FAMILIAL INSENSITIVITY TO PAIN (HSAN V) AND A MUTATION IN THE NGFB GENE. A NEUROPHYSIOLOGICAL AND PATHOLOGICAL STUDY

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The rare hereditary sensory and autonomic neuropathies (HSAN) are classified into five subtypes (HSAN I–V) by their mode of inheritance, pathology, natural history, biochemical, neurophysiological, and autonomic features.10,17

HSAN I is autosomal dominant, slowly progressive, starts between the second and fourth decade, is due to a progressive degeneration of dorsal root ganglia, and is sometimes caused by a mutation in the SPTLC1 gene.4,6,18 HSAN II is autosomal recessive and manifests in infancy with dysautonomia and impaired sensation leading to trophic ulcerations. Sensory nerve conduction is abnormal,10 sural nerve biopsy shows severe loss of myelinated fibers with relative preservation of unmyelinated fibers.29 The mutation is unknown. HSAN III, autosomal-recessive familial dysautonomia, leads to pronounced autonomic dysregulation and loss of pain and temperature sensation in infancy.2 The disease is caused by a mutation in the IKBKAP gene.1,24 HSAN IV, congenital insensitivity to pain with anhidrosis, is a rare autosomal-recessive disorder with recurrent episodes of fever, anhidrosis, and absence of reactions to painful stimuli leading to self-mutilation as well as to burn injuries, multiple painless fractures, and neuropathic joints.10 It is caused by a mutation in the TRKA gene, encoding for receptor tyrosine kinase for nerve growth factor (NGF), which is necessary for survival of nociceptive sensory and autonomic neurons.13 Nerve conduction velocities are normal, but sympathetic skin response (SSR) is absent.23 Nerve biopsy shows absence of unmyelinated fibers and a reduction of small myelinated fibers.22 There is no epidermal or sweat gland innervation.19 Patients with HSAN V, which is also autosomal-recessive and even rarer than HSAN IV, respond normally to touch, pressure, and vibration, but have a selective loss of pain and temperature sensation leading to painless fractures, bone necrosis, osteochondritis, and neuropathic joint destructions. Sweating is normal.10

The responsible genetic mutation is in the nerve growth factor beta (NGFB) gene.7 We have investigated members of a large family from northern Sweden carrying the NGFB mutation with congenital insensitivity to deep pain but with normal sweating, thus fitting the description of HSAN type V. Joint destruction and fractures with-

Abbreviations: ALAT, alanine-amino transferase; CAMP, compound muscle action potential; CK, creatine kinase; ESR, erythrocyte sedimentation rate; MHC, major histocompatibility complex; NGF, nerve growth factor; SNAP, sensory nerve action potential; SSR, sympathetic skin response

Key words: familial insensitivity to pain, HSAN, HSAN V, neuropathic arthropathy, nerve growth factor (NGF)

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ABSTRACT: We have studied a large Swedish family with a mutation in the nerve growth factor beta (NGFB) gene causing insensitivity to deep pain without anhidrosis (hereditary sensory and autonomic neuropathy, type V; HSAN V). Painfree joint destruction and fractures were common. Peripheral nerve conduction was normal, but temperature thresholds were increased. Sural nerve biopsies showed a moderate loss of Aδ fibers and a severe reduction of C fibers. The three most severely affected cases were all born to consanguineous parents, and were homozygotes for the causal genetic mutation. Treatment of these patients is discussed.

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out pain were a common hallmark in the studied patients. According to local history, this condition could be followed in the family history back to the 16th century when they came as immigrants from southern Finland.

CASE REPORTS AND METHODS

Patients. All our six patients are related, and consanguinity in this large family is common (Fig. 1). Four patients, three severely affected and one with milder symptoms, underwent clinical examination, sural nerve biopsy, and neurophysiological examination. Two milder cases, the mother and the maternal aunt to patient 4, are dead and only clinical data and X-rays were available.

