



CASE REPORT

Congenital Insensitivity to Pain with Anhidrosis (CIPA): The First Reported Case in Bangladesh

Mohammed Murad Hossain¹, Md. Abdullah Yusuf²

¹Senior House Officer, Cardiothoracic Surgery, Royal Stoke University Hospital, Stoke-on-Trent, Staffordshire, England; ²Associate Professor, Department of Microbiology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh

Abstract

Congenital insensitivity to pain with anhidrosis (CIPA) is also known as hereditary sensory and autonomic neuropathy type IV. It is an exceedingly rare autosomal recessive disease which occurs due to lack of maturation of small myelinated and unmyelinated fibers of peripheral nerves. These fibers are required for transmission of pain and temperature sensation. This disorder is characterized by insensitivity to pain with intact tactile perception, anhidrosis, self mutilation, recurrent unexplained fever, auto amputation, mental retardation & autonomic nervous system abnormality from infancy. The clinical presentation of a 4-year-old boy with this rare disease is worth to describe, as the first case to be reported in Bangladesh. Rehabilitative treatments for prevention of disease complications and their progress should be given emphasis in every encounter. [*Journal of Current and Advance Medical Research, July 2022;9(2):91-94*]

Keywords: Congenital; insensitivity; pain; anhidrosis; self-mutilation; auto-amputation

Correspondence: Dr. Mohammed Murad Hossain, Senior House Officer, Cardiothoracic Surgery, Royal Stoke University Hospital, Stoke-on-Trent, Staffordshire, England; **Email:** drmuradhossain@outlook.com; mohammed.hossain@uhnm.nhs.uk; **Cell No.:** +8801790438463; **ORCID:** <https://orcid.org/0009-0000-8945-5703>

Cite this article as: Hossain MM, Yusuf MA. Congenital Insensitivity to Pain with Anhidrosis (CIPA): The First Reported Case in Bangladesh. *J Curr Adv Med Res* 2022;9(2):91-94

Conflict of Interest: None

Contributions to authors: Hossain MM involved from patient management; Hossain MM and Yusuf MA both involved in manuscript writing & revision.

Copyright: ©2022. Hossain and Yusuf. Published by Journal of Current and Advance Medical Research. This article is published under the Creative Commons CC BY-NC License (<https://creativecommons.org/licenses/by-nc/4.0/>). This license permits use, distribution and reproduction in any medium, provided the original work is properly cited, and is not used for commercial purposes.

Introduction

Dearborn described a clinical entity named Congenital general pure analgesia¹. Since then many cases have been reported in literature. It was then becoming evident as a syndrome which consists of different clinical manifestations. However, symptomatically clinical pictures were nearly alike in every cases.

Swanson² was the first to describe the clinical syndrome of congenital insensitivity to pain with

anhidrosis. The syndrome of congenital insensitivity to pain was described by Dyck³ as hereditary sensory and autonomic neuropathy (HSAN) with four subtypes (I-IV). He also considered a fifth subtype. Nagasako⁴ wrote a distinctive, detailed and updated review on the five clinical different types of HSAN. He also described their genetic characteristics. HSAN IV is the second most common form of HSAN. This disease occurs as a result of mutation in NTRK1 gene⁵. No case report of HSAN from Bangladesh is available in literature. We report one case of HSAN IV (also

known as congenital insensitivity to pain with anhidrosis). This present case report was to introduce this rarely encountered disease and to present information related to diagnosis, orthopedic manifestations and rehabilitative approach to prevent complications.

Case Presentation

A 4-year-old boy, product of a healthy consanguineous Bangladeshi couple presented with insensitivity to pain from birth with self mutilating behavior and auto-amputation of fingers & toes for last 1½ years. His father stated that the child had no sweating in high ambient temperature. He also complained of recurrent episodes of fever. However, there was no localizing feature. None of his sibling was suffering from similar sort of illness. In addition to that, he gave no history of contact with patients of tuberculosis or leprosy. His motor milestones were delayed but not mentally retarded. On examination, he was found to be mildly pale & febrile. His lower lip was scarred, incisors teeth and tip of the tongue was absent. There was large scar over lateral aspect of left thigh, leg and numerous linear scars over whole of the body. There was blackish, non-tender swelling with discharge over dorsum of the right foot. The entire right great toe and the terminal part of the fingers and others toes were absent. All peripheral pulses were intact. He was conscious, oriented with intact cranial nerves. Muscle was normal in bulk, tone and power. Deep tendon reflexes were normal. There was restricted movement of the left ankle joint. The touch sensation was normal while pain & temperature sensations were absent. However, there was no hypopigmented patch or thickened palpable nerve. Investigations revealed his Haemoglobin below normal (9.5gm/dl), SGPT, Serum Bilirubin, Serum Creatinine, Random blood sugar, Serum Electrolytes and Urine routine examination were within normal limits. X-ray of both leg with tibia and fibula revealed pseudoarthrosis of lower end of tibia-fibula. X-ray of feet showed resorption of distal phalanges of right great toe, left great toe, distal phalanges of 2nd and 3rd toe. CT scan of brain was normal. Nerve Conduction Velocity (NCV) of lower limb was also normal. No lepra bacilli was seen on skin scrapping. Granulation tissue was detected from skin biopsy of right foot. Sural nerve biopsy: Not done. Management of these patients is mainly supportive & aimed at preventing severe & debilitating conditions. Counseling was done with family members about the disease and its complications. Parents were taught how to cope with behavioral problems & educational issues to

