Congenital Insensitivity to Pain and Anhidrosis: A Series of Three cases from Eastern India

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ABSTRACT

Congenital insensitivity to pain and anhidrosis (CIPA) is a very rare genetic disorder caused by mutations in the neurotrophic tyrosine receptor kinase 1 (NTRK1) gene in chromosome 1. The affected children present with congenital lack of pain sensation, inability to sweat, episodes of recurrent hyperpyrexia, mental retardation, and self-mutilating behavior. Here we describe three cases of CIPA from a teaching institute in eastern India.

Keywords: Congenital insensitivity to pain, genetic disorder, self mutilation

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INTRODUCTION

Congenital insensitivity to pain and anhidrosis (CIPA) is an autosomal recessive disorder. It presents as a multitude of clinical features including congenital lack of pain sensation, inability to sweat, episodes of recurrent hyperpyrexia, mental retardation, and self-mutilating behavior.[1]The etiology is mutations in the neurotrophic tyrosine receptor kinase 1 (NTRK1) gene in chromosome 1.[2] It is an extremely rare disorder. The incidence of this disorder is about 1 in 25,000 population.[3]Here we report three cases of CIPA from Eastern India.

CASE REPORTS:

CASE 1

A seven-year-old boy was referred to the Plastic Surgery Department for a non-healing wound over his left knee. He was the second child born out of consanguineous marriage. During infancy he did not respond to painful stimuli like vaccinations and suffered from recurrent febrile episodes from which he recovered spontaneously. He also exhibited self-mutilating behavior like biting of his tongue and lips and chewing his fingers and toes. There was no history of similar illness in the family. On examination the child was thin and poorly developed. Part of his tongue and lower lip had been bitten off (Figure 1).

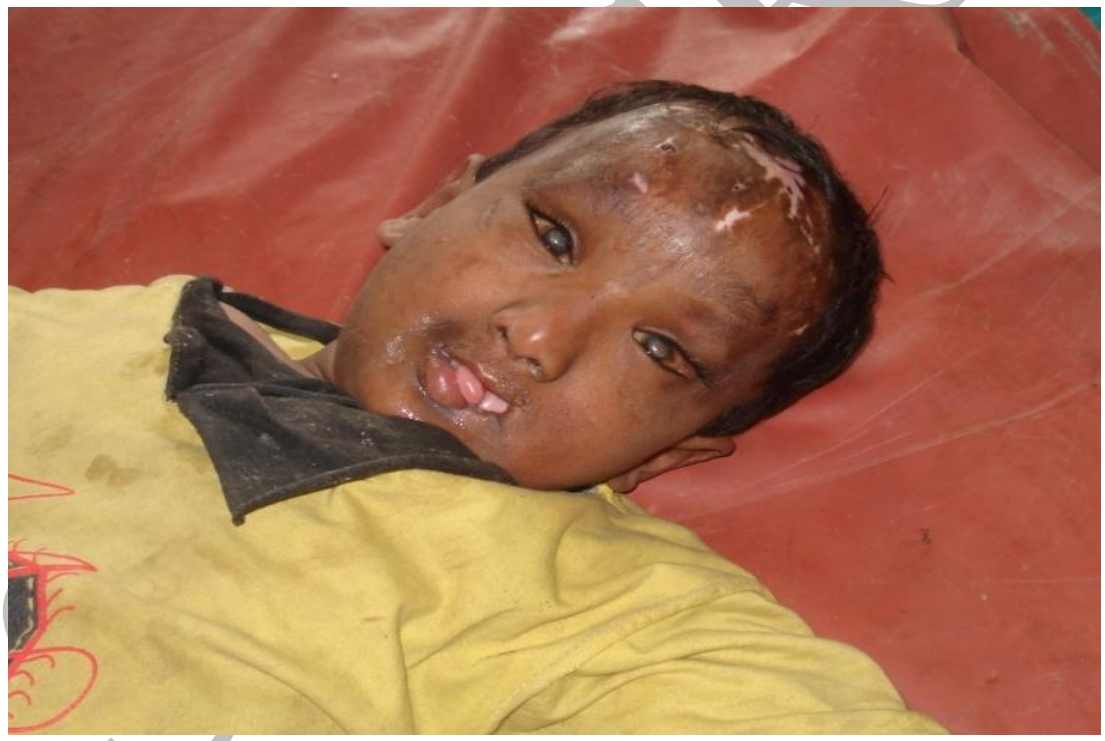

Figure 1: Loss of part of lower lip and old scars on the forehead

There was multiple healed scar over his forehead, both forearms and legs. The tips of all the fingers in his left hand and all the toes of his right foot were missing (Figure 2a,2b). Neurologic

examination revealed intact touch and vibration sensations but loss of pain and temperature. Psychiatric evaluation diagnosed severe mental retardation.

