Introduction

The terms HSAN and hereditary sensory neuropathy (HSN) are synonymous. Prominent sensory abnormalities and, in many forms, autonomic disturbances are the hallmark of HSANs. The HSANs have been classified into five subgroups by P.J. Dyck according to age of onset, mode of inheritance, clinical features, electrophysiological findings and pathology (Table 9.1) [12]. From the onset, it was clear that the subgroups do not represent genetic entities and that, i.e. an overlap between HSAN1 and some variants of hereditary motor and sensory neuropathies (HMSN) with prominent sensory features exists. We will review here the cardinal features of the five HSAN forms. HSAN1 is the only autosomal dominantly inherited form. It is also the mildest form and the only one with adult onset. Some HSAN1 patients do also show distal weakness and atrophy. In contrast, HSAN2 – HSAN5 have a very early, often congenital onset and are autosomal recessively inherited. HSAN2 is characterized by congenital or early infantile onset sensory deficit affecting all modalities and the whole body. Mutilating ulcers and painless fractures are more common than in HSAN1. HSAN3, a very severe autosomal recessively inherited disease with prominent autonomic disturbances, has a high frequency of mutation carriers and affected children in Ashkenazi Jews. Prominent features of HSAN4 are repeated attacks of pyrexia due to the inability to sweat. Severe mutilations and mild mental retardation are additional clinical features. Histopathologic examination shows a prominent loss/absence of unmyelinated fibers in HSAN4. In contrast, severe loss of small myelinated fibers is found in patients with HSAN5. HSAN5 is clinically characterized by a selective loss of pain sensation mainly affecting the extremities. HSAN1 and HSAN3 are the most common HSAN types. Another neuropathy with prominent sensory features is CMT4F, an autosomal recessively inherited severe neuropathy with early onset caused by mutations in the periaxin (PRX) gene [7]. However, ulcerations are not a prominent feature of this neuropathy.
<table>
<thead>
<tr>
<th>Form</th>
<th>Mode of inheritance</th>
<th>Age of onset (years)</th>
<th>Main clinical features</th>
<th>Neurophysiology</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSAN1</td>
<td>AD or AR</td>
<td>20–40</td>
<td>symmetrical loss of pain and temperature sense, legs &gt; arms; ulceration of the feet, slowly progressive, sometimes lancinating pain</td>
<td>MNCV and SNCV normal/ slightly reduced, SNAPs reduced or absent</td>
<td>distal loss of myelinated fibers, increased number of Schwann-cell nuclei, degeneration of dorsal root ganglion cells</td>
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<tr>
<td>HSAN2</td>
<td>AR</td>
<td>congenital-infancy</td>
<td>sensory loss affecting all modalities, legs &gt; arms &gt; trunk, acral mutilation of feet and hands, tendon reflexes absent or weak</td>
<td>absence of SNAPs, MNCV may be slightly slowed and CMAPs reduced or absent</td>
<td>virtual absence of myelinated fibers and decrease of unmyelinated fibers in sensory nerves at distal parts of extremities</td>
</tr>
<tr>
<td>HSAN3</td>
<td>AR</td>
<td>congenital-infancy</td>
<td>predominantly Ashkenazi jews affected, autonomic, sensory and motor involvement, vomiting and poor feeding, defective lacrimation, temperature control with pyrexia, excessive perspiration, skin blotching, emotional hypertension and postural hypotension, insensitivity to pain, but vibration/joint position sense often normal, CNS involvement, but no obvious mental retardation, kyphosis/scoliosis, premature death, absence of fungiform papillae of the tongue</td>
<td>MNCV might be mildly slowed and CMAPs decreased</td>
<td>involvement of pons, medulla oblongata, reticular formation, long tracts of the spinal cord; sural nerve: unmyelinated fibers severely decreased, normal number of myelinated fibers</td>
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<tr>
<td>HSAN4</td>
<td>AR</td>
<td>congenital-infancy</td>
<td>repeated episodes of pyrexia caused by high environmental temperature, sweat glands present but no sweating, no pain sensation: ulcerations and mutilations common, normal muscle strength and tendon reflexes, mild mental retardation (IQ ~ 70)</td>
<td>absence of unmyelinated axons, decrease in the number of small myelinated neurons. Sweat glands have a normal structure but are not innervated</td>
<td></td>
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<tr>
<td>HSAN5</td>
<td>AR</td>
<td>congenital-infancy</td>
<td>selective loss of pain sensation, affecting mainly the extremities relatively preserved tactile, vibration, joint position sense, normal tendon reflexes and muscle strength, no mental retardation, sudomotor dysfunction in glove and stocking distribution</td>
<td>selective severe decrease of small myelinated fibers, small – severe reduction in unmyelinated fibers in sural nerve biopsy</td>
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9.1 Assessment of HSANs with autonomic and neurophysiological examinations

Only two tests, which are not commonly performed in daily clinical practice, are explained here. Other useful tests of autonomic dysfunction which are not described here are the Schellong test or the tilt table test, metronomic breathing, Valsalva’s maneuver, carotid sinus massage, ninhydrin test (sweating of palms and soles), Minor sweat test (whole body) and the sympathetic skin response.

