

# Newborn with Hereditary Sensory and Autonomic Neuropathy Type- IV: A Case Report

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## Abstract:

*Hereditary sensory and autonomic neuropathy type IV (HSAN-IV) is a very rare autosomal recessive disorder characterized by anhidrosis, recurrent fever, insensitivity to pain and temperature, hypotonia, and developmental delay. The most frequent complications of this disease are self-mutilation, febrile seizure, stroke, corneal scarring, multiple fractures, burn, osteomyelitis and joint deformities. There is no definitive treatment for this condition. Early diagnosis can reduce disease complications and number of cases.*

**Keywords:** Hereditary Sensory and Autonomic Neuropathy (HSAN), Hypotonia, anhidrosis, recurrent fever.

## Introduction:

Hereditary sensory and autonomic neuropathy syndrome (HSAN) is a rare genetic disorder and was classified by Dyck and Ohta, are of five types: Sensory radicular neuropathy (HSAN type 1), congenital sensory neuropathy (HSAN type II), Familial dysautonomia or Riley Day syndrome (HSAN III), congenital insensitivity to pain with anhidrosis (CIPA)/ (HSAN IV) and congenital insensitivity to pain (HSAN-V).<sup>1</sup> Congenital insensitivity to pain with anhidrosis (HSAN IV) was first reported by Nishida in 1951.<sup>2</sup>

## Case report:

A 15 - day- old female newborn, of a non consanguineous parent attended for checkup following hospital release. She was delivered prematurely by lower uterine caesarean section at thirty-six week of gestation with birth weight 2.9 Kg due to premature labour pain of mother. The baby was admitted into a hospital for six days due to meconium stain with respiratory distress and treated accordingly. Her prenatal history was uneventful. There was no history of neuromuscular disease or pain insensitivity in the family. The baby was floppy and deep tendon reflexes were absent otherwise she was normal. Thyroid function test was normal. During second visit at the age of four month the mother complained that the baby developed repeated attack of fever during hot weather. The mother reported that her baby never cried during vaccination. Mother also noticed that her baby never sweats. There was no hair or nail abnormality. Relevant investigations were done to rule out infections. There was no evidence of infection. So from history, clinical features and

investigations the baby was provisionally diagnosed as a suspected case of HSAN-IV and counseling was done properly. The patient was on follow up. Floppiness improved and deep tendon reflexes were gradually elicitable in the subsequent visit as the child grown up. There was no cranial neuropathy. At 5<sup>th</sup> month the baby gained neck control. There was developmental delay. She had motor delay as evidenced by sitting with support at the age of 9 month and able to walk independently at the age of twenty one month. Tooth eruption started at 9 month, self mutilation started at one year of age in the form of tongue and finger biting. She also has history of burning of fingers by holding fired mosquito coil. Regarding speech –uttered meaningful word at the age of eighteen month and tearing was normal. Regarding sensory function her pain and temperature sensations were impaired evidenced by self mutilation and burn injury. Her mental function was subnormal than peer group. She is now three year old. Diagnostic skin biopsy was done at the age of 11 month, which revealed hyperkeratosis with increased pigmentation of basal layer, dermis revealed apocrine & eccrine glands but they were decreased in number, hair follicles were found distorted, dermis showed increased collagenation with increased thick nerve fibres. At the age of sixteen month further investigations were done. CBC with PBF, S. ammonia, lactate, thyroid function test, liver function tests, kidney function test, serum calcium, phosphate, glucose, HbA1C, Vit B12, folic acid, uric acid, Vit D3 level all were within normal limit. Nerve conduction study reveals-normal distal latencies, compound muscle action potentials (CMAPs), sensory nerve action potentials (SNAPs) amplitude, conduction velocities and F-wave latencies study, Electromyography(EMG) revealed normal study. Molecular genetic study revealed mutations in NTRK1 gene. (Table-II)

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**Table-I**  
*Features of various HSAN.*<sup>3-5</sup>

Features	HSAN 1	HSAN2	HSAN3	HSAN4	HSAN5
Inheritance	AD	AR	AR	AR	AR
Age of onset	Second decade	Infancy	Birth	Birth	Birth
Insensitivity to pain	++	++	+	++	+
Sweating	Normal	Normal	Decreased	Decreased (widespread)	Normal
Ophthalmic manifestation	Not reported	Slow blink reflex	Alacrima and corneal anaesthesia	Corneal anaesthesia	Corneal anaesthesia
Mental retardation	-	-	-/+	++	-/+
Muscle hypotonia	Absent	Absent	+	-/+	Absent
Biopsy	Loss of UF> MF	Absent MF	Reduced UF	Absent UF	Absent/small MF
Genes	SPTLC1, SPTLC2, ALT1, DNMT1	WNK1, RETREG1	IKBKAP	NTRK1,	PRDM12 6 NGF B, NTRK1

Notes: UF – Unmyelinated fibres, MF – Myelinated fibres, AR – Autosomal recessive, AD – Autosomal Dominant

**Table-II**  
*Results of genetic study*

Gene (Transcript)	Location	Variant	Zygoty	Disease(OMIM)	Inheritance	Classification
NTRK1(+)	Intron 7	c.850+2T>c (5' Splice site)	Heterozygous	Congenital insensitivity to pain with anhidrosis	Autosomal recessive	Likely pathogenic
	Intron7	c.851 2A>G (3' Splice site)	Heterozygous			



