio-venous shunts in the glabrous skin, vascular myocytes and in the vascular endothelium in human skin [1,3,7,8], PEPD has multiple clinical presentations. Symptoms usually begin in early infancy, sometimesbeing apparent since childbirth [5], with intense pain in the lower limbs and around the rectum, a pain that can last from a few seconds to several hours [2]. Erythema and hot skin are other significant symptoms, probably because of the expression of the NaV1.7 channel in smooth muscle cells of skin vasculature [1,8].

The frequency of rectal pain episodes typically falls with increasing age, although ocular and mandibular pain can become more common [6]. Several cases of PEPD in children have been described (Table 1) [9-15].

Table 1: Characteristics of published cases of paroxysmal extreme pain disorder in childhood.

Author	Patient	Mutation	Symptoms	Further Tests	Triggers	Family History	Treatment
Kim et al. [18] Meijer et al. [9]	Female, 6-years-old	c.701T.C (p.I234T)	Global motor delay. Severe PPA lasting 1 min with sweating and erythema of lower limbs, hands, abdomen and perineum which caused acute flexion spasms. Automutilation behaviour between pain attacks indicative of hypoalgesia	Neurological examination: Peripheral hypotonia with diffuse symmetrical hyporeflexia with preserved muscle bulk, cranial nerves, and cerebellar function. CT: Slight asymmetry in the anterior horns of the ventricles. Muscle biopsy: Chronic neurogenic atrophy and non-specific inflammatory myopathy	No	No	Carbamazepine
Akcam et al. [14]	Male, 8 months	-	PPA during defecation, lasting for a few seconds, with harlequin skin changes in the lower half of his body. Spontaneous recovery	Normal	Defecation, bowel movement, probing of the anal areas	Second-degree consanguineous parents	Carbamazepine

Imai et al. [10]	Female, 5-years-old	c.5218G>C (p.Val1740Leu)	Short-lasting, severe, unilateral temporal headaches with ipsilateral lacrimation, nasal congestion, rhinorrhoea and facial flushing. 10–20 times per day.	Normal	Hitting her head or body, taking a bath, experiencing a temperature change, or sleeping	Similar headaches in an older brother, younger sister, mother, maternal aunt and maternal grandfather's brother. Headaches subsided in adulthood in mother, maternal aunt and maternal grandfather's brother. Maternal aunt: episodes of burning pain in lower limbs since adolescence. Maternal grandfather: headaches with conjunctival injection	Carbamazepine
Suter et al. [5]	7 family members, all of them affected since childhood	c.4835T>C (p.L1612P)	PPA in lower limbs and rectal area. Ocular and mandibular pain. Upper limbs pain.	Normal	Light touch such as changing diapers, defecation, warm	7 family members affected with PEPD	Favourable effect of cold exposure. Lack of drug efficacy (including carbamazepine)
Meglic et al. [11]	Female, 3-years-old	c.554G>A (p.Arg185His)*	Extremely painful micturition since birth	Global motor delay (improved by decreasing the frequency of attacks with treatment). Special phenotype: high forehead, low-placed ears, retrognatia, long nose with a narrow tip. Syndactyly	Micturition	Father: same mutation, PPA in jaw triggered by chewing since childhood	Carbamazepine
Beck et al. [13]	Female, 15-years-old		-	Multiple cardiorespiratory arrests since childhood, needing 24 h care from an advanced	-	-	-

				life support provider			
Choi et al. [7]	Male, 3 months	Gly1607Arg	Beginning on the second day of life, PPA that started with tonic contraction of the whole body followed by harlequin skin changes	Normal. Slight cutaneous xerosis, hyperkeratotic lesions on the dorsum of the hand	Inserting a thermometer into the patient's anus, falls on the buttocks, trivial manoeuvres such as pressing one foot or spontaneously during sleep	No	No response to carbamazepine
Estacion et al. [12]	Female, 10-years-old	A1632E	Bradycardia (pacemaker). Symptoms compatible with PEPD and erytromelalgia	Normal	Touching, eating, defecation, bowel movements	No	-

* This mutation had previously been found in patients with small fibre sensory neuropathy.
Abbreviations: PPA: paroxysmal pain attacks

Most of these cases present paroxysmal pain in the lower limbs, as in our patient. However, other symptoms can appear, such as global motor delay (which can be alleviated with suitable treatment, decreasing the frequency of attacks) [9], long-lasting lower limb weakness (probably due to fear of pain reactivation) [5], unilateral temporal headache [10], upper limb pain [5] and painful micturition [11]. The following autonomic manifestations are commonly associated: flushing, lacrimation, rhinorrhoea [10], nonepileptic seizures with normal EEG, apnoea, bradycardia, syncope [2,6,12] and even cardiorespiratory arrest [13].