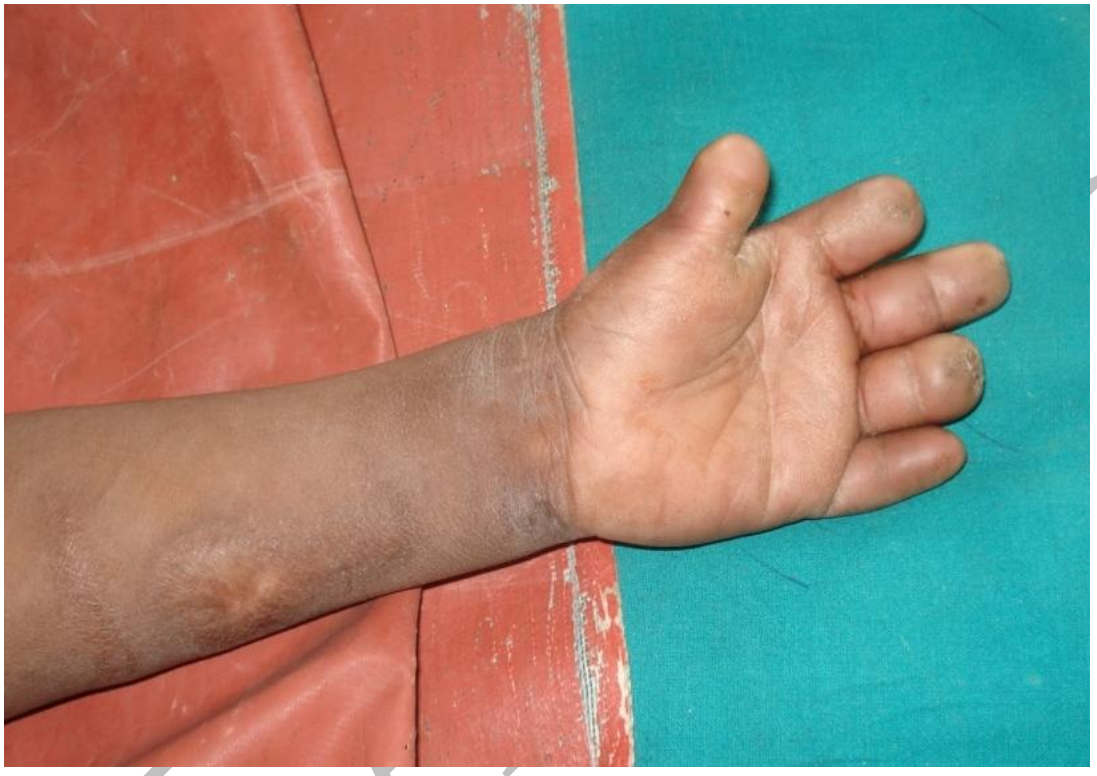

Figure 2a: Loss of tips of fingers of left hand, scars in the forearm

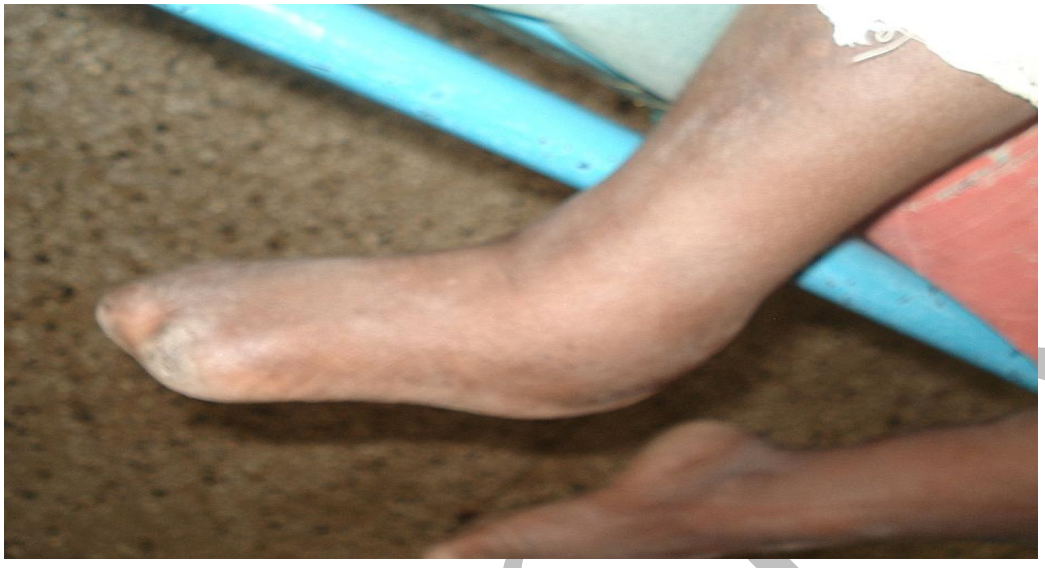

Figure 2b: Loss of all the toes of right foot

Systemic examination was normal. Hematological and biochemical parameters were within normal limits.(Figure 3) On electron microscopy small myelinated and unmyelinated nerve fibres were absent.