**Fig.-1: Self mutilation (finger biting)**



**Fig.-2:** Cut injury at scalp



**Fig.3:** Old bruise mark & old scar of different injury

### Discussion:

HSAN are a group of inherited peripheral neuropathies primarily affecting the peripheral sensory and autonomic neurons. Sensory neuropathy leads to chronic ulcers of hands and feet, corneal ulcers and arthropathy. Autonomic dysfunction leads to manifestations like anhidrosis and fever.<sup>6, 7</sup> Features of HSAN-IV begin in infancy. Affected children also cannot feel temperature and cannot distinguish between hot and cold. Because of the loss of sensation, they may be unaware of injury and may develop chronic skin erosions, ulcers or blisters that are slow to heal. Children with HSAN-IV may show developmental delay and learning disabilities. Diminished muscle tone may be present at birth or during infancy. Although hypotonia is common at birth, strength and tone gradually normalize with age. Eye abnormalities may develop, specifically neurotrophic keratitis, a condition characterized by damage to the corneas of the eyes. Some individual experience postural hypotension.<sup>8</sup>

HSAN-IV is an autosomal recessive disorder and is caused by a mutation in the neurotrophic tyrosine kinase receptor type I (NTRK1) gene. Mutations in the NTRK1 gene result in faulty or deficient neurotrophic tyrosine receptor type 1, which prevents the binding of nerve growth factor and, consequently, the transmission of nerve signals. Ultimately, the affected neurons die prematurely, resulting in loss of pain and temperature sensation. The normally formed sweat glands lack the nerve supply; leading to anhidrosis.<sup>9</sup> HSAN-IV affects males and females in equal numbers. The exact incidence and prevalence is unknown. 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.<sup>10</sup>

The differential diagnoses for CIPA include other HSANs (table 1), hypohidrotic ectodermal dysplasia, Lesch-Nyhan syndrome and Hansen's disease. The battered baby syndrome and osteogenesis imperfecta should also be considered in clinical differentials and needs to be ruled out. The diagnosis of HSAN-Type IV is based upon identification of characteristic symptoms, a detailed patient history, thorough clinical evaluation and variety of specialized tests. Sweating in response to pilocarpine test is minimal or absent. Skin biopsy may reveal a lack of functioning nerves supplying the sweat gland. Sural nerve biopsy may reveal characteristic findings including reduced numbers of myelinated and unmyelinated small-diameter fibers with normal numbers of large-diameter fibers. Molecular genetic testing can confirm a diagnosis, because of the large number of mutations that have been identified in HSAN IV.<sup>11</sup>

Management of such patients needs a multidisciplinary approach. Pediatricians, dermatologists, neurologists, dental specialists, orthopedists, ophthalmologists, and other healthcare professionals may need to systematically and comprehensively plan for an affected child's treatment. Psychosocial support for the entire family is essential as well. Genetic counseling is of benefit for affected individuals and their families. Treatment of HSAN IV is directed toward the specific symptoms. Affected individual may be treated with acetaminophen or ibuprofen when fever is present. Direct cooling in a bath or with a blanket designed to lower body temperature (cooling blanket)

may also be used. Various orthopedic measures may be necessary to treat abnormalities affecting the bones and joints. Various dental procedures may be used to treat individuals. Treatment of neurotrophic keratitis can include tarsorrhaphy, keratoplasty, scleral corneal graft, and scleral bandage lens. Behavioral issues tend to improve with age. Detailed genetic evaluation and counseling of the parents for further prevention is of paramount importance.<sup>12</sup>

The diagnosis of HSAN IV or CIPA requires three clinical criteria: anhidrosis, decreased pain and temperature perception and mental retardation.<sup>13</sup> However, there is wide variability in intellectual performance in these children, and mental retardation does not occur in all patients.<sup>14</sup> Furthermore, low deep tendon reflexes as in my case, are common in patients with HSAN -IV.<sup>15</sup>

As the child had insensitivity to pain and temperature with anhidrosis and recurrent episodes of fever the diagnosis of hereditary sensory and autonomic neuropathy type IV was made. The child has no consanguineous parent though it is a recessive disorder. The child has delayed Development. Another case report also revealed delayed development.<sup>16</sup> Beena Suresh et al. reported a case where there was no developmental delay with repeated corneal ulcer.<sup>17</sup> In this baby no corneal lesion was found, it may be due to alertness of the parents. Fever is a common presentation of HSAN-IV but Muralidhara et al. reported a case presented mainly with self mutilation.<sup>18</sup> Barzegar et al. reported a case presented with stroke along with other usual manifestations.<sup>19</sup> Van Den Bosch et al. reported a case misinterpreted as inflicted burns- child abuse.<sup>20</sup> Tilak KM et al. reported a case presented with chronic lower limb ulceration with global developmental delay.<sup>21</sup> Mukhtiar K et al. reported two cases presented with aggressive behavior with delayed development and repeated attack of fever.<sup>22</sup> Sriram P et al. reported two cases presented with hyperpyrexia with seizure, pain insensitivity and self mutilation.<sup>23</sup> Kim W et al. reported a case presented with repeated attack of fracture which was difficult to treat.<sup>24</sup> Our reported case also developed injury to finger. At that time surgical drainage as well as orthopedic consultation was done. Long time antibiotic treatment was given and the wound healed ultimately after one and half month later. High index of suspicion is required for early detection of cases. Early diagnosis, proper counseling, control of environmental temperature, moreover awareness and alertness can reduce disease consequences.

### Conclusion:

The HSAN-type IV is a congenital disease and there is no specific treatment for it so early diagnosis is important to prevent severe life threatening injuries. Proper genetic counseling can reduce the number of cases and in such way we can reduce family as well as social burden. Health care providers should be aware of presence of such type of illness. Prenatal diagnosis of this disease is possible by genetic study specially if there is positive family history.

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