9.1.1 Quantitative testing of thermal perception

Cutaneous cold receptors and nociceptors are innervated by small myelinated Aβ-fibers, while warmth and heat pain receptors are connected to unmyelinated C-fibers. An adjustable thermal stimulator (e.g. Thermotest, Somedic, Stockholm, Sweden) is used to apply the thermal stimulus. This device contains a Peltier element capable of either heating or cooling the stimulator. The baseline temperature is set at 32°C and the temperature change rate is set to 1°C/s for warming and cooling and to 3°C/s for heating. The stimulator is attached to the skin and the test person presses a button as soon as he feels the stimulus (“method of limits”) or until the stimulus becomes painful (heat stimulation). The difference between the baseline temperature and the perceived temperature is recorded. Normal data are available for several skin sites. Five successive measurements are averaged.

9.1.2 Histamine axonal flare test

The histamine axonal flare test is a commonly used test to examine the innervation of the skin by non-myelinated C-type fibers. Diluted histamine is injected intradermally. Histamine causes a local reaction, but also reaches unmyelinated dermal C-fibers in which it induces an action potential traveling centrally to the point of division of the nerve. Here it is not only transmitted to the dorsal root ganglia but also antidromically to other branches of the nerve in the skin. It then reaches arterioles and causes vasodilatation and plasma exudation through the release of vasoactive substances (neurogenic inflammation). Therefore, in healthy subjects, intradermal histamine injection causes a sharply demarcated local reaction surrounded by a less well demarcated area of hyperemia caused by the neurogenic inflammation, the so called axon flare. Patients with HSAN2, 3 and 4 display a lack of skin innervating C-fibers. The intradermal histamine injection is therefore not only painless but also does not induce the axon flare reaction.
9.2 Forms of HSAN

9.2.1 HSAN1/HSN 1 – serine palmitoyltransferase 1, long chain subunit 1 gene (SPTLC1) (OMIM 162400)

**Clinical features:** HSAN1 is the most common form of HSAN. The age of onset is usually between 15 and 40 years of age [12]. Spontaneous lancinating pain in the extremities, predominant severe loss of pain and temperature sensation compared to other sensory modalities and absence of autonomic nervous system involvement with the exception of disturbed sweating is characteristic for this type of HSAN [2]. The legs are more severely affected than the arms and the trunk and head are usually spared. Many patients develop painful ulcerations of the feet often complicated by osteomyelitis, which sometimes necessitates amputations. Disturbed sweating either hypo/anhidrosis or hyperhidrosis is common. In most HSAN1 patients the motor system is also affected leading to weakness and atrophy of the distal leg muscles [2]. The most important therapeutic measure is the prevention of foot ulcers. Patients should wear comfortable shoes and should inspect the inside of their shoes for foreign objects before putting them on. Activity requiring strenuous use of the feet like long walks should be avoided. Regular foot care and inspection is mandatory. If ulcers develop weight bearing should be avoided and radiographs of the feet, to rule out osteomyelitis, should be performed to initiate adequate treatment. Patients with CMT2B might show a similar clinical picture as HSAN1 patients, but in CMT2B patients all sensory modalities are usually equally affected, motor signs are more severe and the patients do not experience spontaneous lancinating pain [2]. Further differential diagnosis of spontaneous non-healing foot ulcers are given in Table 9.2.

**Electrophysiology:** Most patients show signs of an axonal neuropathy [2, 12]. Sensory nerves are primarily affected and the legs are more severely affected than the arms. Sensory nerve action potentials (SNAPs) are often absent in the sural nerve and reduced in amplitude in other nerves. Compound motor action potentials (CMAPs) can be reduced and slight slowing of motor nerve conduction velocities (MNCVs) may be present.

