

Hereditary sensory and autonomic neuropathy type IV

Author: Doctor Ennio Toscano M.D. Ph.D.¹

Creation date: December 2003

Scientific Editor: Doctor Enrico Bertini

¹Department of Pediatrics, University Federico II, Via Pansini, 5, 80131 Naples, ITALY.
toscaneo@yahoo.com

[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Definition/diagnostic criteria](#)

[Differential diagnosis](#)

[Molecular pathogenesis](#)

[Clinical description](#)

[Diagnostic methods](#)

[Epidemiology](#)

[Genetic counseling](#)

[Prenatal diagnosis](#)

[Management](#)

[References](#)

Abstract

Hereditary sensory and autonomic neuropathy type IV (HSAN IV) is a rare autosomal recessive disorder characterized by episodes of fever, anhidrosis, insensitivity to pain, self-mutilating behaviour and mental retardation. Absence of reaction to painful stimuli and anhidrosis are due to the absence of afferent neurons activated by tissue-damaging stimuli and a loss of innervation of sweat glands, respectively. Nerve growth factor (NGF) supports the survival of nociceptive sensory and autonomic sympathetic neurons as well as cholinergic neurons of basal forebrain. The human NTRK1 gene encodes a receptor tyrosine kinase (RTK), which is autophosphorylated in response to NGF, thus activating various pathways of intracellular signal transduction. NTRK1 mutations cause defects in NGF signalling, leading to death of various NGF-dependent neurons. The diagnosis of HSAN IV is based on clinical features, pharmacological test and neuropathological findings. Screening for NTRK1 mutations represents the ultimate step of diagnosis. No specific therapy is available for HSAN IV. Recurrent traumatic complications, as well as severe episodes of fever, require frequent medical treatments. Close observance of children with HSAN IV is necessary to prevent self-injury and fractures. Fractures must be suspected whenever bruising or swelling are found, mostly close to metaphyses of long bones. Proper and rapid immobilization is mandatory.

Keywords

Hereditary sensory and autonomic neuropathy type IV, HSAN IV, tyrosine kinase receptor, RTK, congenital insensitivity to pain with anhidrosis, CIPA, NTRK1, TRKA, nerve growth factor, NGF

Disease name and synonyms

All the following disease names refer to a single disorder, hereditary sensory and autonomic neuropathy type IV (HSAN IV):

-congenital insensitivity to pain with anhidrosis (CIPA; MIM#256800);

-familial dysautonomia type II ;

-congenital sensory neuropathy with anhidrosis.

HSAN IV will be the only term used in this review. HSAN IV was first described by Swanson (1963) in two brothers affected by defect of temperature sensation and insensitivity to pain.

Definition/diagnostic criteria

HSAN IV is an autosomal recessive disorder characterized by a lack of pain sensation.

The diagnosis is commonly based on *clinical* and *neuropathological* findings and on the *histamine* test. Recently, *molecular analysis of NTRK1 (TRKA)*, the gene mutated in this disease, has been available.

Clinical findings

Constant features (100%): anhidrosis (inability to sweat), episodes of unexplained fever, severe mental retardation, insensitivity to pain, self-mutilating behaviour.

Frequent features: multiple fractures with slow healing, joint dislocations and deformities (Charcot joints), skin infections, bruises, corneal ulcerations, aggressive behaviour.

Rare features: impaired immune response, proteinuria, renal failure, anemia, hyperkeratosis, dry skin, early primary tooth loss.

Neuropathological findings

Absence of unmyelinated axons, decrease in the number of small myelinated axons and normal distribution of large myelinated axons. Sweat glands have a normal structure but are not innervated.

Pharmacological test

Intradermal injection of 1:10000 histamine fails to show the axon flare.

Electrophysiological studies

Motor and sensory nerve conduction are normal.

Molecular studies

Mutations in the *NTRK1* gene (MIM#191315) have been reported in some 80 cases with HSAN IV.

Differential diagnosis

Hereditary sensory and autonomic neuropathies (HSAN) belong to a group of rare inherited disorders. Dyck (1993) classified HSAN in 5 different types:

1. sensory radicular neuropathy (type 1)
2. congenital sensory neuropathy (type II)
3. familial dysautonomia or Riley-Day syndrome (type III)
4. congenital insensitivity to pain with anhidrosis (type IV)
5. congenital insensitivity to pain (type V)

Table 1 (modified by Dyck, 1994) highlights the diagnostic criteria of HSAN, taking into account the following features: natural history of the disease, mode of inheritance, neuropathological alterations and molecular aspects.