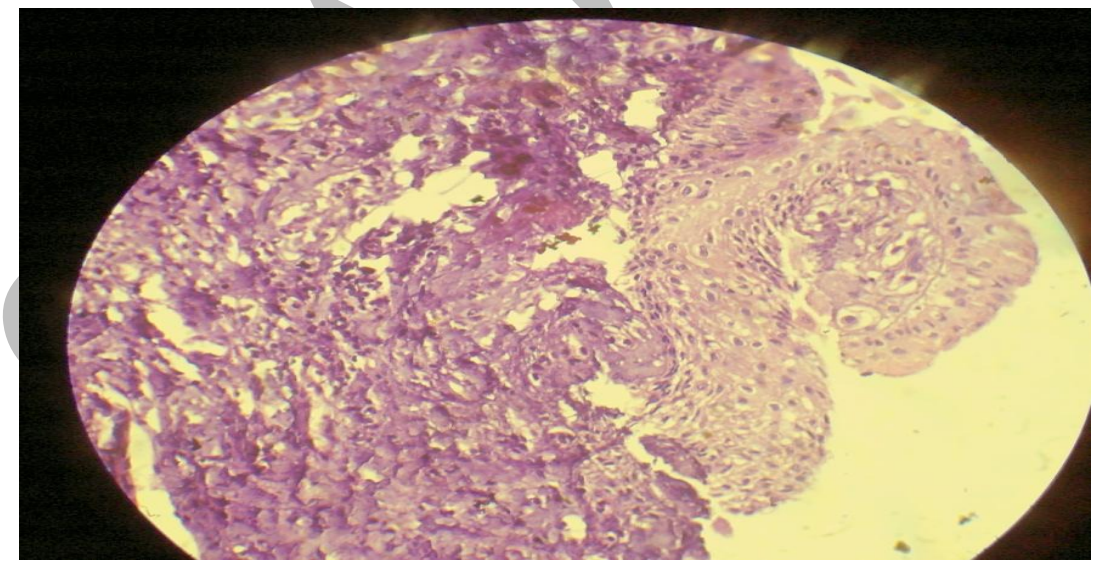

Figure 3: Skin biopsy showing thinned out epidermis with loss of rete ridges, normal dermal adnexae including sweat glands and absence of nerve elements

The diagnosis of CIPA was made based on the above mentioned clinical and histological features.

The wound over his left knee was skin grafted without anaesthesia. The mother was with him during the surgery and the child did not show any discomfort during the procedure. The child is on doing well on follow up and along with his parents is undergoing regular counseling.

CASE 2

The second patient was a 10-year-old boy who was referred to us for the management of heel sores. He was the third child born of consanguineous marriage. The other siblings were normal. He had low birth weight and delayed developmental milestones. He underwent repeated hospitalizations in his childhood because of unexplained fever. He did not feel pain and had developed recurrent heel ulcers and burns over his hands. There was no history of similar illness in the family. On examination, the child had pallor and mild mental retardation. He had a deep sacral pressure sore. There were ulcers in both his soles (Figure 4).

Figure 4: Sole ulcers and deformity in toes

Skin biopsy revealed normal epidermis, dermis and dermal adnexae with loss of small myelinated nerve fibres. The sole ulcers were skin grafted, again without anesthesia and the child was comfortable and cooperative during the procedure. The patient is in regular follow up.

CASE 3

The third patient was a girl 1 year 3 months old. She was also born of consanguineous marriage. She had premature delivery and did not receive scheduled vaccinations. Her febrile episodes started at 3 months of age which did not respond to any medications. The baby was better in the winter but the fever recurred in summer. The mother noticed that she did not sweat. It was also observed that she did not feel any pain when she sustained a burn injury over her forehead at 1 year of age. She exhibited self mutilating behavior like biting her tongue and fingers. On examination she was a thin child with pallor. There were scars over her forehead and both hands. The tip of the tongue had been bitten off.(Figure 5) She underwent a skin biopsy with similar findings as above. The patient was lost to follow up since.

