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Abstract

Congenital insensitivity to pain is a rare hereditary neuropathy. We present patients from a large family in Norrbotten, Sweden with a mutation in the *nerve growth factor β gene (NGF β)*. Using a model of recessive inheritance, we identified an 8.3-Mb region on chromosome 1p11.2-p13.2 shared by the affected individuals in the family. Analysis of candidate genes in the disease-critical region revealed a mutation in the coding region of the *NGF β* gene specific for the disease haplotype. All three severely affected individuals were homozygous for the mutation. The disease haplotype was also observed in both unaffected and mildly affected family members, but in heterozygote form. We have identified 43 patients, 3 homozygous and 40 heterozygous. The homozygous patients have a severe congenital form with onset of symptoms at an early age, most often affecting the lower extremities with insidious progressive joint swellings or painless fractures. Fracture healing was normal, but the arthropathy was progressive, resulting in disabling Charcot joints with gross deformity and instability. These patients lacked deep pain perception in bones and joints and had no protective reflexes, leading to gross bone and joint complications. They also had abnormal temperature perception but normal

ability to sweat. There was no mental retardation. Clinically, they fit best into the group HSAN type V. Sural nerve biopsies showed a moderate loss of thin myelinated fibers (A δ -fibers) and a severe reduction of unmyelinated fibers (C-fibers). 14 of the 40 heterozygous adult patients had mild or moderate problems with joint deformities, usually with only slight discomfort. Treatment was conservative with (if needed) different kinds of orthosis and in three cases joint replacement. Nine patients had neuropathy, and nine patients had no symptoms.

In congenital disorders like these, it is important to evaluate the age and also the slowly progressive nature, when considering treatment. There is an increased risk of growth disturbances in the very young. The orthopedic operations should therefore be planned from a long-term point of view, but patient education and orthosis are cornerstones in the treatment—to delay the development of neuropathic arthropathy. Arthrodesis, limb lengthening and spinal decompression with fusions are the only elective procedures that seem reasonable.

This Norrbottnian disease is also interesting as a model system for the study of pain.

Swedish summary—sammanfattning på svenska

I Norrbotten, med ursprung från Vittangi, finns en ärftlig nervsjukdom som drabbar främst nedre extremiteternas leder med grava felställningar både hos unga och äldre personer. Patienterna har en perifer nervstörning med nedsatt djup smärta och temperatursinne liknande som i tidigare beskriven familjär smärtokänslighet, Hereditär Sensorisk och Autonom Neuropati (HSAN). Däremot har patienterna få autonoma och centrala nervstörningar. Sjukdomsbilden stämmer bäst överens med den tidigare beskrivna mycket sällsynta 5:e HSAN typen, varav det tidigare har rapporterats 20-tal fall i världen, men där man ännu inte kartlagt genotypen. Förmodligen är Vittangi-patienterna drabbade av en ny, tidigare ej beskriven typ. Nervbiopsier har visat nedsatt antal av de nervfibrer som leder smärt- och temperatursignaler (A-delta och C-fibrer). Sjukdomen har en icke-dominant nedärvning och vi har identifierat en mutation i kromosomregion 1p11.2-p13.2 som kodar för *nerve growth factor β* (NGFβ). Detta fynd möjliggör uppdelning av patienterna i två olika former: patienter med dubbel uppsättning av mutationen (3 patienter) och symtomdebut i tidig ålder med markant smärtokänslighet i främst nedre extremiteterna, med smärtfria frakturer, felställda och förstörda leder och en lindrigare form hos 40 vuxna patienter med enkel uppsättning av mutationen och där symtomen debuterar i 20–70

års ålder med känselnedsättning och/eller ledsjukdom av olika grader. I hög ålder har även några av dessa utvecklade avancerade ledförändringar på samma sätt som de förstnämnda fallen. 9 patienter med enkel uppsättning av mutationen saknade kliniska symtom, bland dessa föräldrar till patienterna i första gruppen.

De ortopediska manifestationerna är svåra att behandla och det är nödvändigt att noggrant planera eventuella operationer med hänsyn till patientens ålder, kvarstående längdtillväxt, risk för tillväxtstörningar liksom effekter av sjukdomens fortskridande. Olika typer av ledbandage (ortoser) används i första hand för att skydda leder eller korrigera felställningar. Eftersom dessa patienter saknar normala smärtbetingade skyddsreflexer är information viktigt, speciellt till unga personer. De måste lära sig vad som kan ge smärta och hur man ska undvika smärta och extremt belasta lederna. Den kirurgi som rekommenderas vid avancerad leddestruktion hos yngre är steloperation (artrodes). Vinklingsoperationer (osteotomier) har utförts i enstaka fall med dåliga resultat och har ofta lett till steloperation senare.

Det finns idag ingen känd bot för sjukdomen. Teoretiskt är mutationen intressant som ett modellsystem för att studera smärtmekanismer.

List of original papers

- I Minde J, Toolanen G, Andersson T, Nennesmo I, Nilsson-Remahl I, Svensson O, Solders G.
Familial insensitivity to pain with neurogenic arthropathy but without anhidrosis (HSAN V). A neurophysiological and neuropathological study in a family with a mutation in the nerve growth factor beta gene.
Muscle Nerve 2004; 30(6): 752-60.
- II Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G, Holmgren G, Holmberg D, Holmberg M.
A mutation in the nerve growth factor beta gene (*NGFβ*) causes loss of pain perception.
Hum Mol Genet 2004; 8: 799-805.
- III Minde J, Svensson O, Holmberg M, Solders G, Toolanen G.
Orthopedic aspects of familial insensitivity to pain due to a novel nerve growth factor beta mutation.
Acta Orthop (in press).
- IV Minde J, Fulford M, Andersson T, Magdalena Aguiere, Nennesmo I, Nilsson-Remahl I, Svensson O, Holmberg M, Toolanen G, Solders G.
HSAN V, a phenotype study of patients heterozygous for the *NGFβ*-mutation.
Manuscript.
- V Minde J, Svensson O, Toolanen G, Solders G, Azmitia EC, Lönne-Rahm S.
Skin innervation in congenital insensitivity to pain, HSAN V.
Manuscript.

Thesis at a glance

Paper	Question	Patients	Method	Answer
I	Which clinical type of HSN does the Vittangi family have?	6	Case study	HSAN type V
II	What genetic locus and mutation is associated with the disease?	3	Genome-wide screen	A point mutation in chromosome 1p11.2-p13.2, <i>NGFβ</i> gene
III	Which type of orthopedic symptoms is common in the patients?	6	Case study	Painless fractures, hydrops, osteochondritis, Charcot arthropathy
IV	Which phenotype do the heterozygote patients have?	29 + 28 controls	Case-control study	Some have a mild course with neuropathy and Charcot joint, and others are symptom-free
V	How is the skin innervation in homozygous patients?	3	Case study	Patients have a reduced presence of nerve fibers in skin, especially in the legs

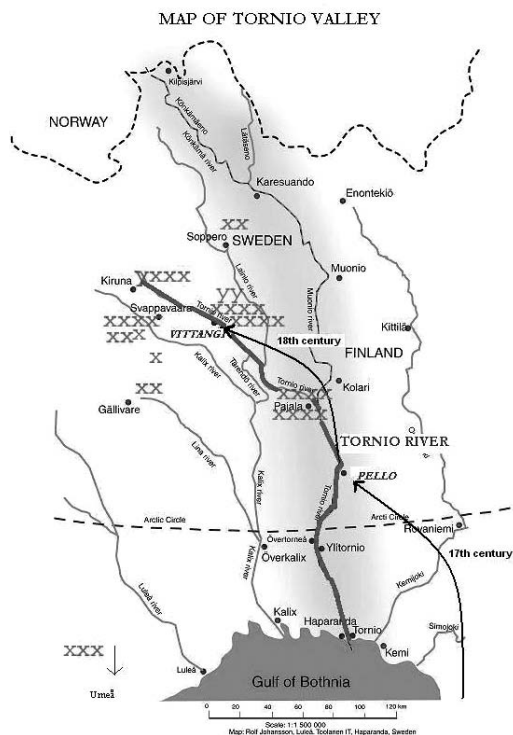


Figure 1. Map of Tornio valley. Tornio River is shown in the middle, and black arrows show how the ancestor moved from southern Finland to Pello, and later up-river to Vittangi. y = homestead for homozygote; x = homestead for heterozygote.