HSANIV and V share some clinical findings, although the involvement of the central nervous system and of the autonomic sudomotor system are present in HSAN IV only. HSAN IV is well defined at clinical, morphological, and molecular levels, whereas HSAN V is far less defined and might represent a heterogeneous group of entities (Toscano *et al.*, 2002).

Table 1. Hereditary sensory and autonomic neuropathies. Modified by Dyck (1994)

HSAN	Onset	Inheritance	Neurons (axons)			Sudomotor	Loci	Gene
			A α	A δ	C			
Type 1	>2 decades	AD	+	++	++	LS	9q22	<i>SPTLC1</i>
Type 2	Co	AR	++	++	+	G	unknown	unknown
Type 3	Co	AR	++	++	++	G	9q31	<i>IKBKAP</i>
Type 4	Co	AR	N	+	+	G	1q21	<i>NTRK1</i>
Type 5	Co	AR	N	N/+	N/+	G	unknown	unknown

Co: congenital; AD: autosomal dominant; AR: autosomal recessive; N: normal; +: affected; ++: severely affected; G: generalized; LS lumbosacral.

Molecular pathogenesis

HSAN IV is caused by mutations of the neurotrophic tyrosine receptor kinase 1 gene (*NTRK1*). The human *NTRK1* gene, located on chromosome 1 (1q21-q22), encodes a receptor tyrosine kinase (RTK) for the nerve growth factor (NGF, see MIM#162030) (Indo *et al.*, 1996). NGF induces neurite outgrowth and promotes survival of embryonic sensory and sympathetic

neurons (Levi-Montalcini, 1987). The binding of NGF to RTK stimulates homodimer formation and activation of tyrosine kinase activity, resulting in the recruitment of a series of signalling proteins to docking sites on the receptor (Barbacid, 1995; Bothwell, 1995). Studies of gene-targeting mutant mice demonstrated an important role for NGF and its specific receptor, RTK, in maturation and

functioning of nociceptive sensory and sympathetic neurons (Crowley *et al.*, 1994; Smeyne *et al.*, 1994). Using a candidate gene strategy, the genetic basis for HSAN IV was identified when *NTRK1* loss-of-function mutations were found in patients (Indo *et al.*, 1996). These studies demonstrated the crucial role of NGF-RTK system in the development and functioning of nociceptive reception as well as in the establishment of thermoregulation via sweating (Indo, 2001a). NGF, in addition to its neurotrophic functions, acts also as an immunomodulator mediating "cross talk" between nervous, immune and endocrine systems. This role is supported by the expression of functional RTK receptor at the surface of cells belonging to these three systems (Levi-Montalcini *et al.*, 1996). Some studies demonstrated a role of NGF/RTK system in the regulation of bone formation in rat and mouse (Yada *et al.*, 1994; Grills and Schuijers, 1998; Asaumi *et al.*, 2000). In this respect, bone involvement observed in HSAN IV might be also related to an impairment of skeletal cell metabolism (Toscano *et al.*, 2000; Toscano *et al.*, 2001).

Clinical description

Association of anhidrosis, absence of reaction to noxious stimuli, and mental retardation is the cardinal clinical presentation of HSAN IV. Other clinical features include frequent bouts of fever, caused by anhidrosis, poor wound healing, limb and tongue amputation, recurrent infections, osteomyelitis, Charcot joints, pelvic dysplasia, corneal ulceration and opacity, neuroparalytic keratitis, and abnormal sympathetic skin response (Swanson, 1963; Swanson *et al.*, 1965; Dyck, 1984; Biedner *et al.*, 1990; Rosenberg *et al.*, 1994; Yagev *et al.*, 1999; Shatzky *et al.*, 2000; Indo, 2001a). A broader multisystem involvement was described in two patients and included: recurrent bone fractures with slow healing, immune system abnormalities and chronic inflammatory state ending in systemic amyloidosis, (Toscano *et al.*, 2000). An infant with primary tooth loss and palmar hyperkeratosis was recently described (Bonkowsky *et al.*, 2003). Life expectancy is shorter due to the high morbidity associated with HSAN IV.