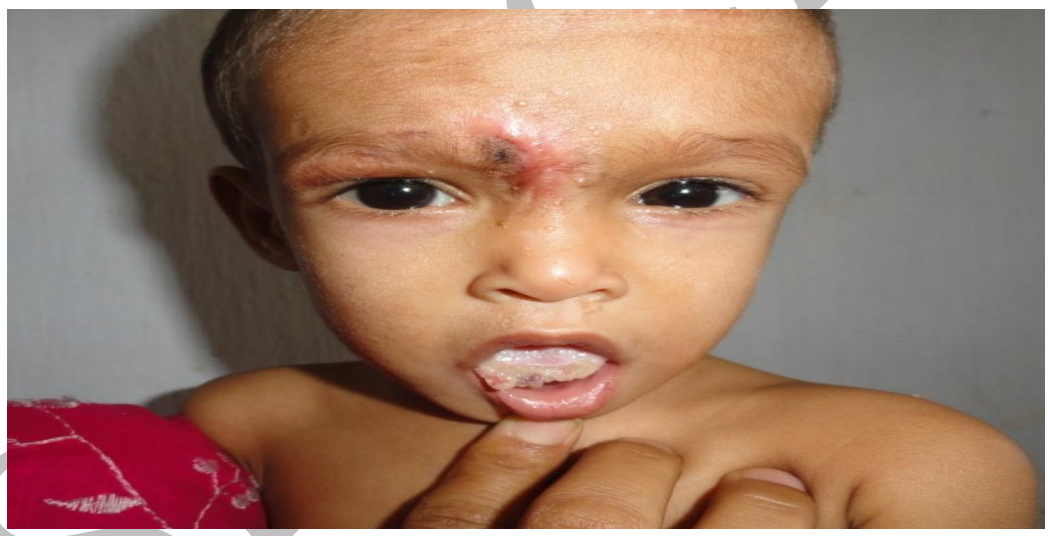

Figure 5: part of tongue bitten off and old scars over forehead

DISCUSSION

Congenital insensitivity to pain is a rare disorder. It was first described in 1932 by Dearborn as Congenital pure analgesia.[4]The term congenital insensitivity to pain and anhydrosis (CIPA) was coined by Swanson in 1963.[1] Individuals with CIPA cannot feel pain. CIPA is extremely

dangerous, and in most cases the patient doesn't live over the age of 25.[5] Although few patients can live an almost normal life, they are in constant risk of cuts, bruises, burns and other injuries which they do not feel. They are also prone to heat strokes and hyperpyrexia because of the absence of sweating.

CIPA is a genetic disorder, caused by in the NTRK1 gene, located on chromosome 1 that encodes the tyrosine kinase receptor for nerve growth factor (NGF).The mutations lead to failure of differentiation and migration of neural crest cells. There is complete absence of small myelinated and unmyelinated nerve fibres due to which pain and temperature sensation is lost. Anhydrosis occurs as the sweat glands are not innervated.[6] CIPA is usually inherited as an autosomal recessive disorder,but sporadic types have also been reported.

CIPA typically manifests in infancy, with anhydrosis, multiple episodes of unexplained fever, insensitivity to pain, mental retardation and self mutilation.[7] Hyperpyrexia secondary to anhydrosis accounts for the death in 20% of these children within the first three years of life.[8] Touch, salivation, and lacrimation are normal. These patients also suffer from recurrent fractures, osteomyelitis, joint dislocations and Charcot joints. These patients invariably have self-inflicted injuries like skin ulcers, burns, bone fractures, auto-amputations of the fingertips, and tongue.[1]

CIPA is also known as Hereditary sensory and autonomic neuropathy (HSAN) type 4. Hereditary sensory and autonomic neuropathy is classified into 5 types. Type 1 is mild, affects only the lower limbs, and manifests in the second decade of life. Type 2 is more severe and involves all the limbs and usually manifests in the infancy or early childhood.

Type 3 is known as familial dysautonomia or Riley-Day syndrome. Its clinical features include decreased pain sensation, hypertension, postural hypotension, recurrent aspiration and disturbed gastropharyngeal motility. Type 4 is CIPA. Type 5 is a relatively benign condition affecting only pain perception.[9]

The differential diagnoses of CIPA are hereditary anhydrotic ectodermal dysplasia, Fabry disease, and Lesch Nyhan syndrome.[10]

Histopathology of skin in CIPA shows normal skin and appendages. On electron microscopy, there is absence of non-myelinated, small -myelinated nerve fibres with normal sweat glands that lack innervation by small-diameter neurons.[11]

There is no definitive treatment of CIPA. Prevention is possible by genetic counseling and avoidance of consanguineous marriages. Supportive care is the only management that can be offered to these unfortunate children. The parents should be taught to avoid excessive heat exposure and seek medical attention in case of any injuries. Regular follow up of the patients is necessary to avoid devastating complications.

CONCLUSION

The three cases presented here had typical features of CIPA and were all born of consanguineous marriages. The cases add to the handful of reports in the world literature and highlights the importance of Identifying this rare genetic disorder.

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