Case Report

Congenital insensitivity to pain with anhidrosis in Sudanese children

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ABSTRACT

Congenital insensitivity to pain with anhidrosis (CIPA), also called hereditary sensory and autonomic neuropathy type IV (HSAN–IV), is an extremely rare autosomal recessive disease. It is characterized by insensitivity to pain, inability to sweat, episodes of hyperpyrexia, and intellectual disability. These factors render the affected persons to repeatedly injure and traumatise themselves to the degree that they become disabled. No specific treatment to the moment, but it needs multidisciplinary approach, and certain life adaptations and education. Here we report 4 unrelated Sudanese children affected with this rare neurological disorder, to raise the awareness on this rare disease, reflecting its spectrum, and the challenges which patients and their families face, especially when living in a hot country.

Keywords:
Anhidrosis; Congenital insensitivity to pain; Hereditary sensory and autonomic neuropathy type IV; Self-mutilation; Hyperpyrexia; Vitamin A toxicity.

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INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA, OMIM 256800), also called hereditary sensory autonomic neuropathy type IV (HSAN–IV), is a rare autosomal recessive disease, which constitutes a subtype of the hereditary sensory and autonomic neuropathies (HSAN, also known as the hereditary sensory neuropathies). These are clinically and genetically heterogeneous, and are characterised by progressive sensory neuropathy often complicated by ulcers and amputations [1]. It is characterized by insensitivity to pain due to lack of unmyelinated and small myelinated nerve fibres in the dorsal root ganglion that are responsible for transmitting pain signals. Patients are also insensitive to heat and cold temperatures, but not pressure. Although their sweat glands are normal in structure and function, they are unable to sweat as they lack innervations by small diameter neurons [2]. The condition is also associated with delayed development and intellectual disability. Common injuries include scarring of the tongue, lips and gums, chronic infections of bones and joints, bone fractures, multiple skin scars, oteomyelitis and joint deformities, which may lead to amputation [3,4]. Another common serious problem is eye related, such as rubbing of the eyes too hard and frequently, or scratching them during sleep, causing corneal scaring and blindness [5].

Pathogenesis is due to a genetic mutation in NTRK1 gene that encoding receptor protein for nerve growth factor (NGF) [1,6]. This protein induces outgrowth of axons and dendrites and promotes the survival of embryonic sensory and sympathetic neurons. A mutation prevents the formation of nerve cells responsible for transmitting signals of pain, heat, and cold to the brain, and does not allow NGF to bind properly, causing defects in the development and function of the nociceptive reception [7]. The disease has no ethnic distribution, but is more prevalent where consanguineous marriage is the trend.

Diagnosis is mainly clinical, plus some laboratory tests [7-9]. Symptoms necessary for diagnosis are insensitivity to pain, anhidrosis and intellectual disability. However, the severity of these symptoms is highly variable. Skin biopsy may reveal a lack of eccrine sweat gland innervation. A biopsy of the sural nerve may reveal characteristic findings including reduced numbers of myelinated and unmyelinated small-diameter fibres with normal numbers of large-diameter fibres. An axonal flare test with a small amount of diluted histamine injected under the skin, fails to cause the normal flare around the site of injection. Molecular genetic testing can confirm the diagnosis, but is not available on many occasions.

Management is through a multidisciplinary approach from a paediatrician, a dermatologist, a neurologist, a dentist, an orthopaedist, an ophthalmologist, and a social worker. Antipyretics, cooling blanket, various orthopaedic approaches, various dental procedures, including smoothing the sharp edges of teeth, prophylactic use of crowns, the use of a night-guard and extracting teeth to prevent self-mutilation, are essential tools for managing such cases. Keratitis can be treated with tarsorrhaphy, keratoplasty, scleral corneal graft, and special contact lenses to protect the cornea (scleral bandage lens). Behavioural abnormalities, though improve with age, require behaviour modification therapy, with sometimes, drugs for hyperactivity and daily inspection for unrecognized injuries [9,10].

CASE REPORTS

Four Sudanese children were seen with this rare condition, 2 females, and 2 males, but with different manifestations and disease spectrum.