Abbreviations

BDNF	Brain-derived neurotrophic factor	OMIM	Online Mendelian inheritance in man
CGRP	Calcitonin gene-related peptide	MNC	Motor nerve conduction
CIPA	Congenital insensitivity to pain with anhidrosis	NGF	Nerve growth factor
CMT	Charcot-Marie-Tooth disease	NGFB	Nerve growth factor beta
EEG	Electroencephalography	NTRK	Neurotrophic tyrosine kinase
EMG	Electromyography	OA	Osteoarthritis
ENeG	Electoneurography	PGP	Protein gene product
FAP	Familial amyloid polyneuropathy	SNC	Sensory nerve conduction
FD	Familial dysautonomia	SP	Substance-P
GAP	Growth-associated protein	SPTL	Serine palmitoyl transferase
HMSN	Hereditary motor sensory neuropathy	SPTLC1	Serine palmitoyl transferase long-chain base subunit 1
HSAN	Hereditary sensory and autonomic neuropathy	SSR	Sympathic skin response
5HT2AR	5-hydroxytryptase 2A receptor	TRKA	Tyrosine kinase A
IKBKAP	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	THR	Total hip replacement
		TKR	Total knee replacement

Introduction

Pain

Pain is an important physiological signal that protects the individual from tissue damage, and appears to be critical for survival. Pain is one of the most common symptoms of disease and is also one of the most important indications for surgery. According to the International Association for the Study of Pain, it is “an unpleasant sensation and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Each individual learns the application of the word through experience related to injury in early life” (Merskey 1979).

Hereditary neuropathies

The hereditary neuropathies are classified according to their clinical manifestations (Bertorini et al. 2004). Depending on whether motor or sensory symptoms predominate, they are classified as hereditary motor and sensory neuropathy (HMSN) or hereditary sensory and autonomic neuropathy (HSAN). Today, causative genes are known for many of them. HSANs are a group of rare and poorly characterized disorders associated with sensory and/or autonomic deficits. Several names have been used for the diseases (Table 1). Mapping of the genetic defects in HSAN patients will provide important clues regarding the molecular mechanisms of pain, and will also bring the promise of new selective therapies.

Congenital insensitivity to pain

Previously, the terms congenital insensitivity to pain and congenital indifference to pain were used interchangeably (Jewesbury et al. 1970, McMurray et al. 1950). However, the presence of peripheral neuropathy has become a criterion for diagnosing congenital *insensitivity* to pain and for distinguishing it from congenital *indifference* to pain (Dyck et al. 1983), which is now reserved for conditions with a defect in the affective-motivational components of pain perception, but with normal peripheral sensory responses (Nagasako et al. 2003). Perception

Table 1. Historical note on HSAN

Year	Author	Term
1852	Nelaton	Affection singuliere des os du pied
1868	Charcot	Description of Charcot joint
1881	Paget	Charcot joint is neurogenic disease
1883	Morvan	Indifference to pain in syringomyelia or acrodystrophic neuropathy
1922	Hicks	Familial lumbosacral syringomyelia (HSAN I)
1932	Dearborn	Congenital pure analgesia
1936	Jordan	Neuropathic joint in diabetes mellitus
1942	Thevnard	Mal perforant du pied. Acropathie ulcero-multilante (HSAN I)
1949	Riley	Riley-Day syndrome or familial dysautonomia (HSAN III)
1951	Denny-Brown	Hereditary sensory radicular neuropathy (HSAN I)
1963	Swanson	Hereditary anhidrotic sensory neuropathy (HSAN IV)
1978	Low	HSAN type V, first case

of pain can be divided into multiple components including sensory-discriminative, affective-motivational and cognitive-evaluative aspects (Melzack et al. 1968).

By definition, peripheral nerve morphology is normal in congenital indifference to pain (Landrieu et al. 1990).

Historical notes

Nelaton (1852) was the first to describe a HSAN patient. Jean Marie Charcot (1868) described neuropathic arthropathy in four syphilitic patients. Later, numerous patients with a plethora of neurological disorders were described as having different joint affections.

HSAN

Dyck and Ohta (1983) classified hereditary sensory and autonomic neuropathy into 5 different types according to the mode of inheritance, neuropathology and clinical symptoms. This classification was recently reviewed by Nagasako et al. (2003). Donaghy classified HSAN genetically (Table 2).

Table 2. Classification of HSAN

Autosomal dominant inheritance	
Dominantly inherited sensory neuropathy	Denny-Brown 1951
Dominantly inherited sensory neuropathy with paraplegia	Cavanagh et al. 1979
Autosomal recessive inheritance	
Recessively inherited sensory neuropathy, HSAN II	Ohta et al. 1973
Hereditary anhidrotic sensory neuropathy, HSAN IV	Swanson. 1963
Familial dysautonomia, HSAN III	Riley et al. 1949
Hereditary sensory neuropathy with neurotrophic keratitis	Thomas et al. 1993
Recessively inherited sensory neuropathy with spastic paraplegia	Cavanagh et al. 1979
X-linked recessive inheritance	
X-linked recessive sensory neuropathy	Jestico et al. 1985
Uncertain status	
Hereditary sensory neuropathy with dysautonomia	Nordborg et al. 1981
Congenital sensory neuropathy with selective loss of small myelinated fibers HSAN V	Low et al. 1978; Dyck et al. 1983

Riviere et al (2004) has published a classification after known gene loci (Table 3).

General symptoms of HSAN

The symptoms often start early in childhood with engagement of the distal extremities affecting pain and temperature modalities. The patients often have autonomic symptoms such as sweating and vasomotor and temperature disturbances, resulting in recurrent episodic fever and hyperthermia. Others have symptoms of autonomic dysreflexia with alacrima, hyperhidrosis, postural hypotension, hypertension, and blotching of the skin. Mild to severe mental retardation is common. The insensitivity to pain may lead to burn injuries, skin ulcers and distal mutilation. In some patients, biting of the tongue, lips and fingers starts after the first tooth has shown. Multiple painless fractures and scars are frequent—and these may be complicated by infections and sometimes osteomyelitis. In much of the published material, such infections have been very common.

Table 3. Genetic classification

HSAN type	Transmission	Gene locus	Onset	Reference
I	AD	SPTLC1/9q22.1-22.3	Adult	Bejaoui et al. 2001
IB	AD	3p22-p24	Adult	Kok et al. 2001
II	AR	HSN2/12p13.3	Early	Lafreniere et al. 2004
III	AR	IKBKAP/9q31-q33	Birth	Slaugenhaupt et al. 2001
IV	AR	TRKA/NGF/1q21-22	Birth	Indo et al. 1996
V	AR	1q21-22	Early	Houlden et al. 2001
VI?	AR	NGFB/1p11.2- p13.2	Early	Einarsdottir et al. 2004

Neuropathic arthropathy

Joint destruction is one manifestation of the reduced sensory function. Neuropathic arthropathy, also called neuropathic arthritis or Charcot joint, is probably triggered by a traumatic event leading to progressive destruction of the bones and joints. Neuropathic arthropathy may result from hereditary neuropathies and from a plethora of other neurological disorders (Table 4). It is characterized by joint hypermobility and instability, bone/cartilage resorption, and often extensive joint destruction. Pain is usually absent or—interestingly—in some cases there may be a diffuse, deep pain. The condition is aggravated by the loss of pain protection reflexes and hypermobility of the joints, which causes a *circulus vitiosus* of injuries. Charcot arthropathy is most common in the foot, ankle and knee. Neuropathic arthropathies in the upper limb are infrequent. Deirmengian et al. (2001) reported 5 patients with neuropathic arthropathy of the elbow, and some patients with shoulder arthropathy have been reported (Hatzis et al. 1998).

Classification of the arthropathy is based on radiological findings (Koshino. 1991):

I: Degenerative stage with narrowing of joint space as in early osteoarthritis. This stage is often diagnosed retrospectively.

II: Destructive stage with appearance of fragmentation and loose bodies.

III: Reparative stage with union of fragments, enhancement and enlargement of the osteosclerotic area.

