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Review Article

Hereditary sensory and autonomic neuropathy types IV and V in Japan

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Abstract Hereditary sensory and autonomic neuropathy (HSAN) is a group of genetic disorders involving varying sensory and autonomic dysfunction. HSAN types IV and V are characterized by congenital generalized loss of pain and thermal sensation. HSAN type IV is additionally accompanied by decreased sweating and intellectual disability. From 2010 to 2013, we (members of the Japanese Research Group on Congenital Insensitivity to Pain) carried out research on HSAN types IV and V. Research by this group included epidemiological data, examination of clinical findings, solutions of disease etiology, investigation of complications and development of their management. Complications were categorized into musculoskeletal complications, oral/dental complications, dermal complications, ocular complications, complications resulting from impaired thermal control, anesthetic considerations, other complications possibly related to autonomic dysfunction, and abnormal mental development and behavior. Treatment and care for patients with HSAN types IV and V require a wide range of knowledge and experience, and a multidisciplinary team approach. Therefore, we produced the "Guideline of Total Management and Care for Congenital Insensitivity to Pain (Ver.1)" in 2012, to provide information for medical specialists based on our knowledge and experience. This guideline includes medical issues, as well as descriptions of social participation and welfare. This review outlines the situation of HSAN types IV and V in Japan, and the recommendations of treatment and care for patients, mostly based on research conducted by the Japanese Research Group.

Key words anhidrosis, Charcot's joint, complications, congenital insensitivity to pain, hereditary sensory and autonomic neuropathies.

Hereditary sensory and autonomic neuropathy (HSAN) is a group of genetic disorders involving varying sensory and autonomic dysfunction. Dyck *et al*. classified HSAN into five types according to the mode of inheritance and clinical features.[1] This classification has been modified with subtyping, addition of new types, and discovery of related genes (Table 1).[2,3] The degree and nature of sensory and autonomic disturbances differ among each subtype, and some of them are accompanied by motor deficit. HSAN type IV (HSAN-IV) and type V (HSAN-V) are characterized by congenital generalized loss of pain and thermal sensation with autosomal recessive inheritance. HSAN-IV, also called congenital insensitivity to pain with anhidrosis, is additionally accompanied by decreased sweating and intellectual disability.

From 2010 to 2013, the Japanese Research Group on Congenital Insensitivity to Pain, consisting of researchers from related medical fields, carried out research on HSAN-IV and -V. The Medical Examination Gathering, which has been annually held since 1994 in collaboration with the non-profit organization Japanese Patients' and Supporters' Society for Congenital Insensitivity to Pain with Anhidrosis, "Tomorrow", has made great contributions to our research. This review outlines the current situation of HSAN-IV and -V in Japan, and recommendations of treatment and care for patients, mostly based on research conducted in Japan.

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Epidemiology

The prevalence of HSAN-IV and -V is not well established worldwide. Reports from countries other than Japan on more than 10 HSAN-IV patients came only from Israel.[4] The only report on HSAN-V was on a large family from Sweden.[5,6] Although there are many articles on Japanese patients with HSAN-IV and only a few on HSAN-V, no epidemiological studies on these conditions have been conducted in Japan.

To collect epidemiological data on Japanese patients, questionnaires were sent to pediatricians, neurologists, orthopedic surgeons, and dentists.[7] We estimated that the number of Japanese patients with HSAN-IV and -V was 130–210 and 30–60, respectively. We identified no sex differences, and patients with a

Table 1 Classification of hereditary sensory (and autonomic) neuropathies

Subtype†	Gene or locus	Heredity	Clinical features	Age at onset	OMIM
HSAN-IA	*SPTLC1*	AD	Loss of pain and temperature sensation; lancinating pain; ulcerative mutilations; variable distal motor involvement	Mostly adolescence to adulthood	162400
HSAN-IB	3p24–p22	AD	Sensory loss with cough and gastroesophageal reflux; foot ulcerations (rare)	Adulthood	608088
HSAN-IC	*SPTLC2*	AD	Loss of pain and temperature sensation; lancinating pain; ulcerative mutilations; variable distal motor involvement	Mostly adulthood	613640
HSN-ID	*ATL1*	AD	Severe distal sensory loss and amyotrophy in the lower limbs; trophic skin and nail changes; ulcerative mutilations	Adulthood	613708
HSN-IE	*DNMT1*	AD	Loss of all somatosensory modalities; lancinating pain; ulcerative mutilations; sensorineuronal hearing loss; dementia	Adulthood	614116
HSN-IF	*ATL3*	AD	Distal sensory loss in the lower limbs; painless ulceration of the feet; no autonomic involvement	Adulthood	615632
HSAN-IIA	*WNK1*	AR	Loss of pain, temperature and touch sensation; mutilation in the hands and feet; acropathy	Childhood	201300
HSAN-IIB	*FAM134B*	AR	Impaired nociception and progressive mutilating ulceration of hands and feet with osteomyelitis and acro-osteolysis	Childhood	613114
HSN-IIC	*KIF1A*	AR	Impaired position and vibration senses; ulcerative mutilation; minor distal weakness	Childhood to adolescence	614213
HSN-IID‡	*SCN9A*	AR	Loss of pain and temperature sensation; autonomic nervous dysfunction; hearing loss; hyposmia	Congenital or adolescence	243000
HSAN-III	*IKBKAP*	AR	No response to painful stimuli and temperature changes; alacrima; absence of fungiform papillae of the tongue; vasomotor instability and hyperhidrosis	Congenital	223900
HSAN-IV	*NTRK1*	AR	No (or reduced) response to painful stimuli; reduced thermal sensation; anhidrosis; episodic fever; intellectual disability and/or learning deficits; skin and corneal lesions; joint deformities	Congenital	256800
HSAN-V	*NGFB*	AR	Insensitivity to pain; reduced thermal sensation; severe loss of deep pain perception; painless fractures; joint deformities	Congenital	608654
HSAN-VI	*DST*	AR	Neonatal hypotonia; joint contractures; alacrima; absent corneal reflexes; lack of psychomotor development	Congenital	614653
HSAN-VII	*SCN11A*	AD	Insensitivity to pain; painless fractures; self mutilation; mild muscle weakness and delayed motor development	Congenital	615548
HSN with spastic paraplegia	*CCT5*	AR	Loss of all somatosensory modalities; mutilating acropathy; spastic paraplegia	Early childhood	256840

