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Congenital insensitivity to pain with anhidrosis: A report of two siblings with a novel mutation in (TrkA) NTRK1 gene in a Saudi family

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ABSTRACT

Congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV (HSAN type IV) is an extremely rare autosomal recessive disorder with an estimated incidence of 1 in 25,000. It was first described in 1963, and since then several case reports and review articles have been published. In this article, we report two brothers with clinical features of CIPA, who presented with recurrent episodes of hyperthermia, anhidrosis, profound loss of pain sensitivity, and unconscious self-mutilation of fingers, lip and tongue. Sanger sequencing analysis confirmed the presence of a novel mutation c.783_785delGAA in the NTRK1 gene in the two affected members of the family. Early diagnosis and management of different systemic complications including orthopedic, visual, and dental may be useful in the reduction of frequency and severity of these complications.

1. Introduction

Congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV (HSAN type IV) is an extremely rare autosomal recessive disorder with an estimated incidence of 1 in 25,000 [1]. It was first described by Swanston et al. at 1963, and it belongs to a group of rare autosomal recessive peripheral sensory neuropathies. It comprises loss of pain sensation, anhidrosis and moderate to severe mental retardation but touch and pressure sensitivity are unimpaired [2]. Peripheral nerve disease was first described by Galen (130–200 CE), and detailed anatomical illustration was documented by Andreas Vesalius in 1543 [3]. Peripheral neuropathy is one of the most common disorder referrals to the neurology clinics. It is caused by disordered function and structure of peripheral motor, sensory, and autonomic nerves [4].

Hereditary sensory autonomic neuropathy (HSAN) is a heterogeneous group of hereditary neuropathies in which the distinguishing features between different types relates to age of onset, clinical characteristics, mode of inheritance, type of the fiber involved, autonomic testing and the molecular biologic cause [5,6]. HSAN type IV is the second most common HSAN that manifests in the first month of life and is caused by mutations in the neurotrophic tyrosine kinase type 1 (NTRK1) gene, previously known as TrkA, encoding for the high-affinity receptor of nerve growth factor (NGF) [7]. NGF is important for the development and function of sympathetic and sensory neurons. It is also present in the brain where it has a trophic function in the development and maintenance of cholinergic neurons of the basal forebrain [2]. NGF also mediates inflammatory and immune responses after tissue injury by initiating and maintaining hypersensitivity to noxious stimuli, a phenomenon called peripheral sensitization [8]. In this study, we present the first family reported from Saudi Arabia with a novel mutation and also review the topic.

2. Methodology

The two affected individuals presented with insensitivity to pain, recurrent fever, and anhidrosis. They were assessed for inherited neuropathy through different modalities including physical examination, laboratory evaluations, nerve conduction studies and radiological imaging (magnetic resonance imaging (MRI) of the brain and spine). Radiographs were performed to evaluate skeletal fractures of the upper and lower extremities. Prior to the beginning of the study, informed written consent was taken from the participants according to the Helsinki declaration. The study was approved the ethical committee of the Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah. The study was also approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC).

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2.1. Case report 1

A twelve-year-old boy presented with recurrent, painless tibial and fibular fractures since the age of 3 years. He also complained of cold sensation and paraesthesias in both hands and feet. He had severe dryness of the skin, and he likes to take a bath several times a day. He suffered from recurrent episodes of high-grade fever without sweating. He was hospitalized many times for evaluation of the pyrexia but no cause could be identified. These episodes of fever were influenced by room temperature and exposure to the sun or hot environment. After his teeth started to grow, he began to chew his fingertips and bite the tip of his tongue (self-mutilation). Although his parents noticed that he was insensitive to pain, they didn't seek medical advice. He underwent several surgeries for fractures, including open wedge osteotomies of the left distal femur with implantation of the backbone. These surgeries were complicated by wound infection and delayed healing. His parents were non-consanguineous, and none of their family members were affected by any genetic disorder. Physical examination revealed severe trophic changes in the skin of distal limbs, hyperkeratosis, fissuring, and ulcers (Fig. 1). He displayed complete anhidrosis with dry and warm skin. He had lost many teeth with poor dental hygiene. There were scars of previous burns and surgeries. Neurologically, he had a low IQ, mild generalized hypotonia, normal power, depressed deep tendon reflexes, and absent response to pinprick and thermal stimuli. He could appreciate touch, vibration, and joint position sensations normally. He was able to walk but had difficulty with running. Basic laboratory evaluations and MRI of the brain and whole spine were normal. Radiographs of his upper and lower extremities showed multiple healed fractures.