**Pathology, genetics and pathomechanism:** Histopathology shows distal loss, predominantly of small myelinated and unmyelinated fibers but also of larger myelinated fibers, an increase in the number of Schwann cell nuclei, thickened perineuria, a discontinuity of myelin and degeneration of dorsal root ganglia [12]. HSAN1 is genetically heterogeneous. About half of the HSAN1 families show mutations in the SPTLC1 gene on chromosome 9q22.1-q22.3 [4, 9]. A number of British HSAN1 families and Australian families of British extraction show a founder effect [23]. For the remainder
of families, no locus has yet been mapped. In addition, a mutation screen of the gene coding for the second subunit of serine palmitoyltransferase (SPTLC2) in 15 HSAN1 families without mutations in SPTLC1 did not yield any mutations, indicating that mutations in SPTLC2 are not a common course of HSAN1 [10]. Serine palmitoyltransferase transfers fatty acids to serine resulting in sphingosine. Addition of a second fatty acid leads to ceramide which in turn is a precursor of glycosphingolipids and sphingomyelin. SPTLC functions as a heterodimer composed of SPTLC1 and SPTLC2. Increased ceramide production causes apoptosis. The initial report of SPTLC1 mutations causing HSAN1 found elevated levels of ceramide in lymphoblasts of patients [9], suggesting ceramide induced apoptosis of peripheral nerve neurons as the pathomechanism. However, more detailed in vitro experiments demonstrated a reduction of serine-palmitoyltransferase activity of mutated alleles, suggesting a different pathomechanism for HSAN1 [5, 11].

**HSAN1 with cough and gastroesophageal reflux – chromosome3p22-p24 (OMIM 608088)**

**Clinical features:** This autosomal dominant disorder has been described in only one family. Patients experienced spontaneous lancinating pain and gastroesophageal reflux and/or cough due to minimal aspiration of the reflux [28]. Some patients also showed sensorineural hearing loss.

**Electrophysiology:** EMG shows signs of a predominant sensory peripheral neuropathy with undetectable SNAPs and normal or slightly reduced MNCVs.

**Pathology, genetics and pathomechanism:** Nerve biopsy showed loss of unmyelinated and myelinated axons [19]. The disorder has been mapped to chromosome 3p22-p24. The causative genetic defect remains to be identified [19].
9.2.2 HSAN2 – hereditary sensory neuropathy II gene (HSN2) (OMIM 201300)

**Clinical description:** HSAN2 is an infantile-onset or congenital, autosomal recessive severe sensory peripheral neuropathy [12]. All sensory modalities are affected but, in contrast to HSAN1, touch sensation is most severely reduced. The disease is not restricted to the extremities, but may affect the trunk as well. Tendon reflexes are often reduced. Ulcerations of the feet and hands as well as secondary osteomyelitis and Charcot’s joints are much more common than in HSAN1. In some patients, autonomic nervous system disturbances such as tonic pupils, swallowing problems, hypotonia and apnea have been found [12], but they are not a feature in the families in which causative mutations in the HSN2 gene were recently found [21]. The central nervous system (CNS) is usually not affected.

**Electrophysiology:** SNAPs are absent. MNCVs and CMAPs may be reduced.

**Pathology, genetics and pathomechanism:** Examination of sensory nerve biopsy specimens shows severe loss of myelinated axons, some loss of non-myelinated axons and the absence of cutaneous sensory receptors and nerve fibers [12, 21]. HSAN2 was recently mapped to chromosome 12p13.33. Three different mutations in a novel gene, HSN2, were detected in five Canadian families [21]. The function of this single exon gene is unknown. It is also not yet known how prevalent HSN2 mutations are in HSAN2.

9.2.3 HSAN3 – (Syn: familial dysautonomia, Riley-Day syndrome) – inhibitor of kappa light polypeptide gene (IKBKAP, protein IKAP)

**Clinical features:** HSAN3 is a severe autosomal recessive disease with infantile or congenital onset [25]. HSAN3 is nearly exclusively found in Ashkenazi Jews where the gene carrier frequency is estimated as 1:30 with a disease incidence of 1:3600 live births [3]. Current survival statistics indicate that newborns with HSAN3 have a ~50% probability of reaching the age of 30 years. HSAN3 mainly affects the development and survival of autonomic and sensory neurons and to a lesser extent of the motor neurons [3]. Patients often present with a history of poor feeding, repeated episodes of vomiting, hypertension, tachycardia, excessive perspiration, cutis marmorata, irritability and insomnia. These features constitute a “dysautonomic crisis”, which may appear in a cyclical fashion every month, week or even day. A dysautonomic crisis presumably results from catecholamines synthesized in the CNS acting on peripheral catecholamine receptors sensitized by the lack of peripheral catecholamine production. Due to the deficits in pain perception, ulcerations and other acral mutilations are common. Visceral pain perception however is preserved. Due to lack of
corneal pain sensitivity and insufficient lacrimation, many patients develop corneal ulcers. Regular use of lubricating eye drops is mandatory. Most patients are of short stature and develop a kyphoscoliosis. Gastrointestinal dysfunction results in abnormal esophageal peristalsis, and gastroesophageal reflux. More than 50% of the patients require a gastrostomy or fundoplication, because reflux leads to recurrent aspiration and chronic lung disease [3]. Respiratory dysfunction is often due to recurrent aspiration, restrictive lung disease caused by kyphoscoliosis and chemoreceptor dysfunction aborting normal reactions to hypoxia and hypercapnia. Chemoreceptor dysfunction is dangerous in high altitude and during swimming and diving, because patients do not feel the urge to breath. Cardiovascular features include postural hypotension, sometimes leading to syncope and attacks of hypertension triggered by lying down or stress. Areflexia and ataxia are caused by the involvement of somatosensory nerves. Cardinal early clinical manifestations which are diagnostic are

