

Congenital Insensitivity to Pain-A Case Report with Review of Literature

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ABSTRACT

Introduction: Congenital Insensitivity to Pain with Anhidrosis (CIPA) is characterized by insensitivity to pain, anhidrosis and disabled intellect. It is also known as Hereditary Sensory and Autonomic neuropathy type IV (HSAN IV). The ability to sense all pain (including visceral pain) is absent, resulting in repeated injuries including: oral self-mutilation, biting of fingertips, bruising, scarring, infection of the skin and multiple bone fractures. An individual with CIPA is not sensitive to pain and can't differentiate even extreme temperatures.

Case report: A 1 year 6 month old child reported to the department with multiple self mutilated injuries on fingers, lower lip and tongue. CIPA is one of the rare genetic diseases which is often undiagnosed or many of the times misdiagnosed as other forms of sensory and peripheral neuropathies. So a useful discussion about the detection, diagnosis and understanding of pathophysiology will be an informative addition to the literature.

Conclusion: early diagnosis and preventable measures of self mutilation in CIPA patient will enhance the quality of life in affected patient by creating awareness among care givers and society.

Keywords: Insensitivity to the pain, Chromosome, Gene, Neuropathy, HSAN

INTRODUCTION

Congenital insensitivity to pain or congenital indifference to pain is a rare pathological condition in which patients do not respond to painful stimuli.¹ This syndrome was first described by Dearborn (1931) and the terms "insensitivity to pain" and "indifference to pain" were used interchangeably. In 1961 Kunkle suggested that the term "congenital insensitivity to pain" is more appropriate because the person exhibits a failure of afferent nerves to transmit the stimuli to the somesthetic cortex.² Affected individuals are not an entirely homogeneous group because the lack of pain has been related to other pathological conditions (the lack of sweat is among them).²

The process of formation of nerve cells transmitting pain, heat and cold sensation is impaired due to mutations. This is transmitted as an autosomal recessive disorder and prevalence increases in consanguineous marriages.³

Neurotropic Tyrosine Kinase receptor K1 (NTRK1), a receptor for nerve growth factor (NGF) is mutated in CIPA. This protein helps in the outgrowth of axons and dendrites and promotes survival of sensory and sympathetic neurons during embryonic period. The mutation in NTRK1 impairs binding of NGF, thus leading to defective development and function of nociception.³

CASE REPORT

A 1 year 6 month old girl child reported to the department of emergency medicine, Narayana Health Pvt Limited with guardians and complained about self mutilated injuries over

legs, hand, lip and tongue, self removal of upper anterior teeth and insensitive to hot or cold temperatures and blunt or sharp injuries. On history of presenting illness guardians revealed that the child has bitten her finger, tongue and lip, removed her teeth by herself, was not crying after fall or injuries, child was not sweating. The child was born normal without any complication during pregnancy and parturition, drug and family history was insignificant, child has two siblings' one elder sister and brother who are apparently normal.

On general physical examination child was moderately built and nourished, well oriented to time and place, responding to the commands. No history of fever, fracture and seizure. On clinical examination self mutilated injury on left and right legs [Fig 1], hands, middle finger of left hand was partially amputated [Fig 2]. On examination of oral cavity, the tip of the tongue was bitten and self amputated, multiple erosions on lip and left corner of the mouth [Fig 3]. There was missing upper and lower anterior teeth [Fig 3]. All vital signs and parameters appear to be normal. Base line investigations like complete blood picture, electromyography, electroencephalogram showed no positive findings. Specialized investigations to rule out intracranial tumors and pathology Magnetic Resonance Imaging with angiography was performed by radiologist there was no positive findings were found.

Further genetic evaluation revealed genetic mutation is in the gene encoding the neurotrophic tyrosine kinase receptor (NTRK1 gene).

Multidisciplinary approach is required to treat such patient by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology. Treated with intravenous antibiotics to reduce infections, genetic counseling for the parents, hand and foot guards to reduce injury and referred to dentist for the oral guard, ophthalmologist to evaluate eyes.