2.2. Case report 2

A seven-year-old boy presented with unexplained episodes of fever and seizures started at the age of one year. He was always dry and hot, and during high fever, he was peevish and cried loudly with appropriate lacrimation. Fever subsided rapidly when a cold towel was applied. At the age of four years, he began to chew his fingers and bit off the tip of his tongue (self-mutilation). At that time, his parents noticed that he was insensitive to painful stimuli, a similar finding to his older brother. Clinically, his temperature was high (38.5 °C) and his skin was dry and warm. His motor milestone, weight and head circumference were normal. Neurologically, he had normal higher mental functions, cranial nerve examination, and power. He had mild generalized hypotonia and depressed deep tendon reflexes. He had impaired pinprick and temperature sensations. He showed normal tactile sensation, lacrimation, and corneal reflexes. His gait was normal. Basic laboratory evaluations and MRI of the brain and whole spine were normal. Radiographs of his upper and lower extremities showed multiple healed fractures.

3. Results

The blood samples were taken from two affected members of the family and 100 unrelated healthy controls of Saudi origin. Genomic DNA was obtained from the blood and NTRK1 gene was amplified by the use of specific primers, derived from the 5/ and 3/intronic or exonic sequences and annealing temperature of each pair was from 56 to 60 °C. We performed Sanger sequencing (ABI 3730) in an affected patient along with 100 normal persons as controls. Our Sanger sequencing results showed a novel deletion of three base pair at position c.783_785delGAA in NTRK1 gene, and it was also confirmed in other available affected individual of the family as shown in Fig. 2(a and b). This is the novel mutation, and we are reporting it for the first time in a Saudi family. This mutation was further validated in 100 unrelated healthy persons, but no one had this sequence variation. Sanger sequencing results were positive for mutation in the gene NTRK1, which has not yet been described as pathogenic in the international database. The deletion of three nucleotides in exon 7 resulted in the loss of the amino acid lysine at the position of 261 in both alleles of the NTRK1 gene (homozygosity). The homozygous appearance of this mutation stands in agreement with the autosomal recessive trait of HSAN type IV.

4. Discussion

The sensory abnormalities are widespread and may include cranial nerves and visceral sensation [8]. Anhidrosis is probably caused by an impaired thoracolumbar sympathetic outflow. This defect in thermoregulation and anhidrosis may cause recurrent febrile seizures, secondary to high environmental temperature [6]. Up to 20% of patients die from high-grade fever by three years of age [9]. The anhidrosis is present on the trunk and upper extremities in 100% of cases, while other areas of the body are variably affected. It causes the skin to become thick and calloused with dystrophic nails, lichenification of palms and feet and areas of hypertrichosis on the scalp [6].

There is severe loss of small myelinated fibers (with possible decrease in the number of unmyelinated fibers) which convey senses of pain and temperature. Touch and pressure sensitivity are unimpaired [10]. Lack of sensitivity leads to skin ulcerations and deep wounds, fractures, osteomyelitis, septic arthritis and charcot joints [2]. Fractures heal slowly, and large weight-bearing joints are particularly susceptible to repeated trauma and infection [6]. Corneal insensitivity to pain may lead to traumatic ulcerations and neuroparalytic keratitis. Other clinical features include delayed wound healing, muscle weakness, and decreased deep tendon reflexes [2]. Tearing is preserved, and fungiform papillae are present on the tongue (both serve to differentiate CIPA from Riley–Day syndrome) [6,11].

The NTRK1 gene maps to chromosome 1q21-q22 and contains 17 exons spanning 25 kb of DNA [2,12]. So far, over 51 mutations have been described in patients and families with CIPA [13]. These mutations

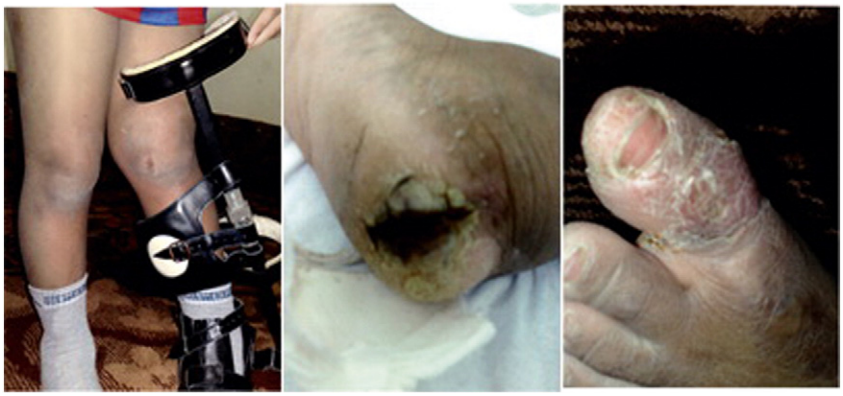

Fig. 1. Severe trophic changes in the skin of distal limbs, hyperkeratosis, fissuring, and ulcers.