- no overflow tearing during crying,
- absent fungiform papillae of the tongue,
- depressed patellar reflexes (in 95% of patients),
- abnormal histamine flare test and
- patient is of Ashkenazi Jewish extraction [15].

Cranial magnetic resonance imaging (MRI) in older patients often shows signs of a generalized atrophy including the cerebellum, which may contribute to the ataxia. Older patients also experience progressive degeneration of the optic nerve. Specialized medical facilities familiar with all diagnostic as well as therapeutic aspects of the disease are available in the state of New York at the New York University School of Medicine and in Israel since ~60% of the patients live in these two areas. It is interesting to note that a dysautonomic crisis and excessive hypertension are best treated with benzodiazepines and clonidine, the latter being a drug that lowers the central sympathetic tone.

**Electrophysiology:** SNAPs are reduced and MNCVs are also slightly reduced. Visual evoked potentials (VEP) may be delayed due to optic nerve degeneration.

**Pathology, genetics and pathomechanism:** HSAN3 is thought to be a developmental disorder mainly of the sensory and autonomic (especially sympathetic) system with further degenerative changes during life. Sural nerve biopsy specimens may show a severe reduction of unmyelinated fibers to 10–15% of normal controls but relative preservation of myelinated axons. Neurons in the spinal dorsal root ganglia, in the Gasserian ganglion and in the sympathetic ganglia are reduced. HSAN3 was mapped to chromosome 9q31 [6] and mutations in the IKBKAP gene were found in 2001 [1, 27]. Over 98% of the patients show allele sharing in the candidate region and carry the same 5’ splice donor site mutation [1, 27]. This splice site mutation alters the
splicing of IKBKAP in a tissue specific manner with very high levels of aberrantly spliced mRNA in the nervous tissue and comparatively low levels of aberrantly spliced mRNA in other tissues. The IKAP protein is part of the “elongator complex” which is associated with elongating RNA-polymerase II. The exact pathomechanism remains to be elucidated.

9.2.4 HSAN4 – neurotrophin receptor tyrosine kinase 1 gene (NTRK1) (OMIM 256800)

- **Clinical features:** HSAN4 also called congenital insensitivity to pain and anhidrosis (CIPA) is an autosomal recessive disorder. Congenital onset, anhidrosis affecting the whole body, frequent bouts of pyrexia related to ambient temperature, absence of reaction to noxious stimuli and mild to severe mental retardation are the cardinal clinical features of this very rare disease [12, 18, 25]. Recurrent pyrexia is due to anhidrosis, which in turn is caused by lack of innervation of the cutaneous sweat glands [24]. Twenty percent of children succumb to hyperpyrexia in the first three years of life. Absence or severely impaired cutaneous as well as visceral pain perception, in combination with self mutilating behavior especially of young children leads to biting of the tongue resulting in a bifid or absent tongue, ulcerated fingertips, osteomyelitis and Charcot’s joints. The children are often mentally retarded, labile, hyperactive and irritable. Peripheral motor and cranial nerve function are normal. Corneal ulcers appear in some cases. Except for anhidrosis, overt severe autonomic dysfunction is not a feature of the disease, but clinical tests reveal signs of autonomic dysfunction [18]. Patients do not develop bradycardia during carotid sinus massage or ocular pressure, the ciliospinal reflex is absent and abnormalities in pupillary function have been described. On examination the skin is warm, dry and thickened on the soles and palms. In contrast to HSAN3, fungiform papillae of the tongue are invariably present. Orthopedic deformities of the knee, elbow and ankle joints are common. Investigations like EEG, cranial MRI or CT are usually unremarkable. The histamine axon reflex shows a normal flare response. Specific treatment is not available. It is very important to prevent self-mutilation, treat hyperpyrexia promptly by physical cooling or acetaminophen and/or ibuprofen. Chlorpromazine or chloral hydrate is used to relax the children and prevent hyperactivity which worsens the pyrexia.

