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Case Report

Congenital Insensitivity to Pain with Anhidrosis: A Case Report

Anhidrozisli Konjenital Ağrıya Duyarsızlık Sendromu: Bir Olgu Sunumu

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Abstract

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disorder that is characterized by insensitivity to pain, anhidrosis and mental retardation. Mutations in the neurotrophic tyrosine receptor kinase 1 gene are responsible for the disorder. A 3.5-year-old male born to healthy consanguineous Iranian parents presented with such symptoms as insensitivity to pain, anhidrosis, self-mutilation and intellectual disability. At the time of presentation he had multiple scars, especially on his hands, feet and knees resulting from previous trauma. It was ascertained that the wounds, caused by trauma and the self-mutilating behaviors of the patient, did not heal easily. CIPA was diagnosed based on clinical findings and information obtained from the family. Wound care was performed and the patient was started on a support program for cognitive function. In the absence of a cure for the condition, the family was informed about the measures to be taken and provided with genetic counseling, and the patient was followed up. The characteristics of the disorder should be well known to ensure its inclusion in differential diagnosis. As there is as yet no cure for this condition, the family of the patient should be informed about the disease and the measures to be taken, and provided with genetic counseling.

Keywords: Congenital, insensitivity to pain, anhidrosis, pediatric

Öz

Anhidrozisli konjenital ağrıya duyarsızlık sendromu; ağrıya duyarsızlık, anhidrozis ve zeka geriliği ile karakterize otozomal resesif geçişli nadir bir hastalıktır. Nörotropik tirozin reseptör kinaz 1 genindeki mutasyonlar bozukluktan sorumludur. Aralarında birinci dereceden akrabalık olan, sağlıklı, İranlı ebeveynlerden doğan 3.5 yaşındaki erkek hastanın; ağrıya karşı duyarsızlık, terlememe, kendini yaralama ve zihinsel gerilik gibi yakınmaları vardı. Başvuru sırasında özellikle ellerde, ayaklarda ve dizlerinde, önceki travmadan kaynaklanan çok sayıda yara izi vardı. Travma ve kendine zarar verme davranışının neden olduğu yaraların kolay iyileşmediği öğrenildi. Tanı, klinik bulgular ve aileden alınan bilgilere konuldu. Yara bakımı yapıldı ve bilişsel fonksiyonları desteklendi. Hastalığın tedavisi olmadığı için aileye, alınması gereken önlemler hakkında bilgi ve genetik danışmanlık verilerek hasta takibe alındı. Bozukluğun, ayırıcı tanıda yer alabilmesi için özelliklerinin iyi bilinmesi gerekir. Hastalığın henüz bir tedavisi olmadığı için aileler hastalık ve alınması gereken önlemler hakkında bilgilendirilmeli ve genetik danışmanlık verilmelidir.

Anahtar Kelimeler : Konjenital, ağrıya duyarsızlık, anhidroz, pediatrik

INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA), known also as hereditary sensory and autonomic neuropathy type IV, is an extremely rare autosomal recessive disorder (1,2). The clinical features of CIPA include congenital lack of pain and temperature sensation, and absence of sweating, which leads to recurrent episodes of hyperpyrexia or hypothermia. The inability to feel pain results in such secondary complications as repeated injuries and self-mutilation, and delayed developmental milestones and intellectual disability may also be observed. CIPA is caused by mutations in the neurotrophic tyrosine receptor kinase 1 (NTRK1) gene on chromosome 1, which encodes the receptor tyrosine kinase for nerve growth factor (NGF). Although CIPA was defined a long time ago, it is rare and clinical data is limited, therefore unfamiliar to many clinicians (2-5). We present this case report to raise awareness about the disorder.

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CASE REPORT

We present the case of a 3.5-year-old male patient who was the fifth child born to healthy, second-degree consanguineous Iranian parents. The parents reported mild developmental delay in infancy, and insensitivity to pain was noticed when he did not respond to injections or accidental traumas. He had repeated injuries and delayed wound-healing, and a habit of biting the tongue and fingertips emerged upon teething, resulting in malformed fingers. He had a history of recurrent episodes of unexplained fever and two previous febrile convulsions at the age of six months. It was ascertained that there were members of the family who had experienced episodes of unexplained fever that resulted in death.