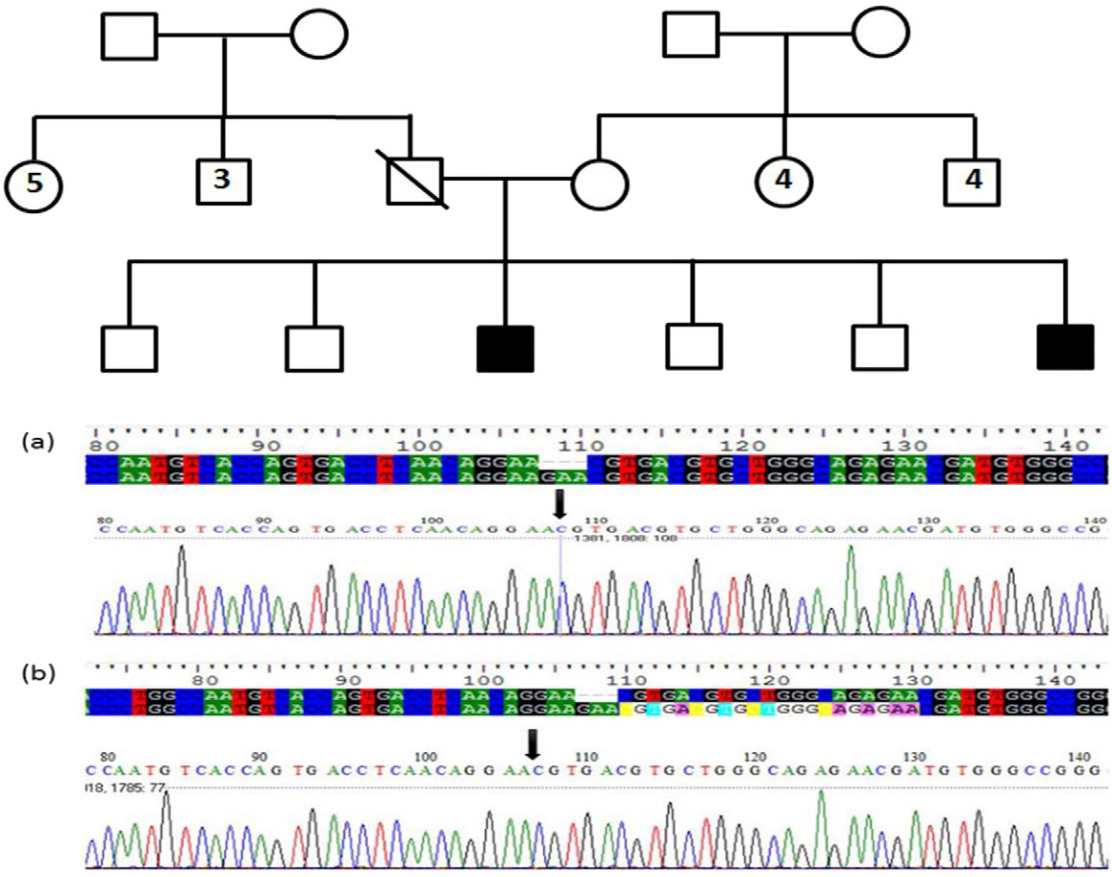

Fig. 2. Sanger sequence analysis: a and b (III-3 and III-6) are the affected members of the family showing a novel deletion mutation c.783_785delGAA in the NTRK1 gene.

are multiple and include deletion, spliced site mutations, frameshift, and missense mutations [2]. The mutations affect the extracellular domain, involved in NGF binding, and the intracellular signal transduction domain [2]. In a series of nine families, the disease was not linked to the NTRK1 gene in one family. This may indicate heterogeneity of CIPA [14]. In this study, we are reporting a novel deletion of three nucleotides in exon 7 that resulted in the loss of the amino acid lysine at the position of 261 in both alleles of the NTRK1 gene (homozygosity). The homozygous appearance of this mutation stands in agreement with the autosomal recessive trait of HSAN type IV as shown in Fig. 2.

NTRK1 is a transmembrane protein composed of an extracellular, a transmembrane, and an intracellular domain. The 3 domains are encoded by exons 1 to 9, exons 10 to 11, and exons 11 to 17, respectively. In the present study, a 3-base deletion at nucleotides GAA from 783 to 785 in exon 7 is reported in a Saudi population which is predicted to cause a frameshift after amino acid lysine 260 and create a downstream premature termination. Both patients in the family carry this mutation. Only 12 deletions have been reported previously in the literature. The phenotype of our patients is similar to the previously known sensory and autonomic neuropathy type IV.

5. Conclusion

In conclusion, we described two brothers affected with CIPA due to NTRK1 mutation (c.783_785delGAA). It is predicted that this deletion in exon 7 has a pathogenic and damaging influence on NTRK1 protein function. In the present study, we are documenting the clinical and genetic analysis of CIPA in a Saudi family, which is considered the first complete report of both clinical and genetic work coming from Saudi Arabia. In addition, the novel mutation described here widened the genetic spectrum of CIPA, which will benefit studies addressing this disease in the future.

Conflict of interest

The authors declare that they have no conflicts of interest.

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