Table 4. Examples of disorders with neuropathic arthropathy

Alcoholism
Congenital insensitivity to pain (CIPA)
Charcot-Marie-Tooth (CMT) disease
Diabetes mellitus
Familial amyloid polyneuropathy
Leprosy
Multiple sclerosis
Myelomeningocele
Paraplegia
Peripheral nerve injuries or tumor
Pernicious anemia
Spinal cord tumor
Syringomyelia
Tabes dorsalis (syphilis)

Taxonomy

McKusick collected information about genetic diseases published in the catalog "Mendelian Inheritance in Man", first in 1966, and later in "Online Mendelian Inheritance in Man" (OMIM) (<http://www3.ncbi.nlm.nih.gov/omim>). This online service provides profiles of specific disorders with a unique identifier and clinical and gene-mapping information.

HSAN type I

Type I (OMIM162400) is the most common one. Nelaton (1852) was the first to describe this type as *affection singuliere des os du pied*. Type I is a sensory neuropathy starting in the second to fourth decade with sensory loss and foot ulcers. HSAN I has autosomal dominant inheritance. All modalities of sensation are affected. In some cases, there is also peroneal muscle atrophy and Achilles tendon reflexes are reduced or even absent. Pain attacks of a lancinating character in the feet and legs are common in some families (Denny-Brown et al. 1951). The disease is caused by a mutation in the *SPTLC1* gene (OMIM605712), one of the two subunits of serine palmitoyl transferase, the enzyme catalyzing a step in sphingolipid synthesis, and maps to chromosome 9q22.1-q22.3 (Bejaoui et al. 2002).

Type I b

This entity was recently described as a new form, with symptoms of cough and gastro-esophageal

reflux and a mutation in chromosome 3p22-p24 (Kok et al. 2003).

Type II

Type II (OMIM 201300) is autosomal recessive. It starts in infancy with various autonomic dysfunctions and severely impaired sensory functions, leading to tropic ulcers. Both upper and lower limbs are involved. The clinical spectrum is variable (Nukada et al. 1982). Sensory nerve conduction is abnormal (Hilz et al. 2002, Nagasako et al. 2003). The causative gene was mapped to 12p13.33 (OMIM608620) in five Canadian families in Newfoundland who carried a mutation within intron 8 of the *PRKWINK1* gene (Lafreniere et al. 2004).

Type III

Type III (OMIM223900), also known as familial dysautonomia or Riley-Day syndrome, has widespread autonomic dysfunction combined with loss of pain and temperature sensation (Axelrod et al. 1984) and occurs primarily in Ashkenazi Jews. The five cardinal clinical criteria are lack of an axon flare after intradermal administration of histamine, absence of fungiform papillae on the tongue, miosis of the pupil following instillation of dilute methylocholine chloride (2.5%), diminished deep tendon reflexes, and lack of overflow tears (Axelrod et al. 1983). The incidence is between 1 in 10,000 and 1 in 20,000 live births (Axelrod et al. 1984). Both sexes are affected equally. Approximately half of all patients die before reaching age 30 (Axelrod et al. 1982). The gene frequency in Israel has been estimated to be 0.91 per 100,000, and the carrier rate to be 1 in 50 (Moses et al. 1967). Sporadic cases have also been reported in the non-Jewish population (Orbeck et al. 1977). The disease is caused by a mutation in the gene encoding IκB kinase complex-associated protein *IKBKAP* (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex associated protein)(OMIM603722) which is located on chromosome 9q31 (Anderson et al. 2001, Slaugenhaupt et al. 2001).

Type IV

Type IV (OMIM256800), also called congenital insensitivity to pain with anhidrosis (CIPA), is a rare disorder with an autosomal recessive transmission. It is characterized by fever, anhidrosis

and lack of reaction to painful stimuli (Mardy et al. 2001, Shatzky et al. 2000). Death from hyperpyrexia early in life is estimated to occur in approximately 20% of patients with CIPA and septicemia is also frequent (Rosemberg et al. 1994). Israeli-Bedouin arabs (Shatzky et al. 2000) and Japanese (Indo et al. 1996) clusters are known to exist. The insensitivity to both superficial and deep pain may lead to burn injuries, multiple painless fractures and neuropathic joints (Hilz. 2002). Type IV is caused by a mutation in the *TRKA* gene (OMIM191315) encoding the receptor tyrosine kinase for nerve growth factor (NGF), which is necessary for survival of nociceptive sensory and autonomic neurons (Indo et al. 1996).

Type V

Type V (OMIM 608654) is the rarest of the five types. The symptoms are similar to those of type IV, with a selective loss of pain and temperature sensation but with intact sweat function and few other autonomic deficits (Low et al. 1978, Dyck et al. 1983, Axelrod et al. 1984, Houlden et al. 2001, Bar-On et al. 2002, Toscano et al. 2002, Karkashan et al. 2002). For a review of reported type V cases, see Appendix 1. The patients respond normally to touch, pressure and vibration, and sweating is normal—but they have a selective loss of pain and temperature sensation, leading to painless fractures, bone necrosis, osteochondritis, and neuropathic joint destruction.

Scandinavian HSAN cases

HSAN disorders are extremely rare. In Scandinavia, a severe case of HSAN type III was described in Norway (Orbeck et al. 1977) and one patient with HSAN type IV was identified in Denmark (Jorgensen et al. 1982). In Sweden, Nordborg et al (1981) presented 3 cases with atypical familial dysautonomia, later classified as HSAN type III. There have been no HSAN type IV or type V patients previously reported from Scandinavia.

Neuropathology

There have been several reports of the neuropathology of HSAN (Table 5). Sural nerve histology differ somewhat in type IV and V. Both types show a severe reduction in A δ -fibers. The reduction in C-fibers is moderate in type IV and severe in type

Table 5. Peripheral nerve pathology in HSAN

Type	A α	A β	A δ	C	Reference
I	↓	↓	↓↓	↓↓	Lambert et al. 1975
II	n	n	↓↓	n	Winkelmann et al. 1962
III	↓↓	↓↓	n	↓↓	Aguayo et al. 1971
IV	n	n	↓↓	↓	Rosemberg et al. 2001
V	n	n	↓↓	↓↓	Nolano et al. 2002
n = normal					

V. Type IV has normal large-diameter myelinated fibers but lacks epidermal and sweat gland innervation (Nolano et al. 2000).

NGF

Nerve growth factor (NGF) was the first neurotrophic factor to be discovered (Levi-Montalcini et al. 1987). NGF belongs to a group of related peptides called neurotrophins, which all have tropic effects on different subsets of neurons. In humans, four different neurotrophins have been identified and denoted NGF: brain-derived neurotrophic factor (BDNF), NT-3, NT-4 and NT-5. NGF is tropic for small fiber sensory neurons and for sympathetic neurons, as well as for the cholinergic neurons of the basal forebrain. NGF has been shown to stimulate both the development and maintenance of sympathetic and embryonic sensory neurons. NGF is a 7S complex of three proteins (alpha, beta, and gamma). The 26-kDa beta subunit is a homodimer of two disulfide-bonded proteins, and constitutes the biologically active NGF (Figure 2). The function of NGF-alpha is not currently known, but the gamma subunit is probably involved in the processing of the beta subunit of NGF. NGF and the other members of the neurotrophin family bind to two main receptors: (1) a “low”-affinity receptor called p75, which is common to all neurotrophins, and (2) a family of high-affinity receptors with tyrosine kinase activity, called TRKA A–C. After binding to the receptor, NGF is subsequently transported to the cell body. The binding of NGF to TRKA constitutes a survival signal to the cell, while binding to p75 in the absence of TRKA will induce apoptosis. It has been shown recently that the apoptotic effect of NGF requires the peptide to be in its proform, and is also dependent on interaction with sortilin, which binds to the propeptide (Nykjaer et al. 2004). The presence of NGF stimu-

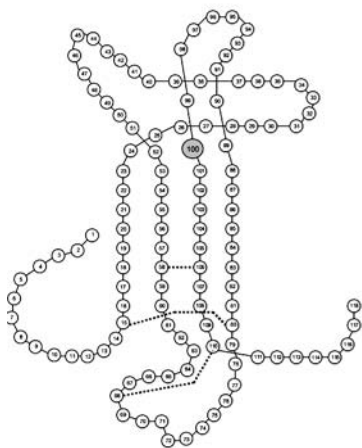


Figure 2. Structure of the NGFB protein with the alternative amino acid at position 100 of the mature protein highlighted (Rydén and Ibáñez. 1997).

lates the expression of substance P and calcitonin gene-related peptide (CGRP), which are involved in modulating central pain transmission (Kessler et al. 1980).