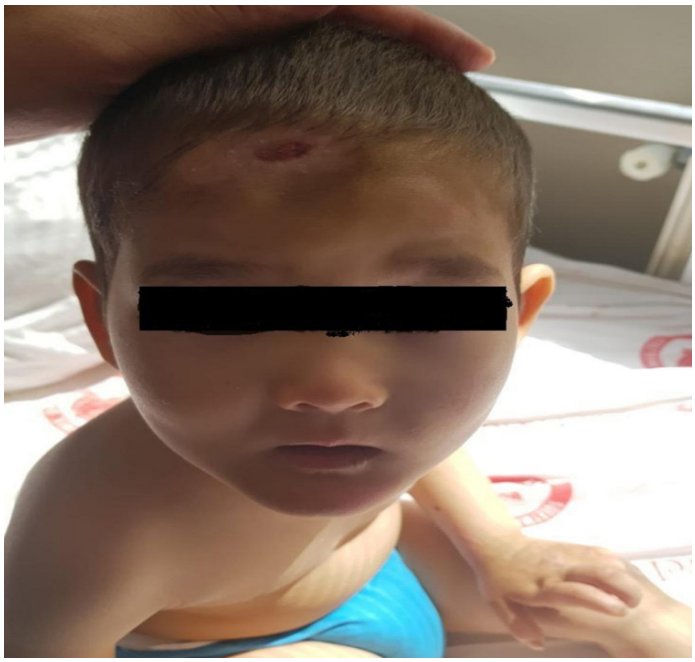

Figure 1. Skin lesions with slow wound-healing

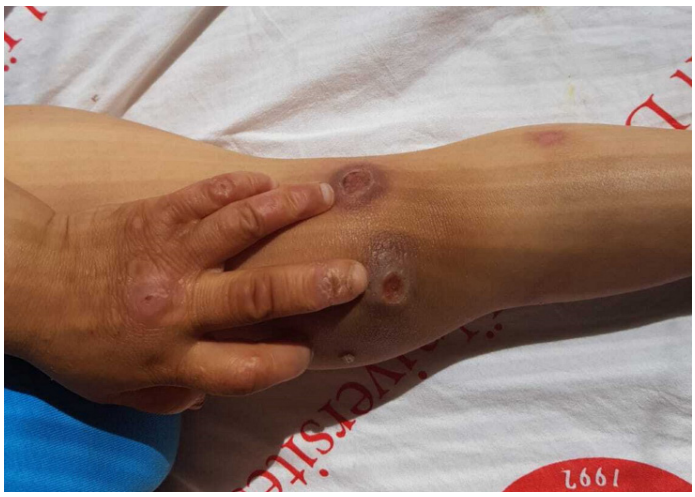

Figure 2. Ulcerated lesions and deformities to the hand and foot

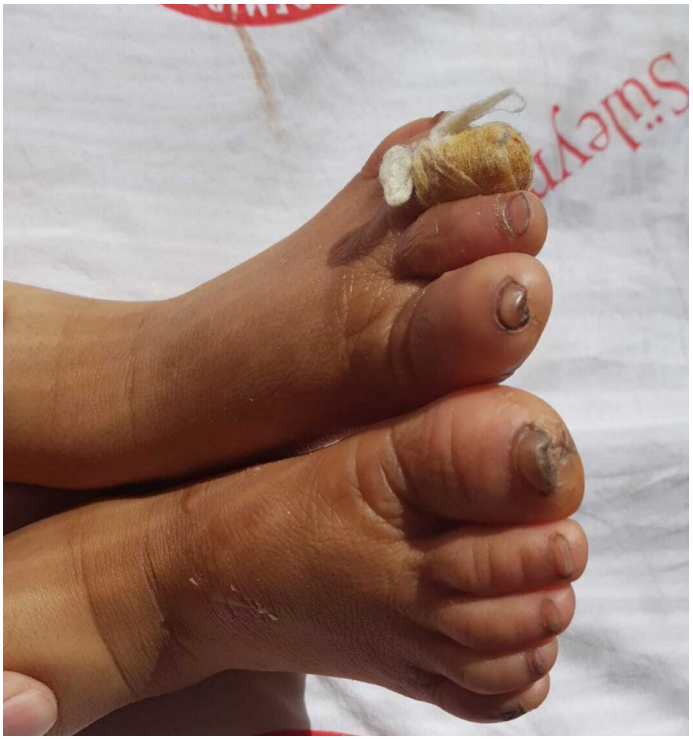

Figure 3. Auto-amputations to the fingertips

A clinical examination revealed multiple scars on the patient's hands, knee joints and feet due to previous trauma. There were signs of biting on the tips of the fingers and toes, and some fingers were amputated, and eroded and ulcerated wounds were noted on his hands and knees. Sweating was absent in any part of his body and he had dry skin with hyperkeratosis and cracking. An oral examination revealed biting injuries, scarring of the tongue, lips and buccal mucosa due to repeated self-mutilation. He had early tooth loss and a lot of dental caries. The patient responded to tactile stimuli, but there was no response to painful stimuli. Sense of vibration and position were normal. He had no fractures. Intelligence was lower than normal and he had a language delay.

NTRK1 gene could not be analyzed as the family had no health insurance and refused to have genetic testing. Based on the patient's history, family history and clinical findings, CIPA was diagnosed. We treated the injuries, provided mental health support and rehabilitation, counselled the parents on appropriate care for the child. Eight months after the diagnosis, he had a period of resistant fever and long lasting febrile convulsion with respiratory arrest that resulted in death.

DISCUSSION

CIPA is caused by mutations in the NTRK1 gene located on chromosome 1 that encodes the receptor tyrosine kinase for NGF. Mutations in this gene result in the failure of differentiation and migration of neural crest cells, leading to a complete absence of small myelinated and unmyelinated nerve fibers causing a lack of pain and temperature sensation. In addition, the sweat glands are not innervated, leading to anhidrosis (2,6-9). Variable

mutations have been identified in NTRK1 gene from CIPA patients and different phenotypic variations can be attributed to these different identified mutations (4,9-11).

The features of CIPA that are present in most of the patients include insensitivity to pain and self-mutilating behaviors, anhidrosis, mental retardation, and episodes of unexplained fever. Children often have self-inflicted injuries in the form of skin ulcers, burns, bone fractures, and auto-amputations of the fingertips and tongue. Self-mutilating behaviors mostly involve the orofacial region and limbs (2,5).