- **Electrophysiology:** MNCVs, CMAPs, SNCVs and SNAPs are usually normal [12]. Somatosensory, visual and auditory brainstem evoked potentials are also normal. The sympathetic skin response (SSR) is absent.

- **Pathology, genetics and pathomechanism:** Histopathological studies of the cutaneous branch of the radial nerve or the sural nerve show nearly complete absence of unmyelinated fibers and mild to severe loss of small myelinated fibers without degenerative or regenerative changes [14]. Skin biop-
cies show morphologically normal sweat glands lacking innervation. Small neurons are absent in the dorsal root ganglia. Using a candidate gene approach, causative mutations were identified in the NTRK1 gene [17]. NTRK1 encodes a receptor tyrosine kinase for nerve growth factor (NGF) (reviewed in [18]). NGF signaling is mandatory for the survival of sympathetic ganglion neurons and nociceptive neurons during development but not for the development of large sensory or motor neurons, which are dependent on the action of other neurotrophins. NTRK1 protein dimerizes upon NGF binding to the extracellular domain leading to tyrosine autophosphorylation of the intracellular domain. The phosphorylated intracellular domain serves as an anchor for binding downstream signaling molecules. While nonsense mutations cause a loss of intact protein, the mechanism of action of missense mutations is more difficult to explain, but it has been shown for a number of missense mutations that they were aberrantly processed and most importantly had diminished autophosphorylation capacity [22]. In one Israeli-Bedouin family, linkage to NTRK1 locus was excluded suggesting that genetic heterogeneity is present [26].

9.2.5 HSAN5 – in some cases: nerve growth factor beta (NGFB), neurotrophin receptor tyrosine kinase 1 gene (NTRK1) (OMIM 256800)

**Clinical features:** HSAN5 is an extremely rare and poorly characterized autosomal recessive or dominant disorder. It is clinically characterized by congenital indifference to pain often combined with mild anhidrosis in the distal parts of the legs and arms. Thermal sensation is preserved but heat might not be perceived as painful. Ulcerations and mutilations of the distal extremities as well as Charcot-joints are common. Signs of mild autonomic system involvement are cutis marmorata and mild to moderate postural hypotension found in some patients. All mechanoreceptor-dependent sensations are normal as well as muscle strength and tendon reflexes. All cognitive functions appear to be normal, too.

**Electrophysiology:** Standard electrophysiology including MNCVs, CMAPs, SNCVs and SNAPs are normal in most cases.

**Pathology, genetics and pathomechanism:** Sural nerve biopsy specimens showed a severe, selective decrease of small myelinated fibers with relative preservation of unmyelinated fibers and large myelinated fibers and no signs of de- or regeneration. Very recently mutations in the NGFB gene were found in an inbred family from northern Sweden with some characteristics of HSAN5 [13]. The onset of symptoms was in the first or second decade, which is rather late for HSAN5. Patients suffered from loss of pain perception and although they could feel heat, burns of the skin did not hurt. Joint problems were common and one patient reported repeated faint-
ing on rising, problems when emptying the bladder as well as slight incontinence. The neurological examination did not show any other sensory or motor problems. Sural nerve biopsy specimens in the family carrying the NGFB mutation showed a prominent reduction of unmyelinated fibers and a much milder reduction of small myelinated fibers. It should be noted that this pattern is characteristic for HSAN4 but patients did not show the characteristic clinical HSAN4 phenotype. NGFB is a ligand for the NTRK1 protein, which is mutated in HSAN4. Because the HSAN5 phenotype presented here is much milder than the typical clinical picture of HSAN4, it seems likely that the NGFB missense mutation does not completely abolish its function. NGF deficient mice suffer from a very severe neuropathy [8]. Only one patient with some features of HSAN5 and a NTRK1 gene mutation, which causes the vast majority of HSAN4, has been reported [16]. The diagnosis was mainly based on a nerve biopsy showing predominant loss of unmyelinated fibers compared to small myelinated fibers. It is not proven that the patient described in this report does not suffer from a rather mild form of HSAN4 since he displayed generalized anhidrosis leading to recurrent attacks of severely elevated body temperature due to hot ambient temperatures which is not a feature of HSAN4. No mutations in NTRK1 were found in other patients with HSAN5 [29].

References