Patient 1, a 12-year-old boy (Fig. 2A) born to consanguineous parents, has slight attention deficit hyperactivity disorder. His early motor milestones were normal. At 4 years of age, he developed a swollen painless right foot without antecedent trauma. Radiographs showed multiple metatarsal fractures. At 6 years of age he stumbled and developed a painless fracture of the tibia and fibula that healed uneventfully on conservative treatment with a cast. In the same year, he also sustained a painless calcaneal fracture. He gradually developed neuropathic deformities in both ankles (Fig. 3A) and was treated with intraarticular steroids in the right ankle. Two months later, at age 7, a fulminant septic arthritis was treated with antibiotics. He walked with an ankle brace. At age 9, an effusion in his left knee was attributed to osteochondritis. Six months later, radiography showed a severe neuropathic knee joint and at age 11 the right knee became similarly affected. He requires Tomas splint orthosis on both sides. He can walk for short distances with crutches, but for most of the time is in a wheelchair. He prefers cold showers to hot because he fears burning himself. He experiences burning sensations even in a normal-temperature shower, but feels only slight pain when he does burn himself (e.g., with a match). He sweats profusely when working hard. He does not faint and has had no gastrointestinal or urinary problems.

Patient 2, a 19-year-old woman (Fig. 2B) born to consanguineous parents, had childhood epilepsy. At
at age 7 she had a severe destruction of the right medial femoral condyle shortly after a painless proximal tibial fracture. A synovial biopsy showed nonspecific synovitis and a bone biopsy from the condyle was normal. After removal of the cast, residual effusions in her right ankle and knee were noted. Over the following years she developed severe neuropathic joints. At age 12, a muscle and sural nerve biopsy was performed. At age 15, she underwent arthrodesis of the right ankle and knee because of severe deformity and instability. At age 16, she fractured her left tibia and shortly thereafter developed destruction of the left calcaneus. At age 18, she was found to have avascular necrosis in her right hip with gross destruction (Fig. 3B). She now has a 12-cm discrepancy in leg length. She likes to dance and swim, but complains of poor balance. She lacks protective reflexes against burns, but can feel burning pain after a latency of about 1 s. She prefers cold showers and baths because of fear of getting burned. Cuts do not hurt, but pinpricks do. She seldom perspires, but when she does the perspiration is excessive. She faints frequently when rising up. She has difficulty in emptying her bladder, has slight urinary incontinence, and also has a gastrointestinal disturbance (abdominal pains, diarrhea, or constipation). Sexual functions are normal. Lately she has developed a slight finger tremor.

**Patient 3,** a 38-year-old man (Fig. 2C) born to consanguineous parents. At age 7 he suffered from destruction and effusion in his right knee shortly after a painless tibial fracture treated with a cast, and loose bodies were removed from the knee. At age 8, he developed destruction in both ankles and was operated for right ankle osteochondritis; loose bodies were again removed. At that time a low sensitivity to pain was noticed. At age 11, neuropathic arthropathy developed in both ankles and knees, and in the same year he underwent right knee and ankle arthrodesis. He has had low back discomfort since the age of 21, and at age 32 radiography showed severe arthropathy at L5-S1. At 34 years of age he was diagnosed with progressive instability and spondylolisthesis in L5-S1 and developed rapidly progressing myelopathy leading to lumbar L2-S1 fusion (Fig. 3C). Later he developed the same spondylolisthesis at L3-L4 and at T11-T12, and was treated twice with posterior fusion. He prefers cold to hot showers.
and feels a burning sensation at normal water temperature. He does not get burns easily. He sweats profusely in a warm environment and also has gustatory sweating. He has never fainted. In the last 6 months he has felt a slight numbness in his feet.

**Patient 4** is a 75-year-old man (Fig. 2D) with mild type II diabetes since age 69, treated by diet control. He has slight hypertension and had a cardiac infarct at age 71. He has worked as a lumberjack and as a construction worker. At age 48 he underwent surgery for a painless fracture of his right ankle; 8 years later he developed advanced osteoarthritis in both talocrural joints, with only slight pain. Later radiography showed osteoarthritis also in his left knee, with effusion and varus deformity. He walks with two crutches. He has an intense pinpricking sensation in his feet when taking a sauna bath. He has no disorder of sweating. His mother, maternal aunt, and maternal uncle have had similar joint disorders.