Diagnostic methods

So far, the diagnosis of HSAN IV has been commonly based on clinical features, pharmacological test and neuropathological findings (see **Definition/diagnostic criteria**). Screening for *NTRK1* mutations represents the ultimate step of HSAN IV diagnosis. As a matter of fact, a substantial number of *NTRK1*

mutations has been reported in HSAN IV patients from various countries (Greco *et al.*, 1999; Mardy *et al.*, 1999; Yotsumoto *et al.*, 1999; Miura *et al.*, 2000; Shatzky *et al.*, 2000; Bodzioch *et al.*, 2001, Mardy *et al.*, 2001; Indo, 2001a; Indo *et al.*, 2001b).

Epidemiology

HSAN IV is a rare inherited disorder described in several ethnic groups (Greco *et al.*, 1999; Mardy *et al.*, 1999; Yotsumoto *et al.*, 1999; Miura, 2000; Shatzky, 2000; Bodzioch *et al.*, 2001, Mardy *et al.*, 2001; Indo, 2001a; Indo *et al.*, 2001b). The frequency of the disease is still unknown.

Genetic counseling

HSAN IV is inherited as an autosomal recessive condition. Consanguinity is often observed.

Prenatal diagnosis

Identification of *NTRK1* mutations is the only tool for prenatal diagnosis (Shatzky *et al.*, 2000).

Management

No specific therapy is available for HSAN IV. Recurrent traumatic complications, as well as severe episodes of fever, require frequent medical treatments. Rosenberg *et al.* (1994) estimated that 20% of children with HSAN IV die from hyperthermia in the first 3 years of life. Sepsis may account for 23% of deaths as reported in a series of HSAN IV patients (Shorer *et al.*, 2001). Close control of children with HSAN IV is necessary to prevent self-injury and fractures. The insensitivity to pain leads to an overuse of bones and joints thus resulting in fractures, dislocations, and Charcot joints. Fractures must be suspected whenever bruising or swelling are found, mostly close to metaphyses of long bones. Proper and rapid immobilization is mandatory (Theodorou *et al.*, 2000).

References

- Asaumi K**, Nakanishi T, Asahara H, Inoue H, Takigawa M. Expression of neurotrophins and their receptors (Trk) during fracture healing. *Bone* 2000;26:625-633.
- Barbacid M**. Structural and functional properties of the TRK family of neurotrophic receptors. *Ann NY Acad Sci* 1995;766:442-458.
- Biedner B**, Dagan M, Gedalia A, David R. Congenital insensitivity to pain with neuroparalytic keratitis. *Ann Ophtalmol* 1990;22:312-313.
- Bodzioch M**, Lapicka K, Aslanidis C, Kacinski M, Schmitz G. Two novel mutant alleles of the gene encoding neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) in a patient with congenital insensitivity to pain with anhidrosis: a

splice mutation in intron 5 and cluster of four mutations in exon 15. *Hum Mutat* 2001;17:72.

Bonkowsky JL, Johnson J, Carey JC, Gordon Smith A, Swoboda KJ. An infant with primary tooth loss and palmar hyperkeratosis: a novel mutation in the NTRK1 gene causing congenital insensitivity to pain with anhidrosis. *Pediatrics* 2003;112:237-241.

Bothwell M. Functional interactions of neurotrophins and neurotrophin receptors. *Ann Rev Neurosci* 1995;18:223-253.

Crowley C, Spencer SD, Nishimura MC *et al*. Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. *Cell* 1994;76:1001-1011.

Dyck PJ. Neuronal atrophy and degeneration predominantly affecting sensory and autonomic neurons. In **Dyck PJ**, Thomas PK, Lambert EH., Bunge R, eds. *Peripheral neuropathy*. WB Saunders Company, Philadelphia, 1984.

Dyck PJ, Chance P, Lebo R, Carney JA. Hereditary motor and sensory neuropathies. In **Dyck PJ**, Thomas PK, Griffin JW, Low PA, Poduslo JF. *Peripheral Neuropathy*. Vol 2 pp. 1094-1123. WB Saunders 1993.