Case 1

A 9-month-old girl, who belongs to a first cousin parents, originating from North Sudan, presented with recurrent episodes of high grade fever from early

neonatal period, failure to grow, irritability, and minor self-mutilations like pulling and peeling skin from her lip, or scratching her skin till it bleeds, without showing concern. According to her parents, she feels comfort and calm only when wrapped in a wet cloth, or kept in a cool place, and during winter month. They claimed that, she was never seen sweaty, but sometimes had mildly clammy skin. She was admitted and investigated many times for her recurrent fever and persistent malnutrition, including HIV screening. She received many courses of antibiotics, and even anti-tuberculous treatment, but all trials were of no benefit. She has 4 elder siblings with similar condition, who died in the neonatal period and early infancy. Examination revealed a miserable infant who is not interested in the surrounding and not dysmorphic, with sparse, light – coloured hair. Her weight was 3.8kg (< 3rd centile for age). She had dry hot skin, and had features of lower tract respiratory infection. She couldn't support her head nor sit. She was not appreciating painful stimuli, or crying to pin brick. Her routine investigations and uric acid level were all normal, and testing for NTRK1 gene was sent, but unfortunately, no result was received till her death. The probability of having insensitivity to pain with anhidrosis was discussed with the parents, and they were counselled and advised to avoid hot weather exposure, to provide a protective environment, and to watch for further injuries. They were helped to possess an air conditioning unit. She was supported with multivitamins and additional high calorie milk through a nasogastric tube feeding. During the period of follow up, she remained well, and started to put on weight, and to regain interaction with her sibs, but she sustained many injuries including cutting the tip of her tongue (Figure 1), chewing on her right proximal interphalangeal joint of the thumb, and rubbing her lower incisors till she lost them. All these injuries are without any pain expression. The latest injury she sustained at the age of 2, was scaring of her left cornea due to frequent scratching on her opened eye (Figure 2), which was misinterpreted by the primary care doctor, as vitamin A deficiency in the context of her failure to thrive. She received a high, toxic megadose of vitamin A on three occasions that led to severe dermatitis, skin cracking, sepsis, severe hypothermia, and death.

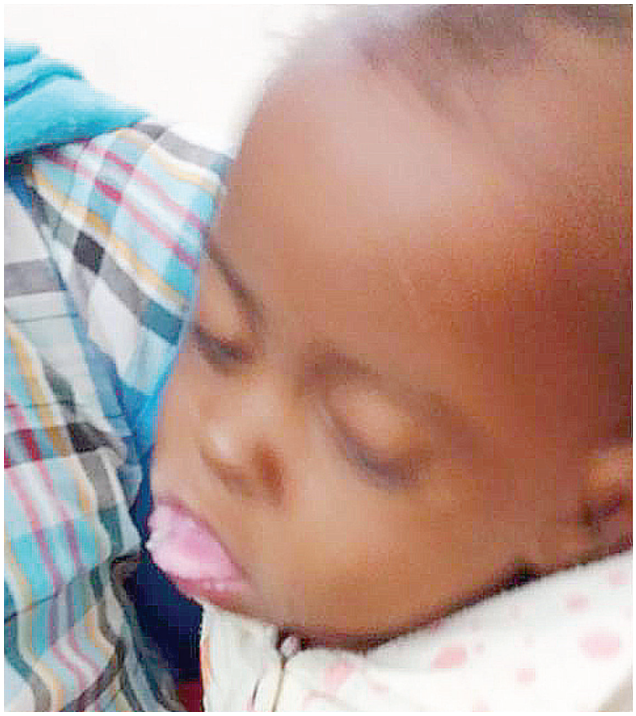

Figure 1 – Case 1. Cutting the tip of the tongue due to biting with teeth.

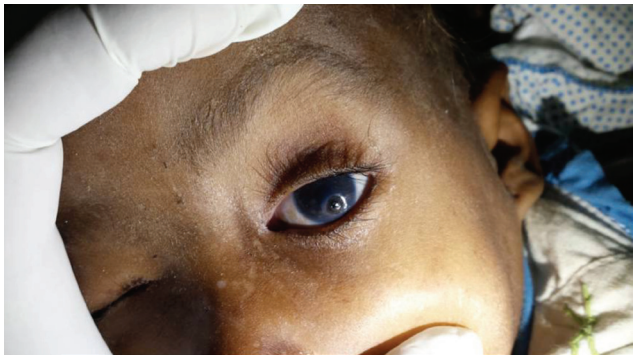

Figure 2 – Case 1. The patient traumatized the left cornea, and this was misinterpreted as vitamin A deficiency