control of hyperthermia, prevention of self-mutilation and treatment of orthopaedic problems.

Discussion

Hereditary sensory and autonomic neuropathies (HSAN) are a group of disorders characterized by insensitivity to painful stimuli associated with autonomic dysfunction. Moreover, there is accompanying pathological abnormalities of the peripheral nerves. Five types of HSANs have been identified by Dyck³. However, Nagasako⁴ described these types elaborately. Clinical manifestations, underlying genetic abnormality and involvement of types of neuron are kept in mind while classifying disease^{4,6-8}. HSAN IV is an autosomal recessive disorder characterized by bouts of unexplained pyrexia, anhidrosis, pain insensitivity and various degrees of mental retardation and absence of cry^{4,6-9}.

Episodic fever is thought to be due to anhidrosis which is the earliest manifestation of the disease^{2,9}. The anhidrosis is considered secondary to impaired thoracolumbar sympathetic outflow. It is present on the trunk and upper extremities in 100% of cases, while other areas of the body are affected in variable proportions⁵. More than 37 different mutations in the neurotrophic tyrosine kinase receptor (NTRKA) gene, which encodes for a high-affinity NGF receptor, on chromosome 1q21-22 are described in HSAN IV¹⁰⁻¹². NGF plays a crucial role in pain generation and hyperalgesia during episodes of acute and chronic pain¹³.

The reported case presented with insensitivity to pain from infancy, self mutilation, auto amputation, anhidrosis and episodic fever. His motor milestones were delayed. However, he was not mentally retarded on formal assessment unlike a typical case¹². Numerous scars were evident on different parts of his body. More often patient suffers from osteomyelitis and bone fracture. There was discharging lesion over his dorsum of right foot. X ray yielded pseudoarthrosis over lower tibia and fibula. Losses of certain acral parts were also evident from radiological study.

It is reported that up to 43.0% of death in these patients is due to combined hyperpyrexia and sepsis¹⁵⁻¹⁶. We considered Lesch-Nyhan syndrome, Tourette syndrome, leprosy, Hypohidrotic ectodermal dysplasia and other variants of HSAN as differential diagnoses. CIPA is diagnosed primarily on the basis of clinical features of impaired senses of pain and temperature,

anhidrosis, the presence of disseminated bruises and scars, bone fractures and joint deformities which may lead to amputation, and mental retardation¹⁷⁻¹⁸. Supporting the diagnosis is the frequent history of bouts of fever in early life¹⁹.

Lack of sweating and absence of the axon reflex on skin testing further favors diagnosis. Skin and nerve biopsies are regarded as confirmatory to diagnosis. The pathology of the skin is normal in most cases of CIPA similar to our case. Sometimes nonspecific changes are found in the epidermis that are considered secondary to repeated trauma¹⁹⁻²⁰. Granuloma was the only finding on skin biopsy of our patient. Electron microscopic examination, however, reveals lack of innervation of the eccrine sweat glands with loss of unmyelinated sudomotor fibers²⁰⁻²¹. There is no atrophy of Sweat glands in CIPA²². Nerve biopsies show myelinated nerve fibers are present but unmyelinated fibers are absent²³. Unfortunately, we could not do electron microscopy and nerve biopsy in our case.

CIPA is one of the rarest disease except in Japanese and Israeli-Bedouins. In Japan, the estimated number of this disease was between 130 and 210 in the year of 2009¹⁴. Shatzky et al¹⁷ reported relative prevalence of CIPA in Israeli-Bedouins along with their genetic analysis. Regarding management supportive therapy involving multidisciplinary team like orthopaedic, dental, paediatric and ophthalmology is crucial since there is no specific therapy. Genetic counseling and family education also remains as an important tool in managing these patients.

Conclusion

CIPA is one of the rarest diseases all over the world. However, it is a serious clinical entity. Appropriate management of hyperpyrexia and prevention of complications are the mainstay of providing a prolonged and quality life to them. We predict more advancement in genetic field would be a blessing to establish a definite therapy in near future.

