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Clinical report

Twins with hereditary sensory and autonomic neuropathy type IV with preserved periodontal sensation

Yeliz Guven [a], Umut Altunoglu [b], Oya Aktoren [a], Zehra Oya Uyguner [b], Hulya Kayserili [b], Massupa Kaewkahya [c,d,e], Piranit Nik Kantaputra [c,d,e,f,*]

[a] Department of Pedodontics, Faculty of Dentistry, Istanbul University, 34093 Istanbul, Turkey
[b] Medical Genetics Department, Istanbul Medical Faculty, Istanbul University, 34093 Istanbul, Turkey
[c] Center of Excellence in Medical Genetics Research, Chiang Mai University, Thailand
[d] Division of Pediatric Dentistry, Department of Orthodontics and Pediatric Dentistry, Thailand
[e] Craniofacial Genetics Laboratory, Faculty of Dentistry, Chiang Mai University, Thailand
[f] DENTALAND CLINIC, Chiang Mai 50200, Thailand

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ABSTRACT

Turkish twin brothers affected with hereditary sensory and autonomic neuropathy type IV (HSAN IV) are reported. Their clinical findings were generally typical for HSAN IV. Interestingly they both had preserved periodontal sensation. Mutation analysis of the NTRK1 gene showed a homozygous c.2001C>T substitution in exon 15 in both twins. This base substitution is predicted to change a polar, positively charged amino acid arginine to the highly active amino acid cystein at position 654 (p.Arg654Cys). The parents were heterozygous for the mutation. This mutation has been reported previously in one Japanese and one Arab patients. The preserved periodontal sensation has not previously been reported in patients affected with HSAN IV. This preserved sensation in our patients might have been through Ruffini endings, the periodontal mechanoreceptors which have been reported to be present in TrkA knockout mice. Here we report the first twins affected with HSAN IV and the observation that periodontal sensation is not affected by mutation in NTRK1.

1. Introduction

Hereditary sensory and autonomic neuropathy type IV (HSAN IV; OMIM #256800), also known as congenital insensitivity to pain with anhidrosis (CIPA), is an autosomal recessive inherited disorder, which belongs to a group of rare genetic neuropathies that affect the peripheral nervous system. The disease is present at birth and the first sign of this disorder is recurrent episodic fever in infancy due to the inability to sweat [Sarasola et al., 2011]. HSAN IV is mainly characterized by recurrent and unexplained episodic fever, anhidrosis, absence of reaction to noxious (or painful) stimuli, and mental retardation [Swanson, 1963]. The insensitivity to pain when accompanied with mental retardation leads to self-mutilating behavior [Shatzky et al., 2000]. The self-mutilating behavior involves mainly the orofacial region. The oral manifestations include premature loss of teeth, scarring of soft tissues (tongue, lip and buccal mucosa) and osteomyelitis of jaws. In infants, oral self-mutilation is typically characterized by tongue ulcers. Most affected infants also exhibit fingertip biting that begins when the primary incisors start to erupt [Schalka et al., 2006]. The insensitivity to superficial and deep pain is due to the absence of small myelinated (A-fibers) and unmyelinated nerves (C-fibers), whereas the lack of sympathetic innervation of eccrine sweat glands results in anhidrosis [Verpoorten et al., 2006].

The pathogenesis of HSAN IV is known to be associated with the loss-of-function mutations in the neurotrophic tyrosine kinase receptor type 1 (NTRK1) gene, also known as tyrosine kinase receptor A (TRKA). The NTRK1 gene encodes the high-affinity tyrosine kinase receptor I for Neurotrophic Growth Factor (NGF), which is responsible for the differentiation and survival of sympathetic ganglions and nociceptive sensory neurons [Indo, 2001; Sarasola et al., 2011]. To date, 74 different NTRK1 mutations have been identified in patients with HSAN IV from various ethnicities. So far, 21 frameshift, 11 splice-site, and 43 missense and nonsense mutations, and 1 gross NTRK1 deletion mutation have been detected. [Human Gene Mutation Database, 28.12.2013].

* Corresponding author. Center of Excellence in Medical Genetics Research, Chiang Mai University, Thailand. Tel.: +66 81 9524529; fax: +66 53 222 844.
E-mail addresses: dentaland17@gmail.com, nikmutation@gmail.com (P. N. Kantaputra).

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Here, we report the clinical and molecular findings of the first twins affected with HSAN IV. Interestingly, periodontal sensation was preserved in both of them, leading to increased understanding of periodontal innervation. Mutation analysis of NTRK1 revealed a previously known mutation, p.Arg654Cys in the affected patients.

2. Clinical reports

2.1. Patient 1

Patient 1, a 17-year-old Turkish man, was seen at Pediatric Neurology clinic, Istanbul Medical Faculty, Istanbul University due to pain insensitivity (Figs. 1 and 2A). He was seen for the first time at the age of 1 year. The propositus was a twin male born to healthy double first degree cousins at 32 weeks of gestation after the normal pregnancy and delivery. The other twin (patient 2) was also affected. He had two healthy female siblings (Fig. 1). His birth weight was 2200 g. Birth length and OFC were not recorded but were told to be within normal ranges. He sat unsupported at 9–10 months, walked at 2 years, said his first word at 2 years, and spoke in 2–3 word sentences at age 3 years (Table 1). He was recognized as having pain insensitivity during the first month of life and hospitalized due to prolonged high fever at 2.5 months. He was clinically diagnosed as having HSAN IV at the age 4.5 months by a pediatric neurologist based on the characteristic clinical features of HSAN IV including insensitivity to pain and prolonged high fever. Sural nerve biopsy findings at the age of four years confirmed the clinical diagnosis. Intellectual disability was mild with IQ score of 63 obtained by Stanford Binet test. He seemed to be introverted and hyperactive with emotional lability.