Case 2

A 3-year-old boy, whose parents are first cousins originating from East Sudan, presented with delayed motor development due to malnutrition (marasmus; weight 6 kg) and amputation of his fingers at the level of middle and distal interphalangeal joints of the left hand. This happened due to repeated chewing of his fingers, and cutting them without feeling pain (Figure 3). No significantly high fevers were reported, but the patient felt hot without sweating in hot weather. There is no similar condition in the family. All his investigations, including uric acid level, were normal. Other systems examinations were also normal. He was managed with nutritional support and teeth extraction (Figure 4). He is now thriving, without additional injuries till the moment of writing (4 months of follow up).

Figure 3 – Case 2. Chewing of the fingers resulted in amputation of the left hand fingers.

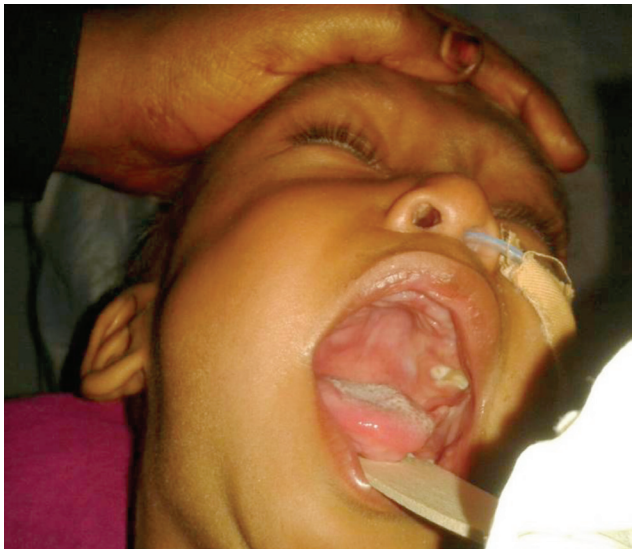

Figure 4 – Case 2. Teeth were removed.

Case 3

An 11-month-old girl, whose parents are non-consanguineous but share the same tribe (indigenous in Eastern Sudan), presented with trauma to the right thumb, by continuously biting it without feeling pain. There were no fevers, but also no significant sweating in hot weather. She was not crying to pin brick or other painful stimuli (Figure 5). All investigations, including uric acid, were normal. Two months later, she came with right leg swelling, associated with hotness without tenderness on pressure (Figure 6). Mother claimed that the baby used to frequently hit the leg against the edge of her bed. X-ray showed no obvious fracture but periosteal reaction along the tibia possibly due to osteomyelitis (Figure 7).