HSAN treatment

Concerning treatment of orthopedic manifestations in HSAN, the prevailing opinion is that conservative measures with information and different types of orthosis or braces should mainly be used (Fath et al. 1983). Activity should be reduced and the patient instructed to be careful (Scöke et al. 1996). Prolonged cast immobilization can cause skin ulcers and should be avoided (Krettek et al. 1997). The importance of early diagnosis is stressed, in order to avoid unnecessary, pointless or even harmful treatment (Guille et al. 1992, Theodorou et al. 1985). The overall aims of the orthopedic treatment are to prevent severe articular destruction and to avoid the need for amputation. Fractures in children are treated initially with non-operative treatment, but in patients with hypertrophic nonunion, operation with internal fixation may be warranted.

There have been few reports on Charcot spine arthropathy. Here, decompression alone is pointless; this condition requires rigid internal fixation and both posterior and anterior fusion (Piazza et al. 1988).

Aims of the studies

- To describe the phenotype in patients with HSAN of the Norrbottnian type (in both homozygous and heterozygous subjects).
- To describe orthopedic manifestations of the disease and to evaluate the treatment of Norrbottnian patients.
- To correlate the clinical symptoms and signs with the neurophysiological and neuropathological findings of the disease, and to define the type of HSAN from existing classifications.
- To perform a genome scan based on the genealogic family pedigree in order to identify genetic loci associated with the disease.
- To study nerve fiber distribution and their neuromediator expression, as well as mast cells, in skin from the upper and lower extremities of homozygous patients

Materials, methods and findings

Study population of the Norrbottnian type of HSN

The patients with Norrbottnian hereditary sensory and autonomic neuropathy are clustered around the Tornio River valley, which is characterized by large rivers flowing from the mountains of northern Sweden into the Gulf of Bothnia (Figure 1). Settlements were strictly concentrated along the rivers from south to north.

The affected family resides in the Vittangi area of Norrbotten. The family emanated from southern Finland and immigrated in the 1600s. The earliest immigrant was a juryman in the small village of Pello along Tornio River at the Finnish border, who died in 1549. The index person was the founder of Vittangi village in the 1600s. He stemmed from the immigrant family in Pello. As in other isolated remote communities, consanguinity was common. It is likely that the disorder followed the migrants settling in Tornio valley. According to local history, a peculiar disorder was known in earlier generations among people in the Vittangi area. Dislocated and deformed bones were common, along with various types of neuropathic symptoms.

The study was initiated when I met two adult patients, a mother and her son (patients 4 and 5), both with Charcot joints in the knee and ankle without an explanatory diagnosis. Shortly thereafter, a young boy (patient 3) was admitted to the orthopedic floor of Gällivare hospital with painless foot fractures, noted by his mother as a swollen foot. The correct diagnosis escaped us for a long time, until another patient (patient 2) with a similar clinical presentation turned up. This prompted an active search for more patients with similar symptoms. I therefore surveyed the catchments area of Gällivare hospital for people with insensitivity to pain and/or Charcot arthropathy, concentrating on patients from the affected families in the Vittangi district. We found 2 additional patients with severe clinical symptoms, and from them we built up a family tree. When new patients were identified, we attempted to fill up the family tree (Figure 3).



Figure 3. The pedigree: a 16-generation family tree with complex consanguinity.

Genealogical information was obtained from relatives, genealogists and church records. We used a genealogy program (Min Släkt version 3.1, Dannberg Data, Sweden) to register data for the pedigree. The genetic program used was Cyrillic Pedigree Editor for Windows 3.1.

All patient numbers refer to Appendix 3 and 4, which show all data and images.

Paper I

We studied 3 severely affected and 3 mildly affected patients (cases 1–6), all of whom were related to each other (Figure 4). Four patients were alive and were examined. Two mild cases, the mother and the maternal aunt of case 4, had died and only clinical data and radiographs were available. Clinical, neurological, neuropathological and radiographic examinations were performed, and muscle and sural nerve biopsies were also performed. The following specific tests were done: histamine test, tilt test, peripheral nerve conduction (ENeG), the R-R interval variation test, sympathetic skin response test (SSR), vibratory thresholds and warm and

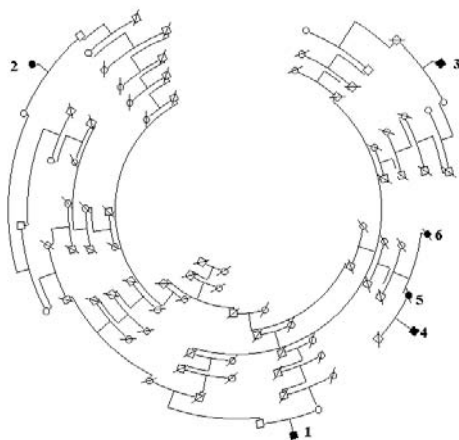


Figure 4. Pedigree from papers I and III. A nine-generation family tree is shown. The numbers represent the patients in papers I and III. Patients 1–3 are homozygous severe cases, patients 4 and 5 are heterozygous mild cases, and case 6 is probably heterozygous.

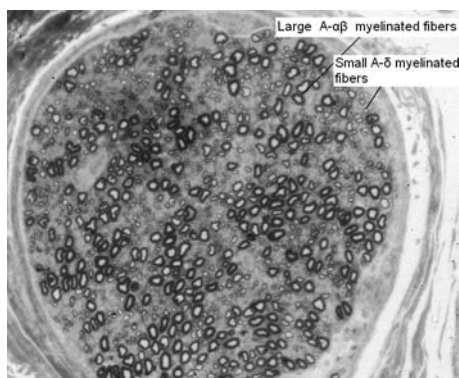


Figure 5. Normal control sural nerve biopsy showing a transverse section with normal distribution of myelinated nerve fibers.

cold perception thresholds, and needle EMG. For muscle biopsy, a percutaneous conchotome technique was used. Nerve biopsy was taken from the sural nerve behind the lateral malleolus under local anesthesia; 2–4 nerve fascicles were sampled for histology. The total transversal area of each section was photographed and the photocopies were used to identify the myelinated nerve fibers. All myelinated nerve fibers at one level of the nerve biopsy were measured. Laboratory investigations were done, including routine hematological tests to exclude other causes of polyneuropathy. ANA, HLA-B27, and RA tests were all negative.

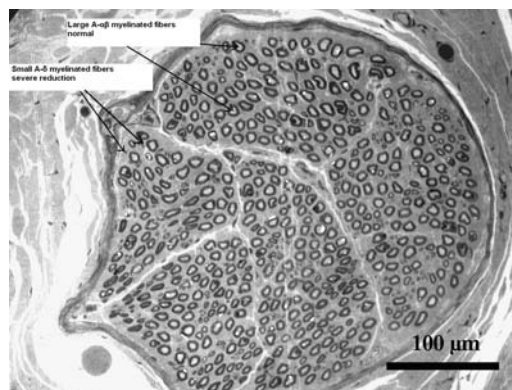


Figure 6. Sural nerve biopsy from a homozygous HSAN patient (case 1) showing a transverse section with severe reduction small-diameter A δ myelinated fibers and normal large-diameter myelinated fibers.

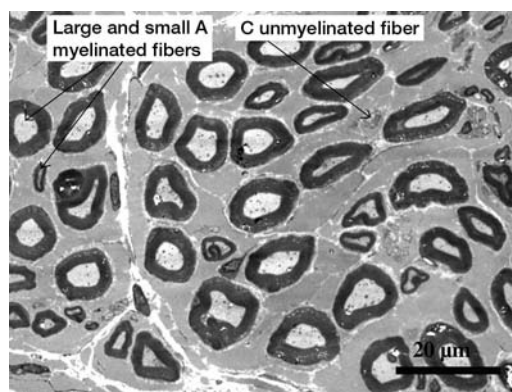


Figure 7. Electron microscopy from the sural nerve (case 1) showing severe reduction in number of C fibers.

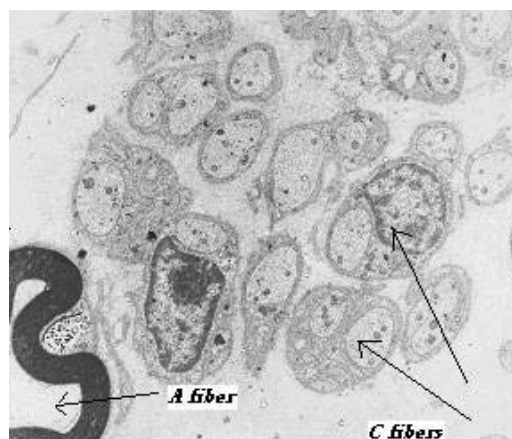


Figure 8. Electron microscopy of a normal sural nerve showing A and C nerve fibers.