Pain attacks are usually related to mechanical stimuli [1], including defecation [5,12,14], trauma [10], birth [2], mastication [10] or light touch such as changing diapers [5]. In addition, stressful events [2], cold [2,10] or warm [5] temperatures, taking a bath [14,15] or sleeping [10] may trigger an attack. There is usually a correlation between the distribution of the attack and the trigger [7], but pain can sometimes appear with no identifiable triggers [9], as in the case of our patient.

Diagnosis of PEPD relies on medical history takenby the relatives, either by direct observation or by video recording of the episodes in infants and children– as happened in our case – and can be confirmed by genetic testing [7]. Between episodes, the results of physical examination are all normal [6]. PEPD is an autosomal dominant disease, so the presence of a compatible family history is common [5,10,11]. On the other hand, the mutation may occur sporadically [7,9,12,14]. Different *SCN9A* gene mutations have been described in patients with PEPD. Those described in children are listed in Table 1.

Mutation c.5825c>T (p. Thr1942ile), detected in this family, has never been reported in the literature or in the dbSNP and EXAC databases. This variant affects a moderately conserved region and the bioinformatic analysis performed suggests it is benign. However, its presence in the patient and in his father, both of whom were affected, together with the presence of symptoms in other members of the paternal side of the family,reinforce its possible pathogenicity and are suggestive of mutation segregation with the disease in this family.

The presence of the heterozygous mutation in the older brother (asymptomatic) does not contribute to clarifying its pathogenicity, because PEPD symptoms usually appear in the neonatal period or during childhood. Nevertheless, cases have been reported of patients who suffered the first symptoms of the disease in adulthood [2].

According to the available information, the clinical significance of the variant c.5825c>T (p. Thr1942ile) is unknown.

A differential diagnosis of PEPD must be made with diseases that may be caused, fundamentally, by a change in the electrical activity of the brain [16]. Epileptic seizures should be considered, given the triggers and the paroxysmal nature of the attacks, but harlequin colour changes are exceptional in epileptic seizures [7]. In addition, EEG results in PEPD are usually normal [5-7,9-11,13].

Hereditary hyperekplexia has also been considered in infants with PEPD [7]. This disease manifests shortly after birth with a violent jerking response to noise and touch, and massive, sustained stiffening of the trunk and limbs, clenching fists, and attacks of high-frequency trembling. Newborns affected are at risk ofcot death due to laryngospasm and cardiorespiratory failure. Stiffness attacks may resemble epileptic seizures, although sleep can reduce or even abolish stiffness and jerking and EEG findings are normal [17]. Unlike PEPD, children with hyperekplexia tend to have high muscle tone between attacks, and the nose-tap test is considered to be a pathognomonic sign in this condition [7].

Another differential diagnosis that should be considered is primary erythromelalgia, which is also produced by *SCN9A* gene mutations. This condition, too, is characterised by attacks of severe pain and skin flushing. However, it usually involves the feet and hands, is more symmetrical, does not manifest in a harlequin pattern, and is triggered by warmth and exercise. Pharmacotherapy is generally ineffective in relieving the symptoms of this condition. For both disorders, patients with a mixed clinical phenotype and changes in channel function have been reported [7,12,18-20].

Patients with PEPD can benefit from drugs for neuropathic pain such as the sodium channel blocker carbamazepine, which is the treatment of choice. However, it fails to alleviate pain in some patients [2,5,7]. Other options are amitriptyline, lidocaine and mexiletine, [21]. It is also important to educate patients and parents' to avoid possible triggers [7]. Some patients develop strategies over the years to avoid pain, for example by immersing themselves in ice-cold water [5].

An important adverse effect of rectal pain is constipation, caused by pelvic floor dysfunction. Pelvic floor retraining with biofeedback has proven to be useful for some patients [2].

In some cases, bradycardia, syncope and cardiorespiratory arrest have required the insertion of a pacemaker in early childhood [12].

Changes in the NaV1.7 channel that occur in loss-of-pain-sensation conditions such as congenital insensitivity to pain are currently been studied, as part of the search for effective analgesic NaV1.7 inhibitors that could be useful in PEPD treatment.

Conclusion

Although these are very rare diseases, we consider that it is a family case of interest to the pediatrician, for several reasons: 1) Firstly, because knowing this type of neuropathy, it will be easier and earlier to carry out a diagnosis in stages early and, 2) Be able to confirm its existence through the corresponding genetic study.

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