Although there was no reaction to painful stimuli; touch, position, and vibration senses were intact. Temperature sensation was decreased. The parents claimed that he reacted to temperature changes in the water while showering. The repeated episodes of high fever were due to the inability to sweat. Sweat gland structure and function were assessed using skin biopsy and pilocarpine iontophoresis. No sweat was obtained on sweat induction test, although skin biopsy showed presence of normal sweat glands. Hypo- and hyper-pigmented skin lesions of the hands were observed. His skin was dry, thick and calloused. Nonhealing skin ulcerations on the dorsum of the hands, particularly at the knuckles, feet and right knee were noted. He had brachydactyly with broad fingers (Fig. 2C, D). Radiological skeletal survey showed multiple joint deformities, Charcot joints, on large peripheral joints including both knees and ankles (Fig. 4A, B). He had a history of recurrent traumatic fractures of tibia and femur. Anteroposterior radiograph of the hands showed hypoplasia of the distal phalanges, and metaphyseal irregularity of the left proximal surface of the first metacarpal (Fig. 4A). Anteroposterior radiograph of the feet also displayed hypoplasia of the distal phalanges (Fig. 4B).

Ophthalmologic examination revealed bilateral corneal opacity suggestive of previous neurotrophic keratitis. Neurotrophic keratitis was first noticed around two years of age and became more evident around the age of 4. Corneal opacity appeared to cover one third of the lower segment of the iris of both eyes (Fig. 2A). Emotional tearing was normal but reflex tearing was decreased and he was using artificial tear drops (Table 1). There was neither history of self-mutilating behaviors on eyes such as eye rubbing nor history of bacterial infection.

The patient displayed long face, midfacial hypoplasia, prominent chin and deep-set eyes (Fig. 2A). Oral examination at age 17 years showed scarring of the tongue due to self-mutilation. Intraoral examination revealed multiple amalgam fillings. Gingivitis associated with poor oral hygiene and midline deviation were also noted (Fig. 2E). Panoramic radiograph showed the presence of several poorly obturated root canals, periapical lesions, and single rooted second molars (Fig. 5A). Lateral cephalograph showed mandibular prognathism (Fig. 5B). The tip of his tongue was excised by self-mutilation, causing a crater-like appearance (Fig. 2E). His dental caries proceeded to an advanced stage as a result of the absence of pulpal pain. The dentist who had provided the dental care for him had described that he did not have dental pulp pain. Without the use of a local anesthetic, both twins had had several dental restorations and root canal treatments performed with no pain. Teeth that had acute apical periodontitis were sensitive to percussion test and had caused discomfort.

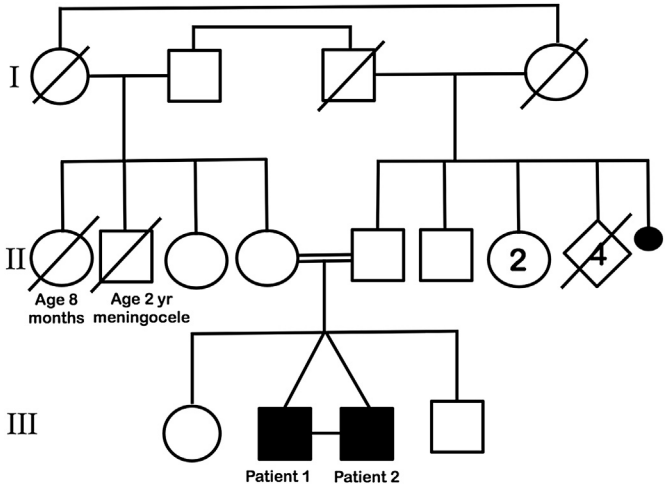

Fig. 1. Pedigree of the family. The twin brothers are children of double first degree cousins.

2.2. Patient 2

Patient 2, the twin brother of Patient 1, was seen at Pediatric Neurology clinic, Istanbul Medical Faculty, Istanbul University due to pain insensitivity (Figs. 1 and 3A). He was seen for the first time at the age of 1 year and was reevaluated again at the age of 17. He was born to healthy double first degree cousins at 32 weeks of gestation after the normal pregnancy and delivery (Fig. 1). His birth weight was 2400 g. Birth length and OFC were not recorded but were told to be unremarkable. He sat unsupported at 9–10 months, walked at 1.5–2 years, spoke first word at 2 years, and in sentences at 3–4 years (Table 1). He also was clinically diagnosed as HSAN IV at the age of 4.5 months based on the characteristic clinical features of HSAN IV. Confirmatory diagnosis by sural nerve biopsy was not possible due to the insufficient biopsy specimen. He was insensitive to painful stimuli and the temperature sensation was decreased. The parents claimed that he reacted to temperature changes in the water while showering. However, touch, position, and vibration senses were intact. Sweat gland structure and function test results were similar to those of his brother. Intellectual disability was mild with an IQ of 75 on Standford Binet test. He was described by his parents as being hyperactive, irritable, and short tempered. Similar to his twin brother he had emotional liability and appeared to be more introverted than his brother. However, their behavior pattern has improved with age (Table 1).

Ophthalmologic examination revealed bilateral corneal opacity suggestive for previous neurotrophic keratitis, which was initially noticed around two years and became more evident at age 4 years