The 3 patients who had early onset at 4–7 years of age had severe symptoms, including painless fractures and progressive arthropathy. The second group had onset in adult age with different grades of neuropathy and arthropathy.

Nerve conduction was normal in all patients, except for one who also had diabetes mellitus. Temperature thresholds were increased in all three homozygous patients. SSR was absent in 2 patients.

Sural nerve biopsies showed a moderate loss of thin myelinated nerve fibers and a severe reduction in unmyelinated fibers in all homozygous patients.

Paper II

We studied the 3 severely affected patients (cases 1–3). The pattern of inheritance for the severe cases was consistent with autosomal recessive transmission of the disease. Inbreeding and the fact that the parents of the severe cases were related support this interpretation. The number of possible cases present in the family, however, suggested a gene dosage effect, resulting in less pronounced symptoms in heterozygous individuals. The genotypes for each individual were then ordered into whole-chromosome haplotypes and regions of homozygosity were assessed visually.

Using a model of recessive inheritance for the 3 severe cases, we screened for shared homozygosity and identified an 8.3-Mb region on chromosome 1p11.2-p13.2 shared by the affected individuals in the family. Candidate gene analysis revealed a point mutation in the coding region of the *nerve growth factor beta (NGFβ)* gene specific for the disease haplotype. The haplotype for both groups was identified as homozygous for severe cases and heterozygous for mild cases.

Paper III

We presented the same patients as in paper I. These were three homozygous individuals with a mutilating arthropathy starting in early life, and two heterozygous patients and one patient (presumably heterozygous) with a milder course starting in adulthood (cases 1–6; Appendix 3). The symptoms were more pronounced in the early cases, with painless fractures and joint destruction. One patient had problems with joint infections and another developed a spinal deformity. For a more detailed description of the specific orthopedic symptoms and treatments, see Appendix 2. We compared our patients with those of Bar-On and his classification (Bar-On et al. 2002). In general, it seems that our cases had a less destructive course, although fractures with avascular necrosis and growth disturbances were also common in our patients with early onset. Surgery for these young patients requires careful planning because of the progressive and lifelong nature of the disease. Deformity and instability are the main problems and arthrodesis, corrective osteotomy and limb lengthening are the most commonly indicated operations.

Patients with spinal neuro-arthropathy (Table 6) often need surgery because of neurological deficits, and in some rare cases for loss of sitting balance. Most authors recommend both posterior and anterior fusion because of the gross instability. In HSN cases with progressive weakness, spinal deformities should be excluded.

Paper IV

We screened the pedigree involving 105 subjects and identified 40 heterozygous patients. 29 of them were available for examination in this study (cases 8–37), and as controls we had 28 relatives without the mutation. They answered a questionnaire and were examined using the Michigan neuropathy screening protocol (MNSI), originally intended for diabetic neuropathy (Feldman et al. 1994). An orthopedic examination including radiographs of knees, ankles, and spine was performed and previous radiographs were re-evaluated. We examined all heterozygous patients using nerve conduction (EneG), electromyography (EMG), SSR, and mea-

Table 6. Spinal Charcot patients

A	B	C	D	E	F	G	H	I	J	K
1	Petrie et al. 1953	F	25	P	Th10–Th11	PF, L	P	N	N	IV
2	Piazza et al. 1988	F	28	I	L1–L2	AF, PF	R	N	?	IV
3	Heggeness et al. 1994	F	17	P	L3–L4	AF, PF, L	R	N	N	IV
4	Igram et al. 1996	F	12	P	L4–L5	PF, L	R	N	?	IV
5	Tsirikos et al. 2004	M	11	P	L1–L2	AF, PF	R	Y	N	IV
6	Minde et al. 2005	M	21	P	L4–L5	PF, L	R	Y	N	V

A. Case
 B. Author
 C. Gender
 D. Age at onset
 E. Onset of symptom
 I spinal instability
 P paresis
 F. Spine level
 G. Treatment
 AF anterior fusion
 PF posterior fusion
 L laminectomy
 H. Treatment result
 P paresis
 R recovery
 I. Recurrent Charcot level
 J. Mental retardation
 K. Dyck type

surement of temperature thresholds. Nerve biopsies from the sural nerve behind the lateral malleolus were sampled from 6 patients and examined by light- and electron microscopy. None of the patients had mental retardation or anhidrosis, commonly found in HSAN. None had painless fractures or multiple ulcers (Appendix 3).

Clinical and radiographic examination showed that 11 of the 29 subjects had Charcot joints, compared to none in control group. Charcot arthropathy was graded according to Koshino (1991) and a slow progression over time was noted. The most commonly affected joints were the knee and ankle and 4 patients had Charcot arthropathy in more than one joint. Furthermore, signs of peripheral neuropathy were present in 15 of the patients and in 3 individuals in the control group.

13 of the heterozygous patients also had carpal tunnel syndrome with typical findings by neurography. Two of these have been treated surgically. Clinically 10 patients were examined and 8 patients have positive Tinel and Phalen sign. One patient (case 21) had a history of Guillain Barre Syndrome (GBS) and had severe abnormalities in peripheral

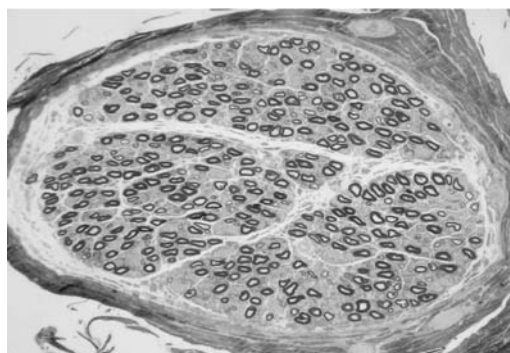


Figure 9. Sural nerve biopsy from a heterozygous HSAN patient (case 22) showing a transverse section with moderate reduction small-diameter A myelinated fibers and normal large-diameter A myelinated fibers.

nerve conduction. Two elderly patients (case 8 and case 15) also had signs of a severe neuropathy. One of them had diabetes mellitus. Nerve biopsy from 6 heterozygous patients showed moderate loss of both thin myelinated A δ fibers and unmyelinated C fibers (Figure 9). The same picture could be seen in both symptom-free and neuropathy patients, regardless of whether they had any symptoms.

Paper V

Skin biopsies were taken from 3 homozygous patients from the lateral upper arm under local anesthesia, 10 cm from the lateral margin of the acromion, from the gluteal region, and from 10 cm behind the trochanter major. Samples from each patient were analyzed for PGP 9.5, GAP-43, substance P and its receptor neurokinin-1(NK-1), CGRP, mast cells and the serotonin receptor 5-HT1A. In addition we studied the number of A δ ,

NF 200 positive nerve fibers. Immunohistochemistry was performed from cryostat sections. Six individuals served as healthy controls.

We found a small number of PGP 9.5 positive nerves, more in the arms than in the legs. There were few GAP 43-, substance P and CGRP-positive nerves. There was no difference in the number of NF 200 positive fibers and NK1 receptor positive cells, nor regarding mast cells. 5-HT1A positive cells were increased in the legs compared with the arms.

Discussion

General aspects

All HSAN types are rare, and in many of the cases the diagnoses seem uncertain. In addition, there are many semantic difficulties in discussing pain with patients who have no experience of it (Thrush et al. 1973). The orthopedic manifestations are often disabling and difficult to treat. The diagnosis was delayed in our first patients (cases 1 and 2), since we had no experience of this disease and some patients were unnecessarily and extensively investigated for suspected malignancy or infection. The pain insensitivity was also puzzling in 3 homozygous patients with no pain in fractured bone but with dysesthesia. Our heterozygous patients presented either with neuropathy and Charcot arthropathy of different grades, or without any symptoms at all. Surprisingly, nerve biopsy showed similar changes. Most heterozygous patients with arthropathy developed symptoms at 40–70 years of age. The disease typically started in the same manner as in the homozygous cases, with inflammation and joint effusion. The clinical picture resembled a mild, slowly progressive osteoarthritis. However, they also had other symptoms—with discomfort such as burning sensations in the feet. Despite partial or total sensory loss for pain, many patients with HSAN can experience pain, especially in HSAN I (Dyck et al. 1993). These patients can also have phantom pain in amputated extremities and lancinating pain due to inflammation within nerves containing actively degenerating fibers (Danziger et al. 2005).