Acknowledgement: Department of Paediatrics, Shaheed Suhrawardy Medical College and Hospital, Sher-e-Bangla Nagar, Dhaka-1207, Bangladesh.

References

- Dearborn G, Van N. A case of congenital general pure analgesia. *J Nerv Ment Dis* 1932;75:612
- Swanson A. Congenital insensitivity to pain with anhidrosis. *Arch Neurol* 1966;8:299-306
- Dyck P, Mellinger J, Reagan J, et al. Not indifference to pain but varieties of hereditary sensory and autonomic neuropathy. *Brain* 1983;106(2):373-90
- Nagasako E, Oaklander A, Dworkin R. Congenital insensitivity to pain: an update. *Pain* 2003; 101: 213-219
- Felicia B Axelrod and Gabrielle Gold-von Simson, Department of Pediatrics, New York University School of Medicine, New York, USA. Hereditary sensory and autonomic neuropathies: types II, III, and IV. *Orphanet Journal of Rare Diseases* 2007;2:39
- Sudqi A. Hamed, Falah Z. Harfoushi, Congenital insensitivity to pain with anhidrosis-CIPA: a case report. *Journal of the royal medical services* 2008; 15(3): 61-66
- Zafeiriou D, Vargiami E, Economou M, et al. Self-mutilation and mental retardation: clues to congenital insensitivity to pain with anhidrosis. *J Pediatr* 2004; 144(2): 200-205
- Alabousi A. Congenital insensitivity to pain with anhidrosis (CIPA). *McMaster Meducator* 2005; 6: 20-21
- Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T, Mitsubuchi H, Tonoki H, Awaya Y, Matsuda I. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet.* 1996;13:485-8
- Prashanth GP, Kamate M. A case of hereditary sensory autonomic neuropathy type IV, *Ann Indian Acad Neurol.* 2012; 15(2): 134-136
- Schwarzkopf R, Pinsk V, Weisel Y, Atar D, Gorzak Y. Clinical and genetic aspects of congenital insensitivity to pain with anhidrosis. *Harefuah.* 2005;144:433-7
- Axelrod FB, Gold-von Simson G, Oddoux C. Hereditary Sensory and Autonomic Neuropathy IV. In: Pagon RA, Bird TC, Dolan CR, Stephens K, editors. *GeneReviews* [NCBI GeneTests Web site] Seattle (WA): 2009. Nov 24
- Kim JS, Woo YJ, Kim GM, Kim CJ, Ma JS, Hwang TJ, Lee MC, Congenital insensitivity to pain with anhidrosis: a case report. *J Korean Med Sci.* 1999; 14(4):460-4
- Haga N, Kubota M, Miwa Z. Epidemiology of hereditary sensory and autonomic neuropathy type IV and V in Japan. *Am J Med Genet A.* 2013;161A:871-4
- Schwarzkopf R, Pinsk V, Weisel Y, Atar D, Gorzak Y. Clinical and genetic aspects of congenital insensitivity to pain with anhidrosis. *Harefuah.* 2005;144:433-7
- Shorer Z, Moses SW, Hershkovitz E, Pinsk V, Levy J. Neurophysiologic studies in congenital insensitivity to pain and anhidrosis. *Pediatr Neurol.* 2001;25:397-400
- Shatzky S, Moses S, Levy J, et al. Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: Genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies. *Am J Med Genet* 2000; 92: 353-360
- Rosemberg S, Nagahashi Marie SK, Kliemann S, (1994) Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV). *Pediatr Neurol* 11:50-56
- Indo, Yasuhiro, Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV: Clinical, biological and molecular aspects of mutations in TRKA(NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor, *Clinical Autonomic Research*,2002;12(suppl. 1): I20-I32
- Rafel E, Alberca R, BautistaJ, Navarrete M, Lazo J. Congenital insensitivity to pain with anhidrosis. *Muscle Nerve* 1980;3:216-220
- Langer J, Goebel HH, Veit S. Eccrine sweat glands are not innervated in hereditary sensory neuropathy type IV. An electron-microscopic study. *Acta Neuropathol Berl* 1981;54:199-202
- Itoh Y, Yagishita S, Nakajima S, Nakano T, Kawada H. Congenital insensitivity to pain with anhidrosis: morphological

and morphometrical studies on the skin and peripheral nerves.
Neuropediatrics 1986;17:103-110
23. Dyck P, Ohta M, Neuronal atrophy and degeneration

predominantly affecting peripheral sensory neurons. In
Peripheral Neuropathy Volume 2. Edited by: Dyck PJ, Thomas
PK, Lambert EH. Philadelphia: WB Saunders; 1975:791.