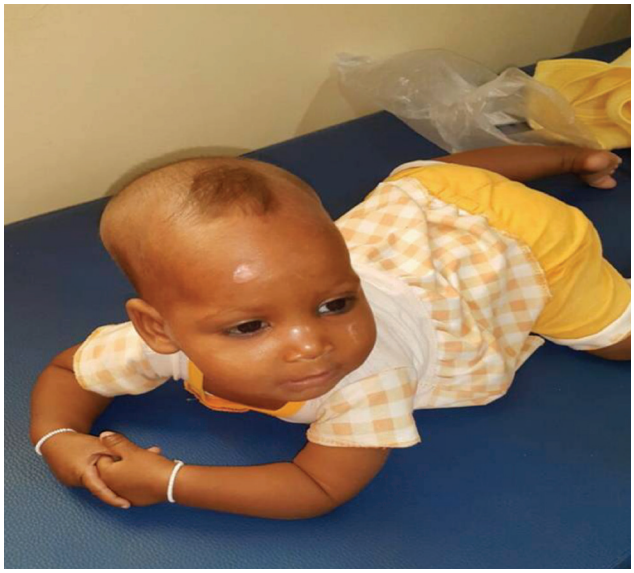

Figure 5 – Case 3. Sequelae of nonpainful repeated trauma to the face and head

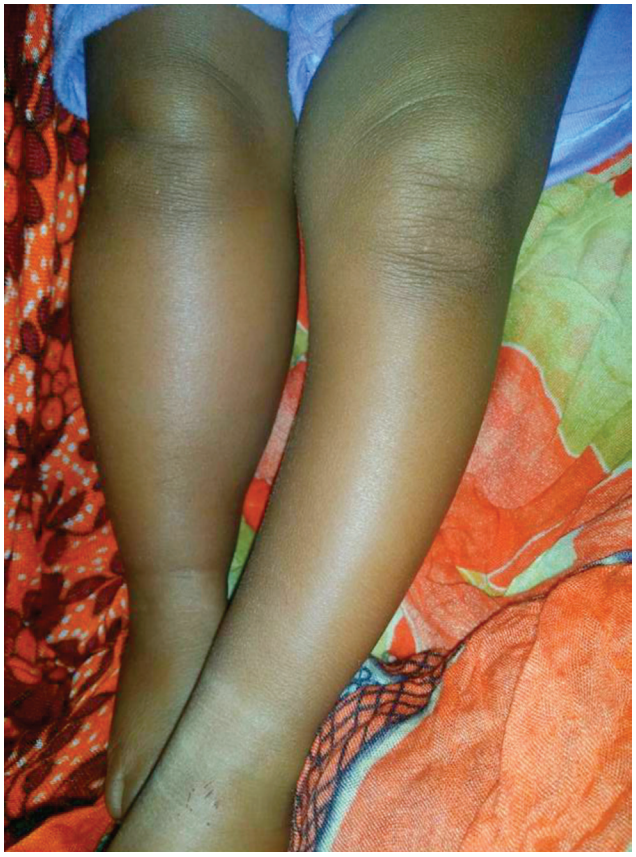

Figure 6 – Case 3. The patient presented with swollen and hot right leg without pain.

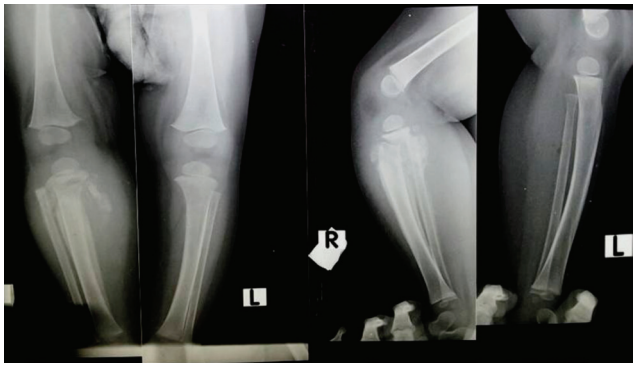

Figure 7 – Case 3. X-ray legs showing periosteal reaction of the right tibia likely following osteomyelitis.

Case 4

A 3.5-year-old boy, who originates from North Sudan, was brought to the hospital on wheel chair by his mother, as he could not walk, or talk. History revealed that he has also frequent febrile episodes, and was never seen sweaty, and never cried to blood sampling punctures. He couldn't talk as well. There was no family history of similar condition, and parents are second-degree cousins. His condition was not previously recognized as CIPA, as he has been living in Saudi Arabia, with continuous air conditioning facility. Examination revealed a small, miserable child with bilateral scarred cornea, dry skin, but no other mutilating injuries at that time. He was mildly hypotonic, with normal reflexes, absent reaction to pin brick and other painful stimulations, but normal other system examination. He had normal hearing, but was clumsy, due to his bilateral corneal scarring. All investigations, including uric acid level were normal. Parents were advised to consider protective measures to avoid injuries, and hot weather.

DISCUSSION

Universally, CIPA is a rare disease, and because of this no one of our cases had been recognized before. But to detect 4 cases in one city, and from different

tribes, means that we have to put this diagnosis in our mind, when dealing with a child who doesn't tolerate hot weather, has self-mutilations, or both. Our patients are both males and females and showed different severity spectrum. The first and the fourth cases (both from Northern Sudan) were severely affected and intellectually impaired, while the second and third ones (from East of Sudan), were moderately affected, with no prominent fevers, but self-mutilations. In Sudan, where the weather is hot most of the year, there are still economically disadvantaged areas without electricity supply. Cases living in these areas suffer twice; the inability to sweat in the hot weather, with the hyperpyrexic episodes, and the poor resources becoming an obstacle that jeopardizes multidisciplinary management, and different treatment modalities.

CONCLUSION

Congenital insensitivity to pain with anhidrosis (CIPA) is present in our community. Paediatricians should be aware of this, and anticipate the disease scenario.

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