Many of our heterozygous HSAN patients had dysesthesia, burning sensations, and—in lieu of pain—sometimes a dull diffuse feeling of discomfort, burning, pinpricking sensations and paresthesias. Many patients also had dysesthesia to heat. When taking his traditional Norrbottnian weekly sauna, one patient (case 4) had to put his feet in a bucket of cold water to avoid an intense pinpricking sensation. Two patients were excessively ticklish, and this sensation was distinctly unpleasant, probably due to the neuropathy.

All biopsied heterozygous patients had a moderate reduction of A δ and C-fibers in suralis nerve. The peripheral nerve fiber reduction seems not to have a major influence on the clinical presentation, because we found the reduction also in symptom free patients.

Homozygous patients however had moderate reduction of thin myelinated (A δ) fibers and severe reduction unmyelinated (C) fibers and in skin biopsies there was also a severe reduction of epidermal nerve fibers and GAP 43-, substance P and CGRP-positive nerves. There was no change in the number of mast cells between arms and legs, but there was an increased number of 5-HT1A positive mast-like cells in the legs. This might indicate a trial to compensate for the decreased innervation of C-fibers, by this receptor being responsible for the formation of new dendrites. In homozygous patients few visceral pain symptoms appeared, except in one having low abdominal pain from pyelonephritis. The heterozygous patients experienced pain both from the stomach and the gall bladder. Cholecystectomy had been performed in some of the patients. Thus, we believe that most of our HSAN patients experience a fairly normal visceral pain.

There have been few reported HSAN type V patients, involving only nine reports and 20 patients (Appendix 1). Low et al. (1978) were the first to report a type V case: a child with selective loss of pain perception but with normal findings on clinical neurological examination. Later, one patient with insensitivity to pain and tongue bite (Dyck et al 1983) and 3 patients with insensitivity to pain and fever were reported (Axelrod et al. 1984). Also, 3 isolated unrelated Kashmiri individuals with sensory neuropathies have been identified (Donaghy et al. 1987). Obviously, the Norrbottnian neuropathy differs clinically from the previously described type-V patients, and furthermore, it is likely that some of the patients already described in the literature probably had a variety of other diagnoses.

Genetic aspects, and classification

As previously discussed, HSAN is classified into 5 subtypes originally based on clinical characteristics. Subsequently, the genes for most of the subtypes have been identified but it is clear that all the genes that cause HSAN are not yet known. Some cases/families do not carry mutations in the gene/genes identified as being responsible for other cases in the same HSAN subtype. However, in HSAN IV all cases identified to date have been shown to be due to mutations in the NGF receptor TRKA, and all cases of HSAN III analyzed so far have been due to mutations in the *IKBKAP* gene. In HSAN I, most families have been shown to carry mutations in the *SPTLC1* gene, but families with a HSAN I phenotype without mutations in the *SPTLC1* gene also exist, suggesting genetic heterogeneity. For HSAN II, a gene designated *HSN2* has been shown recently to be mutated in five Canadian families (Lafreniere et al. 2004) It remains to be shown, though, whether this gene would explain all known HSAN II cases.

In the case of HSAN V, the situation is still unclear. This is so far the rarest form of HSAN, and is also considered to be the most pure form of pain insensitivity of the five. There is currently some controversy as to what cases really constitute type V cases (Appendix 1). Houlden et al (2001) reported one HSAN type V case caused by a TRKA (NTRK1) mutation. Pavone et al. (1992) also reported 2 cases with mental retardation and symptoms that better resembled HSAN type IV. Donaghy, Houlden, Dyck and Bar-On reported 5 patients with anhidrosis who also had typical HSAN type IV symptoms (Donaghy et al. 1987, Houlden et al. 2001, Dyck et al. 1983, Bar-On et al. 2002). Houlden et al. still consider these patients to be a separate entity from HSAN IV even though the mutation responsible is the same. Others consider these patients to be a HSAN IV subtype, as they have similar but less pronounced clinical symptoms including anhidrosis and mental retardation (Toscano et al. 2003). Other cases classified as HSAN V have not carried a mutation in TRKA and have had an unknown genetic cause. Toscano et al. reported absence of any TRKA gene mutation in a patient defined as HSAN type V (Toscano et al. 2002). Histology showed normal A δ and C fibers,

and Klein et al. suggested that the correct diagnosis in this patient was indifference to pain (Klein et al. 2003, Landrieu et al. 1990).

Is the Norrbottnian disease a *bona fide* HSAN type V? The main difference between HSAN type IV and V is the pattern of nerve fiber loss and the lack of mental retardation and anhidrosis. In a recent classification of HSAN type V (Houlden et al. 2004), it was divided into 3 different groups: (1) HSAN type V caused by a TRKA mutation; (2) HSAN type V caused by an NGFB mutation; and (3) HSAN type V with no mutation identified. We believe that group 1 patients are indeed HSAN type IV patients. Group 2 and some of the patients in group 3 are similar, and could constitute a clinical HSAN type V. HSAN type IV patients have a mutation in the NGF high-affinity TRKA receptor. The TRKA mutation is likely to be a partial loss-of-function mutation (Anand et al. 2004) and we believe the same is true for an NGFB mutation. The three sets of neurons that are dependent on NGF are sensory neurons, sympathetic neurons and cholinergic forebrain neurons, except for large diameter myelinated fibers.

Considering the confusion emerging in the clinical classification and also the latest developments in the genetics of these disorders, a reconsideration of the present taxonomy is needed preferably based on larger, pooled materials. The classification should concentrate on the genetic background of the disorders rather than clinical classification. It is likely that the taxonomy of HSANs will need to be changed as our understanding of the basic mechanisms behind the disorders increases.

Neurological aspects

The neurological symptoms expected from a lack of NGF function should come from lack of somatosensory, sympathetic and thin myelinated cholinergic forebrain neurons.

Except for the lack of skeletal and joint pain our patients reported surprisingly normal cutaneous sensation, similar in the homozygous and heterozygous cases. Dysesthesia to heat was the most common symptom, compatible with a thin-fibre dysfunction. There were only 6 cases with clinical signs of polyneuropathy (the 2 with diabetes and 1

with GBS excluded), and those patients were older than the patients with normal clinical findings. All patients reported normal sweating ability, only six patients had a pathological orthostatic test, and symptoms of other autonomic dysfunctions were surprisingly rare. Also, visceral pain seemed to be fairly normal judged from the case histories. None of our cases were mentally retarded.

Thus, the *NGF*-mutation found in our family with HSAN V gives different and milder neurological phenotype than the *NGF*-receptor *NTRK1*-mutation in HSAN type IV. The forebrain function, the sympathetic visceral pain and the high incidence of carpal tunnel syndrome need to be further explored.

Orthopedic aspects

The most frequent orthopedic manifestations in HSAN patients are multiple fractures, Charcot joints, avascular necrosis with possible leg length discrepancy, osteomyelitis, septic arthritis, dislocations, auto-amputations, self-mutilations and self-inflicted soft-tissue injuries. The knee was the most commonly affected joint, but the shoulder, hip, ankle, foot and spine could also be affected. However, only our homozygous cases had the above-mentioned symptoms, while the heterozygous individuals only had distal arthropathy.

Fractures in HSAN tend to heal with hyperplastic bone formation (Scöke et al. 1996). This is not surprising, since it is likely that there is considerable motion at the fracture site in patients with reduced pain. Another reason may be that the fracture is not diagnosed until late, when a considerable amount of swelling and inflammation has occurred. Also, the intriguing role of neurotransmitters in local bone metabolism offers further theoretical perspectives. The predominant fracture locations are the lower leg and foot (Bar-On et al. 2002) and these fractures heal with excessive callus formation within the same time frame as seen in healthy children. Calcaneus and talus fractures were seen in most of our cases as *en passant* findings, often with some deformation at diagnosis. The final outcome was disappointing even though we treated them with ankle orthosis for long periods and later on with orthopedic shoes. Although most fractures

heal with cast treatment, hypertrophic pseudarthrosis is not uncommon in HSAN. Good surgical results after fracture treatment have been reported. (Krettek et al. 1997; Karmani et al. 2001; Bar-On et al. 2002), but in our patients fracture surgery was not necessary. To avoid fractures in these young patients, we consider it important to inform the parents and teachers about the disorder in order to teach the young patients about normal pain reaction and about situations that usually induce pain. In school, they need additional support and positive reinforcement to minimize exposure to injury.