As physical trauma do not cause normal reaction, it may go unnoticed and lead to multiple scars and bone/joint fractures that are slow to heal. Recurrent trauma may cause deformity and affect functionality of the patient. These manifestations are frequent between 1 and 7 years of age, but other complications have no apparent age relation (2).

Anhidrosis, on the other hand, impairs the homeostasis of the core body temperature, since sweating is essential to normothermia. Depending on the environmental temperature, children with CIPA may develop hyperthermia or hypothermia, and recurrent febrile convulsions may occur in high environmental temperatures (2,5,6). Recurrent febrile episodes due to anhidrosis can begin in early childhood and initially are described as febrile episodes with non-infective origin. The febrile seizures frequently occur during these febrile periods and are causes of death in 20% of cases in first 3 years (2,10). Thermoregulation is imperative in management of CIPA and must include treatment of pyrexia with cooling, paracetamol and non-steroidal anti-inflammatory drugs.

The high incidence of skin and bone infections with antibiotic resistance also affect survival rate. They should be diagnosed in early period for better results.

There is no specific treatment and therapeutic options aim at treating symptoms and preventing self-mutilation, fractures and wound infections that may lead to amputation.

A special multidisciplinary approach is necessary in CIPA patients for better development, to reduce complications and sequelae. Also family members must be trained to avoid all events that cause a risk for the patients.

CONCLUSION

Since the condition is rare, it may be unfamiliar to physicians. The condition must be considered in the differential diagnosis of patients with insensitivity to pain and non-healing wounds. Due to the absence of a cure, the family should be informed about the measures to be taken, and efforts should be made to avoid potential complications from recurrent traumas.

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Conflict of interest: *The authors declare that they have no competing interest.*

Informed Consent: *The family provided consent for publication.*

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