**Patient 5** (the mother of patient 4), deceased, was born in 1905, and at age 30 developed deformed knees with increased varus deformity (Fig. 3D) and also bilateral hip osteoarthritis and arthropathy. At age 64, radiography of the left hip showed destruction of the femoral head and neck. At 73 years of age, radiography showed increased osteoarthritis in both shoulders and also destructive changes in the right elbow and ankle, with severe talar necrosis. She also suffered from numbness and pinching sensations in her hands. She had no pain despite all the joint deformities and could walk for short distances with two canes until she died at the age of 93.

**Patient 6** (sister of patient 5), deceased, was born 1903, developed knee deformity with varus position and destructive arthropathy when aged 30, and underwent right knee arthrodesis which failed to heal, prompting the use of knee orthosis at age 39. At 79 years of age she developed a right footdrop. Also, the left humerus came to be dislocated anteriorly with resorption of the humeral head and destructive arthropathy. At age 81 she had advanced instability and deformity in both knees. She had restricted range of motion in her left hip because of advanced arthropathy, with severe destruction of the femoral head and neck. Radiography of her ankles showed destructive arthropathy. Despite the extensive joint destructions she had only slight discomfort but no deep pain. She died at the age of 96.

**Clinical Evaluation.** The clinical history (with special emphasis on symptoms of polyneuropathy and autonomic dysfunction) and clinical neurological examination of patients 1–4 was performed by the same neurologist (GS). Any weakness or muscle atrophy was noted. Reflexes in upper and lower limbs were graded quantitatively, as was sensation of vibration, touch, heat (40°C), cold (20°C), and pain (pinprick).

Tilt test was performed with passive tilting from a supine position after 5 min rest to 60° upright position. Heart rate and blood pressure were recorded before tilting, directly after tilting, and 3 min after tilting.

The response to histamine was noted 15 min after the intradermal application of 1 drop of histamine hydrochloride (10 mg/ml) on the lower forearm. The size of the erythema and presence of itching were recorded.

Routine hematological and biochemical tests, that is, blood count, hemoglobin, erythrocyte sedimentation rate (ESR), and serum creatine kinase (CK), alanine-amino transferase (ALAT), C-reactive protein, creatinine, thyroid stimulating hormone, thyroxine, vitamin B₁₂, folic acid, homocysteine, sodium, potassium, calcium, glucose, protein electrophoresis, antinuclear antibodies, rheumatoid factor antibodies, and serological tests for syphilis, were performed to exclude other causes of polyneuropathy.

**Neurophysiological Studies.** Nerve Conduction and Electromyography. Motor and sensory nerve conduction velocities and amplitude of the compound muscle action potential (CMAP) were measured in the median, peroneal, and tibial nerves. F-wave latencies were recorded in the median and tibial nerves. Sensory conduction velocities and amplitude of the sensory nerve action potential (SNAP) were measured in the median, superficial radial, and sural nerves. Skin temperature was measured at the base of the second finger and at the dorsum of the foot, and maintained at or above 30°C. Concentric needle electromyography of the anterior tibial muscle was performed using a conventional technique.

**Autonomic Tests.** The R–R interval variations during normal and deep breathing were recorded and expressed as the relative variation (percentage) of mean R–R interval. The SSR was recorded with surface electrodes placed over the dorsum and palm of the left hand. An electric stimulus was delivered over the median nerve at the opposite wrist. The latency and amplitude of the response were measured.