Dyck PJ. Diseases of peripheral nerves. In Engel AG, Franzini-Armstrong C, eds. *Myology*. 2nd edition. McGraw Hill, New York 1994.

Greco A, Villa R, Tubino B, Romano L, Penso D, Pierotti MA. A novel NTRK1 mutation associated to insensitivity to pain with anhidrosis. *Am J Hum Genet* 1999;64:1207-1210.

Grills BL and Schuijers JA. Immunohistochemical localization of nerve growth factor in fractured and unfractured rat bone. *Acta Orthoped Scand* 1998;69:415-419.

Indo Y, Tsuruta M, Hayashida Y *et al*. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet* 1996;13:485-488.

Indo Y. Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. *Hum Mutat* 2001a;18:462-471.

Indo Y, Mardy S, Miura Y *et al*. Congenital insensitivity to pain with anhidrosis (CIPA): novel mutations of the TRKA (NTRK1) gene, a putative uniparental disomy, and a link-age of the mutant TRKA and PKLR genes in a family with CIPA and pyruvate kinase deficiency. *Hum Mutat* 2001b;18:308-318.

Levi-Montalcini R. The nerve growth factor: thirty-five years later. *EMBO J* 1987;6:1145-1154.

Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli R, Leon A. Nerve growth factor: from

neurotrophin to neurokinin. *Trends Neurosci* 1996;5:514-520.

Mardy S, Miura Y, Endo F *et al*. Congenital insensitivity to pain with anhidrosis: novel mutation in the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor. *Am J Hum Genet* 1999;64:1570-1579.

Mardy S, Miura Y, Endo F, Matsuda I, Indo Y. Congenital insensitivity to pain with anhidrosis (CIPA): effect of TRKA (NTRK1) missense mutations on autophosphorylation of the receptor tyrosine kinase for nerve growth factor. *Hum Mol Genet* 2001;10:179-188.

Miura Y, Mardy S, Awaya Y *et al*. Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families. *Hum Genet* 2000;106:116-124.

Rosemberg S, Nagahashi Marie SK, Kliemann S. Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV). *Pediatr Neurol* 1994;11:50-56.

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.

Shorer Z, Moses SW, Hershkovitz E, Pinsk V, Levy J. Neurophysiologic studies in congenital insensitivity to pain with anhidrosis. *Pediatr Neurol* 2001;25:397-400.

Smeyne RJ, Klein R, Schnapp A *et al*. Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. *Nature* 1994;368:246-249.

Swanson AG. Congenital insensitivity to pain with anhidrosis. *Arch Neurol* 1963;8:299-306.

Swanson AG, Buchan GC, Alvord EC. Anatomic changes in congenital insensitivity to pain. *Arch Neurol* 1965;12:12.18.

Theodorou SD, Klimentopoulou AE, Papalouka E. Congenital insensitivity to pain with anhidrosis. Report of case and review of literature. *Acta Orthop Belgica* 2000;66:137-145.

Toscano E, Della Casa R, Mardy S. *et al*. Multisystem involvement in congenital insensitivity to pain with anhidrosis (CIPA), a nerve growth factor receptor (TrkA) related disorder. *Neuropediatrics*. 2000;31:39-41.

Toscano E, Andria G. Congenital Insensitivity to pain with anhidrosis: an NGF/TrkA-related disorder. *Am J Med Genet* 2001;99:164.

Toscano E, Simonati A, Indo Y, Andria G. No mutation in the TRKA (NTRK1) gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with hereditary sensory and autonomic neuropathy type V. *Ann Neurol* 2002;52:224-227.

Yada M, Yamaguchi K, Tsuij T. NGF stimulates differentiation of osteoblastic MC3T3-E1 cells. *Biochem Biophys Res Commun* 1994;205:1187-1193.

Yagev R, Levy J, Shorer Z, Lifshitz T. congenital insensitivity to pain with anhidrosis: ocular and

systemic manifestations. *Am J Ophthalmol* 1999;127:322-326.

Yotsumoto S, Setoyama M, Hozumi H *et al.* A novel point mutation affecting the tyrosine kinase domain of the TRKA gene in a family with congenital insensitivity to pain with anhidrosis. *J Invest Dermatol* 1999;112:810-81.