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

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Abstract

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.

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