**Quantitative Sensory Testing.** The amplitude of the vibratory thresholds (in μm) were measured over the dorsum of the foot and over the second
metacarpal bone in the hand. The stimulus intensity was increased until the patient noted the stimulus and then decreased until the patient reported that the sense of vibration disappeared. The temperature thresholds for heat and cold were measured over the dorsum of the foot and over the thenar region in the hand. The temperature of the applied Peltier element was slowly increased or decreased and the patient pressed a button when the stimulus was felt (method of limits). The procedure was repeated with patients instructed to press the button when the stimulus became painful.

**Neuropathological Studies.** Biopsies from the sural nerve were obtained from patients 1, 2, 3, and 4. The lateral vastus muscle was biopsied in patient 2 and the anterior tibial muscle in patients 1, 3, and 4.

Sural nerve biopsy was performed under local anaesthesia from behind the lateral malleolus. One to seven nerve fascicles were dissected and 3–4 cm were sampled for analysis. One part was snap frozen in isopentane and dry ice, and 6–8-mm thick cryostat sections were used for immunohistochemical stainings with the same antibodies as for muscle. One part was fixed in 2.5% glutaraldehyde in Sörensén’s phosphate buffer, pH 7.4, for 1 day and sampled for paraffin and plastic embedding as well as for teasing. Paraffin longitudinal and transverse sections (3-μm thick) were stained with hematoxylin–eosin and Luxol fast blue. Semithin (1-μm thick) plastic sections were stained with toluidine blue. Furthermore, ultrathin sections for electron microscopy were processed.

For muscle, a percutaneous conchotome technique was used. After orientation of the tissue using a stereo microscope, it was snap frozen as described above. Sections (6- to 8-μm) were cut in a cryostat. The routine analysis included staining for hematoxylin–eosin, Gomori trichrome, oil red, periodic acid–Schiff, NADH (reduced form of nicotinamide-adenine dinucleotide) and adenosine triphosphatase (ATPase) at three different pH levels.

Immunohistochemical stainings for major histo compatibility complex (MHC) class I and II antigens, and for CD3+, CD4+, CD8+, and CD19+ positive cells were also performed.

**Morphometric Analysis.** Measurements were performed using a Nikon Eclipse 600 Microscope equipped with a 100× objective, and a Nikon CP 4500 digital camera (Tekno Optik AB, Stockholm, Sweden). The images were transferred to a Macintosh G4 computer (Apple, Cupertino, CA). The total transverse area of each section was photographed and the photocopies were used for identifying myelinated nerve fibers. The perimeter of each myelinated nerve fiber was measured using Image J software for Image Analysis 1.30 (National Institutes of Health, Bethesda, MD). All myelinated nerve fibers at one level of the nerve biopsy were measured. The perimeter of the nerve fibers was recalculated to circular diameter (circular diameter = perimeter/π). At least 300 (340–2262) nerve fibers were measured in each biopsy. The perimeter of each separate nerve fascicle was measured and the fiber density, expressed as the number of myelinated nerve fibers per square millimeter, was calculated. Mean values (± SD) of the fiber density and circular diameter were calculated for each biopsy separately. The grand mean values (± SD) of the four sural nerve biopsies were compared to the grand mean values from 10 healthy control subjects5 using Student’s t-test.

**RESULTS**

**Clinical Evaluation.** Dysesthesias to heat were present in patients 1–3, and all four patients also reported a slight distal numbness in the feet. Furthermore, a high propensity for itch and to get burns was reported, and all examined cases reported a normal ability to sweat.

Clinical neurological examination (including complete sensory and reflex testing of all limbs) was normal in patients 1 and 2 despite severe lower-extremity arthropathy. None of the patients had ataxia and all had normal corneal reflexes. Patient 3 had slightly diminished appreciation of vibration, heat, and cold in his feet. Patient 4 showed signs of a mild symmetrical distal polyneuropathy, with reduced stretch reflexes in the arms and absent reflexes in the legs, and diminution of all sensory modalities in the legs. None of the patients had mental retardation.

Routine hematological, biochemical, and serological tests (see Methods) to exclude other causes of polyneuropathy were normal.