DISCUSSION

Hereditary sensory and autonomic neuropathy (HSAN) is a rare syndrome characterized by congenital insensitivity to pain and temperature changes and by autonomic nerve formation disorder, as described by Dua.⁴ HSAN has four types. HSAN type IV exhibits defective maturation of peripheral nerves (both

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myelinated and unmyelinated) which carry pain and temperature sensation and inherited as autosomal recessive disorder.^{4,5} This type IV is also called CIPA. CIPA, which was first described in 1951, results from a defect in neural crest differentiation and the system responsible for pain and temperature sensation, the

first order afferent system.⁷ Electron microscopic study reveals loss of myelinated and unmyelinated nerves and absence of innervations to sweat glands.⁵

Greco et al, described that, the defective differentiation and migration of neuronal crest elements and degradation of NGF/NTRK1 pathway may be responsible for CIPA.⁵

Though CIPA is a very rare disorder, more than 300 cases have been reported from Japan, with about 60 cases reported from the United States of America.⁶ The manifestations of CIPA are usually seen during childhood as repeated trauma and self mutilation which are unnoticed. But progressive structural deformities due to loss of bony and soft tissues of extremities, orbits, nasal and oral cavities may be the usual symptoms where parents seek medical advise and treatment.⁶

Seyon et al.⁷ have called CIPA, the mystery of broken bones after the case of a 15-years-old boy who was wrongly labeled as a case of osteogenesis imperfecta due to recurring fractures since the age of 4.⁷

Dental and oral cavity complications, including tooth loss (auto-extraction), bitten tongue, ulceration and lip injury are also common.⁸ Use of mouth guard and early tooth extraction are described to prevent these complications. Skin complications due to anhidrosis⁸ and ocular complications due to painless injuries⁸ are not uncommon. Overheating has in fact been described in the literature to kill more than half of the number of children by CIPA before the age of 3.⁸

CIPA usually presents with the following clinical features: 1) Traumatic injuries including bruising, bone fractures and painless joint dislocations often associated with neurogenic arthropathy (Charcot joint) of the knees and ankles. There may be a history of failure to recognize burns and other injuries. 2) Infants present with recurrent episodes of febrile illness due to absence of sweating (Anhidrosis) 3) Intellectual disability.^{8,9}

Neurologic examination supports the diagnosis: 1) Insensitivity to superficial and deep painful stimuli is confirmed when painful stimuli fail to evoke either withdrawal or emotional change [Swanson 1963]. For example, no tenderness or pain sensation is elicited even when apparently injured joints or broken bones are moved passively or actively. 2) Impaired temperature perception is confirmed when: 3) Consistent errors are made in distinguishing between hot and cold moist substances. 4) Extreme cold or heat fails to elicit the usual withdrawal response. 5) Visceral pain perception is also impaired. 6) Impairment of the autonomic nervous system may be evident by the presence of Horner syndrome and the cold pressure test. Normal findings are: 1) Touch, vibration and position senses 2) Motor functions (unless repeated trauma has caused secondary dysfunction



Figure-1: Patient profile photo showing normal stature and superficial injuries on right and left legs



Figure-2: Self mutilated injuries on right and left hand with left middle finger tip amputated



Figure-3: Shows mutilated anterior part of tongue,ulceration on tongue, lip, corner of the mouth.

Classification	HSAN type	Chromosomal alleles	Mutations	Hereditary inheritance
Hereditary sensory radicular neuropathy	I	9q22.1-22.3	SPTLC1	AD
Congenital sensory neuropathy	II	12p13.33	HSN2 (?)	AR
Familial dysautonomia/Riley Day syndrome	III	9q31	IKBKAP	AR
Congenital insensitivity to pain with anhidrosis (CIPA)	IV	1q21-22	NTRK1(TRKA)	AR
Congenital insensitivity to pain with partial anhidrosis	V	NK	NTRK1	NK
Congenitalautonomic dysfunction with universal pain loss (CAD)		NK		NK
Progressive panneuropathy		NK		NK

NK: Not Known, AR: Autosomal Recessive, AD: Autosomal Dominant

Table-1: Genetics of Hereditary Sensory and Autonomic Neuropathies (HSAN)¹⁰

of motor neurons or limbs). Additional tests supporting the diagnosis of CIPA: 1) Skin tests demonstrating abnormalities in sweating and the lack of the axon reflex.^{8,9}

Management of such patients needs a multidisciplinary approach. A detailed general physical examination is required to note self-mutilation of tongue, lips and buccal mucosa. Detailed orthopedic evaluation for bony injuries with poorly healing fractures and dislocations with radiographs is essential. Neurological assessment for behavioral and developmental dysfunction is advised. Comprehensive dental examination to assess auto-extraction of teeth, dental caries and abscesses may improve oral health. Ophthalmologist consultation for neuropathic keratitis may help the patient. Detailed genetic evaluation and counseling of the parents for further prevention is of paramount importance.¹⁰

The present case amply highlights many of the complications of CIPA.

CONCLUSION

Early diagnosis based on the clinical features, differentiating it with other sensory neuropathies and definitive genetic testing is of paramount importance. Parent education and preventable measures of self-mutilation and injuries are essential. The quality of life in affected patient can be improved by creating awareness among care givers and society.

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