Mechanical factors play an important role in the development of osteoarthritis (OA); injuries and severe overuse increase the risk. According to one somewhat controversial—and perhaps not testable—theory for idiopathic OA, it is due to accumulated microtrauma secondary to subclinical neuromuscular incoordination, i.e. “microklutziness” (Radin et al. 1991). These authors have shown that individuals who are microklutzes tend to have prearthrosis. The way to stop microklutzes is to stop impulsively loading their joints, and we believe that this is an important factor for our patients also. Central pattern generators, the neural circuits that generate patterned stereotyped autonomous movements, may also change in diseases and reduce the protective proprioception, also in less extreme circumstances than in full-fledged Charcot joints.

Normally, joints are densely innervated organs, and this has a highly protective function. Even so, it was surprising that some of the patients could manage so well, and that the disease progressed so slowly. Neuromuscular mechanisms in OA warrant further studies. OA is an unspecific end stage of joint destruction that has been called “joint failure”, by analogy with heart failure. Radiographs are unspecific, at least early in the course, the only characteristic of neuro-arthropathy being that the changes are extreme.

Orthosis is the basic treatment for patients with neuro-arthropathy. The aim of this treatment is to relieve pressure on the joints, to preserve normal joint axis, and to protect deformities under an active Charcot process. We used orthosis and prescribed reduced activity to protect the joints. The splints were uncomfortable and often broke, and it was necessary to use light but strong materials. In

severe cases, we had difficulty in adjusting the joint axis for the orthosis to enable joint movement.

Apart from initial conservative treatment, surgery may be needed later on in advanced cases with leg length discrepancy and joint destruction. Avascular necrosis, commonly of the distal femur, resulted in progressing knee deformity. Growth plate disturbance is also a cause of joint deformity (Bar-On et al. 2002). Arthrodesis is sometimes necessary for the young homozygous patients to give stability and to enable walking. In patients with Charcot arthropathy in both knees, it is, of course, only possible to treat one side with arthrodesis—often resulting in limb shortening. One patient with arthrodesis in the knee and ankle and severe Charcot arthropathy of the ipsilateral hip (case 2) had a limb-lengthening procedure performed, with uneventful bone healing. Some patients with HSAN develop symptoms from the hip, often due to limb length discrepancy. It is generally believed that hip arthroplasty is contraindicated in Charcot arthropathy. One patient (case 2) with hip destruction and extreme limb length discrepancy had no pain. A destroyed hip does not necessarily give serious functional consequences, as was seen in our cases. The few Charcot joint patients treated with total hip replacement (THR) have reported mostly bad results (Robb et al. 1988). Until now, our case is doing well as far as the hip is concerned but has lancinating pain in her left knee and ankle.

Treatment of Charcot knee arthropathy also remains controversial. Some authors have considered Charcot joint to be an absolute contraindication for TKR (Scott 1983), but there have been recent reports indicating better outcome (Fullerton et al. 1997, Yoshino et al. 1993, Kim et al. 2002, Parvizi et al. 2003), although the reported complication rate is certainly a deterrent. In general, indications for TKR seem to be very limited indeed in HSAN. We have performed TKR in 3 heterozygous patients, in two of whom we were not aware of the diagnosis at the time of surgery (cases 9 and 15). One patient (case 9) got unicompartmental prosthesis but rapid progressive joint destruction necessitated a total knee replacement (TKR) 2 years later. One heterozygous patient (case 11) with extremely unstable knees got hinged rotating TKR on both sides, and we plan the same procedure in another patient (case 4). Still, we have had

no complications with loosening of the prosthesis in these patients, but the time that has elapsed after surgery is only 2–6 years. Anesthetic complications from the cardiovascular system and hypothermia have been reported in these cases (Rozentsveig et al. 2004), but we have used both general anesthesia and local blocks without problems so far.

Spinal neuro-arthropathy is rare and does not seem to be particularly common in patients with HSAN neuropathy (Table 6). Our patient (Appendix 3, case 1) illustrates the progressive nature of the disease, with a recurrent spinal Charcot arthropathy above the fused level with subsequent impeding neurological symptoms. We consider it important to exclude spinal deformity in all HSAN cases with suspected neurological deficit.

Patients with severe neuropathy often have bone and joint infections. In some neuropathy syndromes, this is probably due to coexisting immunological dysfunction, but other contributing factors may be that the injuries generate a *locus minoris resistentiae*, a suitable *milieu interne* for microorganisms to thrive. Another possibility is, of course, that the absence of pain delays diagnosis of the infection, so that the patients are not treated early and bone and joint infections are allowed to develop into more difficult-to-treat stages. This was probably the case in a young boy (case 3) who, one month after an intraarticular steroid injection into the ankle joint, developed acute septic arthritis. Antibiotics together with arthroscopic synovectomy led to healing. We had no indications that our patients were immunologically deficient, and other infections were rare. Previous reports have indicated that patients with HSAN neuropathies often have self-inflicted injuries and chronic wounds. Tongue and mouth lesions and even auto-amputations occur, but we experienced no such complications. It seems that these manifestations are often associated with mental retardation. There were no signs of cognitive impairment in our series. On the contrary, most of our patients appeared to be very receptive and cooperative. Unsurprisingly, there were some ulcers in cast treatment, but otherwise superficial wounds were very rare.

Model system for disease

Though rare, the HSAN neuropathies give an insight into a natural experiment. In 1656, the year before he died, William Harvey wrote: “Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path, nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly

perceived unless we are deprived of them, or they become deranged in some way”. Recent studies of rare genetic diseases have identified many of the critical transcription factors and signaling pathways specifying the normal development.

The Norrbottnian patients have no autonomic dysfunction or impaired mental ability. The findings of these studies may contribute to our increasing knowledge of pain and how neuropathic pain can be alleviated. Further studies of the NGF gene mutation are under way. Investigations of joint proprioception and visceral pain would also be interesting.

Conclusion

Congenital insensitivity to pain is a rare hereditary sensory and autonomic neuropathy. Patients from a northern Swedish family with a mutation in the *nerve growth factor β* (*NGF β*) gene were diagnosed as having the disease in a homozygous form with advanced orthopedic manifestations in childhood, or a heterozygous adult form with mild joint involvement or without symptoms. There was no mental retardation. Nerve conduction was normal, but temperature thresholds were impaired. Sural nerve biopsies showed a moderate loss of thin myelinated fibers (A δ fibers) and a severe reduction in unmyelinated fibers (C fibers). Homozy-

gote patient had also severe reduction in sensory innervation of the skin. The treatment was mainly conservative with different kinds of orthosis, but surgical treatment with arthrodesis, limb lengthening or (rarely) with prosthetic replacement was sometimes needed in the more advanced cases.

The disease was classified clinically as HSAN type V, although it differs somewhat from earlier described HSAN type V cases in several respects. To date, our series involves the largest number of genetically linked cases ever reported with this disorder, and our HSAN type may be a novel disease.