The intradermal histamine test showed a small region of erythema in patients 1, 3, and 4 (10, 14, and 12 mm in diameter, respectively) and a larger region in case 2 (20 mm in diameter). Patients 1 and 2 felt an itching sensation, whereas patients 3 and 4 did not.

The tilt test was normal in patients 1, 3, and 4, but was abnormal in patient 2, with a heart-rate increase of 23 beats/min and a decline in blood pressure from 99/66 to 75/45 mm Hg.
Neurophysiological Studies. Nerve conduction velocity was normal in patients 1–3, and slightly decreased in patient 4. Reliable measurements of response amplitudes (CMAP or SNAP) in the legs could not be made because of grave deformities of the limbs. Electromyography (performed in the right anterior tibial muscle) was normal in patients 2 and 3, and revealed chronic neurogenic findings (reduction in numbers of motor unit potentials, with an excessive number of high-amplitude potentials) in patient 4. Electromyography was not performed for patient 1. Vibration thresholds were normal in patient 1 and slightly increased in patients 2–4. Temperature thresholds were increased in all four cases (most severely in patients 2 and 3). No reliable heat-pain thresholds could be detected in any patient. The SSR was normal in patients 1 and 4, and absent in patients 2 and 3. R–R interval variations were normal in all four patients.

Neuropathological Studies and Morphometry. The muscle biopsies were normal in the youngest patients (patients 1 and 2). In patient 3, areas with atrophic muscle fibers were found and in patient 4 (the 75-year old man with type II diabetes) type grouping was seen, indicating denervation and reinnervation.

In all four sural nerve biopsies, a moderate loss of thin myelinated nerve fibers and a severe reduction of unmyelinated fibers were found. In addition, a moderate loss of thick fibers was observed in patient 4, and occasional fibers with segmental demyelination were found in the two oldest patients (Figs. 4, 5).

The mean fiber density for the four patients was 7431 fibers/mm² (± 2946) and the mean circular diameter was 7.77 μm (± 1.27). Corresponding values from 10 healthy control subjects (Borg et al.) were 9600 fibers/mm² (± 1457) and 5.78 μm (± 0.62). Statistical analysis gave P values of 0.083 for fiber density and 0.002 for circular diameter. The myelinated fiber density was low (below –2 SD of the 10 healthy controls) in patients 3 and 4. The mean circular diameter was increased (> 2 SD) in patients 1, 2, and 3 because of the selective reduction of thin myelinated fibers. In patient 4 the fiber diameter distribution was normal due to a reduction also of the thick myelinated fibers (Fig. 6). The intraindividual variation of fiber density between separate nerve fascicles was slight.

DISCUSSION

Pain, according to the International Association for the Study of Pain, is “an unpleasant sensation and emotional experience associated with actual or potential tissue damage, or described in terms of such a damage. Each individual learns the application of the word through experience related to injury in early life.”

FIGURE 4. Sural nerve biopsies (transverse sections) from (A) patient 1 showing loss of thin myelinated nerve fibers and (B) a normal control.
Our patients could identify some pain such as pinprick, but had dysesthesias to heat. Superficial pain elicited normal corneal reflexes but they lacked deep pain sensation in bones and joints and thus had no protective reflexes, leading to gross bone and joint complications. They reported no disturbances of sweating, and some sweated easily and profusely.

Intradermal histamine elicited erythema in all four, but itching only in the two youngest patients. The tilt test was normal in patients 1, 3, and 4, but showed an abnormal postural reaction in patient 2. Thus, clinically they best fit into HSAN type V, which is autosomal recessive and characterized by clinically normal responses to touch, pressure, and vibration, and by normal sweating, but with selective impairments of temperature and pain sensation (as shown by quantitative sensory testing) leading to painless fractures, bone necrosis, osteochondritis, and neuropathic joint destructions.

Nerve conduction mainly assesses function in large myelinated nerve fibers and was normal in all but patient 4, in whom conduction velocities were slightly reduced, probably due to a diabetic neuropathy. Vibration thresholds were slightly increased in patients 2, 3, and 4, possibly due to the gross joint deformities and edema. The R–R interval test assesses a parasympathetic vagal reflex arc and was normal. The SSR was absent in two of the cases, and all had increased thermal thresholds. These findings indicate impaired function in thin myelinated fibers and in C fibers. Similar findings have been reported also in HSAN IV during childhood and even in infancy.

Sural nerve biopsy with morphometric analysis confirmed a moderate loss of thin myelinated fibers (Aδ fibers) and also a severe reduction of unmyelinated C fibers in all our patients. The morphometric analysis showed that the loss was selective for the thin myelinated fibers in patients 1, 2, and 3, but more uniform in patient 4, who was 75 years old and also had type II diabetes. The uniform fiber density in separate nerve fascicles argues for an early developmental reduction of fibers rather than acquired nerve damage.

There are few earlier reports on sural nerve biopsies in phenotypically classed HSAN, and most of these have addressed HSAN IV. In a young girl with HSAN IV, no small myelinated fibers and very few unmyelinated fibers were found in the sural nerve. Similar findings were reported in another case by Polo and colleagues. Skin biopsy in a case of HSAN IV showed absence of fibers immunoreactive to neuropeptide Y, nitric oxide, and vasoactive intestinal polypeptide, and thus profound developmental alterations of the peripheral nervous system. These results indicate that lack of innervation of the skin by Aδ and C fibers is the basis of HSAN IV. Two main differences from this pattern in our patients are the preserved superficial pain sensation and autonomic function, both mediated by thin myelinated and unmyelinated fibers, including those mediating sweating. However, the absence of an SSR in patients 2 and 3 may indicate subclinical impairment of sudomotor fibers as well.

In HSAN IV a mutation in the TRKA gene leads to defects in NGF signal transduction at its receptor,
and thus a failure of NGF-dependent neurons to survive.\textsuperscript{13} No mutation was found, however, in the \textit{TRKA} gene in our patients\textsuperscript{7} nor in another patient with HSAN type V.\textsuperscript{26} Instead, a homozygotic point mutation (661 C \textgreater T) in exon 3 in a conserved region of the nerve growth factor beta (\textit{NGFB}) gene was found in our three most severely affected cases\textsuperscript{7} (patients 1–3). Thus, a mutation in the \textit{NGF} gene causes a different, and less severe, phenotype than a mutation in the main NGF receptor, the \textit{TRKA} gene. This suggests that the mutation in our family does not completely abolish the ability of NGF to activate the TRKA receptor. Alternatively, the mutation affects the ability to activate the low-affinity p75 receptor. Knock-out mice, null for p75, have sensory deficits, but have a milder phenotype than mice null for NGF or TRKA.\textsuperscript{15,25}

Patients 1–3 had early onset and a more severe phenotype than patients 4–6, who had adult onset and a milder course. Patients 1–3 were all born to consanguineous parents and were all homozygous

for the \textit{NGFB}-mutation, whereas the milder phenotype in cases 4–6 suggests that they are heterozygous. However, the parents of patients 1–3, who should be heterozygote carriers of the mutation, had no overt symptoms. We are conducting further studies in this large family to detect any subclinical evidence of HSAN in heterozygote carriers.

Difficulties in orthopedic treatment of HSAN patients in the absence of sensory feedback are well known.\textsuperscript{3,27} The patients were poorly motivated to wear braces or orthosis due to lack of pain. Arthrodesis is the most commonly indicated surgical procedure, but timing is difficult. Spinal deformity is common and fusion is recommended to prevent paraplegia. Careful patient and family education in order to avoid trauma may delay the progression of joint destructions.

This work was supported by grants from Norrbotten Research Institute, Norrbotten Academy, and the Kempe Foundation. We are grateful to Professor Mårten Risling for generously sharing technical equipment for the morphometry.

FIGURE 6. Histograms of circular diameter of myelinated nerve fibers from the four biopsied patients and from one healthy control subject.

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