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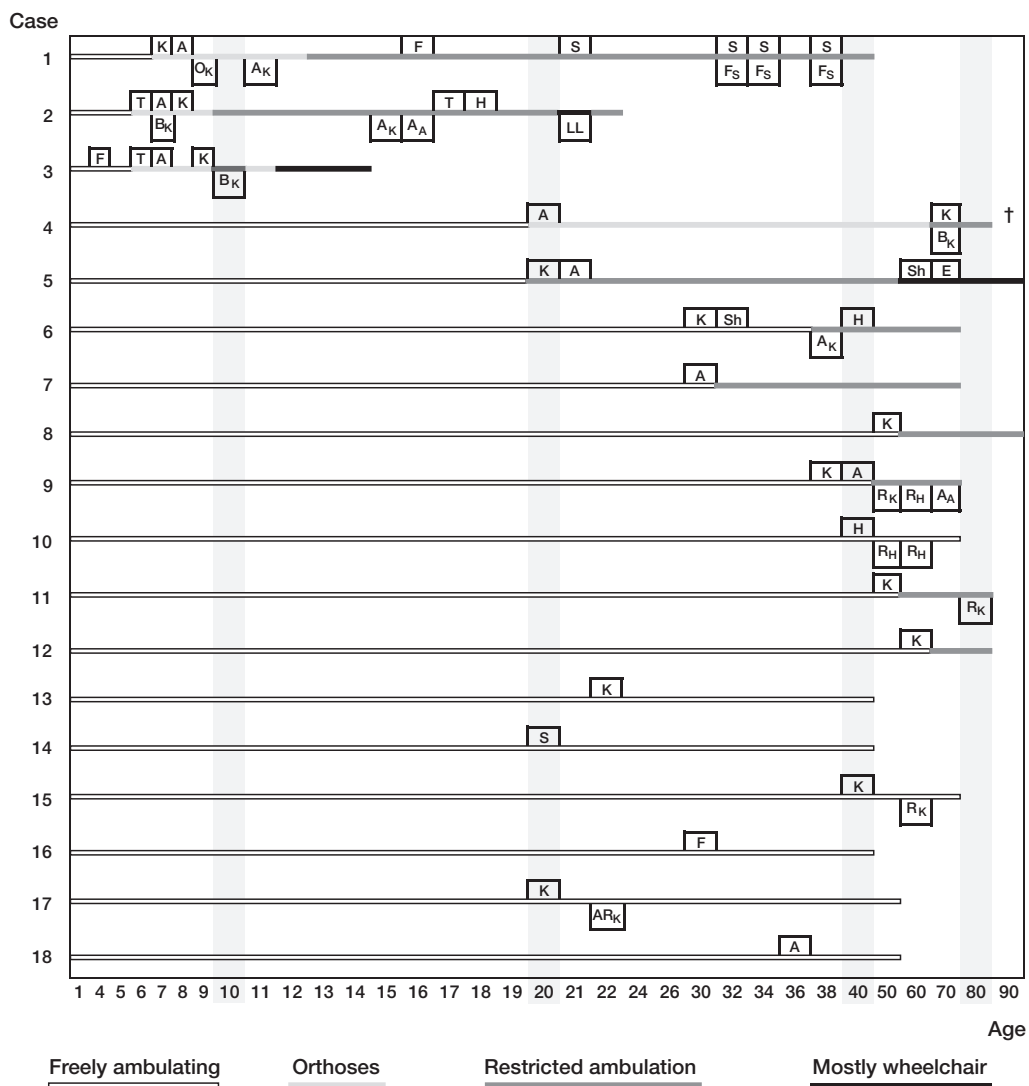
Appendix 1

Reported HSAN type V patients.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	Low	F		0.5		u						fr		Ch	C
2	Dyck	F	Y	2	ITP					mr					A
3	Axelrod	M	?	?	ITP			fe							?
4	Axelrod	M	?	?	ITP			fe							?
5	Axelrod	M	?	?	ITP			fe							?
6	Donaghy	M	Y	3	ITP		t						amp	Ch	C
7	Donaghy	F	Y	3	ITP		t						?		?
8	Donaghy	F	Y	1.5	ITP								?	?	?
9	Pavone	M	Y	1	ITP		t			mr		fr	amp	Ch	B/C
10	Pavone	M	?	2	ITP		t			mr					B
11	Houlden	M	Y	3				fe	fa		TRKA	fr			B
12	Karakashan	F	?	1	ITP							fr			B
13	Karakashan	M		1	ITP							fr			B
14	Karakashan	F	Y	1	ITP							fr			B
15	Karakashan	M		1	ITP							fr			B
16	Karakashan	M	Y	1	ITP							fr			B
17	Toscano	F	Y	1	ITP		t							Ch	C
18	Bar-On	F	Y	5								fr	amp	Y	B
19	Bar-On	F	Y	6								fr		Y	B
20	Bar-On	F	Y	1.5								fr		Y	B

- A. Case
- B. First author
- C. Sex
- D. Consanguineous parents
- E. Age at onset
- F. ITP: insensitivity to pain
- G. Ulcer
- H. Tongue bite
- I. Fever
- J. Fatigue
- K. Mental retardation
- L. Mutation (TRKA: tyrosine kinase A gene)
- M. Fracture
- N. Auto-amputation
- O. Charcot joint
- P. Type Bar-On

Appendix 2



Semilogarithmic time scale (patients 1–3 homozygotic, the others heterozygotic). Shading of time line indicates the patient's mobility.

Box above line shows anatomic location of disease: Sh, shoulder; S, spine; H, hip; K, knee; T, tibia; A, ankle; F, foot.

Box below time line represents surgery. The anatomic location is shown by subscripts: A, arthrodesis; B, biopsy; O, osteotomy; F, fusion; R, total joint replacement; LL, limb lengthening; AR, arthrotomy.

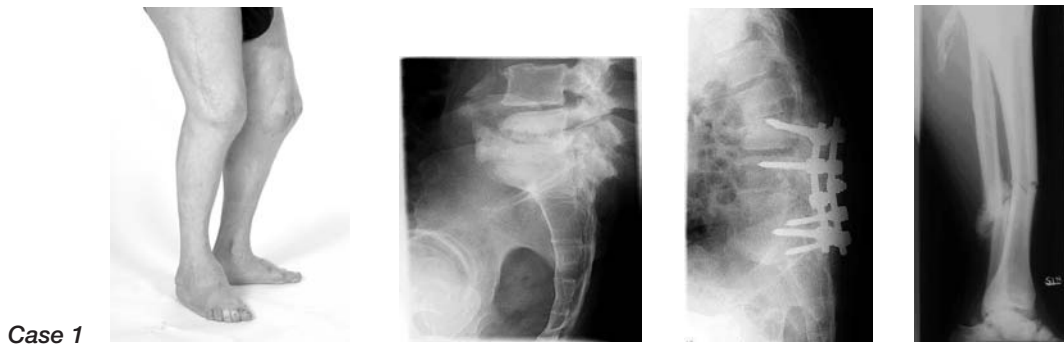
Appendix 3

Data from patients with Norrbottnian insensitivity to pain (HSAN V). Patient 1–3 homozygous mutation 4–37 heterozygous mutation

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
1	39	M	3	Y	7	F	0	1	f	Ch		a	k		s		np	u	inf	sp
2	21	F		Y	7	O	0	0	f	Ch		a	k	h			np	u	inf	sp
3	13	M		Y	4	O	0	1	f	Ch		a	k				np	u	inf	sp
4	77	M	1		30	A	1	3		Ch		a	k				np			
5	†	F		Y	20	A	1	6		Ch		a	k			sh	?			sp
6	†	F		Y	30	A	1	6		Ch		a	k	h			?			
7	75	M	1	Y	40	A	1	3		Ch		a	k				np	u	inf	sp
8	87	M	1		60	A	0	7		Ch		a	k				np			sp
9	73	M			50	A	1	0		Ch		a	k				np			
10	80	F			50	A	1	0		Ch				h?						
11	83	F	2	Y	70	A	1	0		Ch			k							
12	81	M	3	Y	70	A	1	0		Ch			k				np			sp
13	52	M		Y	20	0	3	0		Ch			k							
14	48	F	1		20	0	3	0		Ch					s?					sp
15	77	M	1		50	A	3	1		Ch			k				np			
16	47	M	3	Y	30	A	0	0		Ch	f									
17	53	F		Y	20	A	3	0		Ch			k							
18	56	M			40	A	0	0		Ch		a					?			
19	71	F				N	0	0									np			sp
20	65	F				N	0	0									np			sp
21	76	F				N	3	1									np			sp
22	59	F	2				3	1												
23	49	M					3	0												
24	13	M	3				0	0												
25	45	F		Y			1	3												
26	40	F		Y			1	3												
27	63	M					0	0												sp
28	63	F					0	0												sp
29	29	F					0	1												
30	37	F		Y			3	0												
31	24	M	3				1	0												
32	20	M	3				1	0												
33	47	M		Y			1	0												
34	16	F					0	1												
35	69	F					0	0												sp
36	19	F					0	1												
37	16	M					0	2												

A. Case	L. Foot
B. Age, 2005 (median age 52 years)	M. Ankle
C. Gender	N. Knee
D. Occupation	O. Hip
E. Consanguineous parents	P. Spine
F. Age at onset (median age 30 years)	Q. Shoulder
G. Onset symptom	R. Neuropathy
H. Affected siblings (average 1.0)	S. Skin ulcer
I. Healthy siblings (average 1.1)	T. Multiple infection
J. Fracture	U. Spinal disease
K. Charcot arthropathy	

Appendix 4





Case 8



Case 9



Case 11



Case 13



Case 14



Case 17