This table has been modified from Rotthier *et al*.[2] and Yuan *et al*.[3] †Based on the description in OMIM, except for the use of Roman numbers according to the Dyck *et al*. original description.[1] ‡In OMIM (243000), this subtype is named "channelopathy-associated insensitivity to pain", and the clinical features differ among reports. HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; OMIM, Online Mendelian Inheritance in Man

family history of the disorder were limited to affected siblings in both conditions. Most patients with HSAN-IV were 5–40 years of age, whereas half of the patients with HSAN-V were ≥40 years. We found no significant difference in the prevalence of HSAN-IV and -V among different regions in Japan (Table 2; N. Haga, unpubl. data, 2012).

Pathoetiology

The common and basic manifestations of HSAN-IV and -V are generalized insensitivity to pain and reduced thermal sensation. In HSAN-IV, perception thresholds of touch/pressure, vibration, and two-point discrimination are higher and proprioception sensitivity is lower compared with healthy controls.[8] Tomioka *et al*. reported on a patient with HSAN-IV who complained of itching as a sequel of Herpes zoster infection, and they suspected that this itching was a symptom of post-herpetic neuralgia.[9] Indo, however, noted that patients with HSAN-IV lack pain and itching sensation because of a lack of nerve growth factor (NGF)-dependent primary afferents.[10] In addition, HSAN-IV manifests reduced sweating, various degrees of intellectual

Table 2 Prevalence of HSAN-IV and -V in Japan

	No. patients per 10 000 000 population							
	Hokkaido	Tohoku	Kanto	Chubu	Kinki	Chugoku	Shikoku	Kyushu
HSAN-IV	3.6	8.3	8.9	9.6	6.2	5.2	0.0	5.4
HSAN-V	1.8	1.0	2.2	2.3	1.8	1.3	2.4	2.0

HSAN, hereditary sensory and autonomic neuropathy.

disability and/or learning deficits, and self-mutilating behavior.

In HSAN-IV and -V, conventional nerve conduction studies were apparently normal, and nerve biopsies showed selective loss of unmyelinated and small myelinated fibers.[1,11] Patients with HSAN-IV show loss of innervation of eccrine sweat glands by sympathetic neurons.[11]

In 1996, Indo *et al*. reported mutations in the tyrosine kinase domain of the *NTRK1* (*TRKA*) gene in Japanese and Ecuadorian patients with HSAN-IV.[12] Mutations of *NTRK1* have been reported in patients of various ethnic origins, including additional Japanese patients[13] and Bedouin people in northern Israel.[4] *NTRK1* encodes tropomyosin-related kinase A (TrkA), a receptor tyrosine kinase for NGF. Patients with HSAN-IV lack NGF-dependent neurons because defects in NGF-TrkA signal transduction lead to failure of survival of various NGF-dependent neurons.[14]

Mutations in the *NGFB* gene encoding nerve growth factor-beta have been reported in a large family from Sweden[5,6] and in a consanguineous Bedouin family with HSAN-V.[15] In the former family, homozygous patients had severe clinical manifestations, including progressive joint swelling, painless fractures, and progressive arthropathy. Temperature perception was impaired with normal sweating, and mental retardation was not observed. Heterozygous patients were mildly affected or not affected. In the Bedouin family, homozygous patients had multiple painless injuries of varying severity and had mild mental retardation. These findings suggested phenotypic overlap between HSAN-IV and -V because of changes in the NGF-TrkA signaling pathway.

Complications and their management

Musculoskeletal complications

Musculoskeletal complications are frequent in HSAN-IV and -V, and include repeated fractures and joint dislocations, arthritis and osteomyelitis, avascular necrosis, and Charcot arthropathy, mainly in the lower extremities.[16–19] A review of Japanese patients with HSAN-IV showed that fractures are frequent between 1 and 7 years of age, whereas other complications have no apparent age relationship.[20]

Fractures and dislocations develop in HSAN-IV and -V, even without any apparent trauma or following minor trauma, such as short falls (Fig. 1).[20] Although the reason for these fractures and dislocations has not been clarified, decreased sensation, including deep sensation, intellectual disability, and mutilating behavior, may be related. Video gait analysis for patients with HSAN-IV and -V has shown that younger patients walk faster with a longer stride length and higher heel contact angular velocity than controls.[21] This finding may explain the high incidence of musculoskeletal trauma in the lower extremities.

Charcot arthropathy may develop following malunion of fractures, avascular necrosis, and unreduced/recurrent dislocations in the absence of pain sensation (Fig. 2). Kawashima *et al*. measured grip force and acceleration of a held object in patients with HSAN-IV and -V.[22] They found greater grip force during the object grasp-lift-holding task and greater fluctuation in acceleration of the object. Such impaired motor control ability may lead to overuse and/or misuse of the extremities and cause joint destruction.

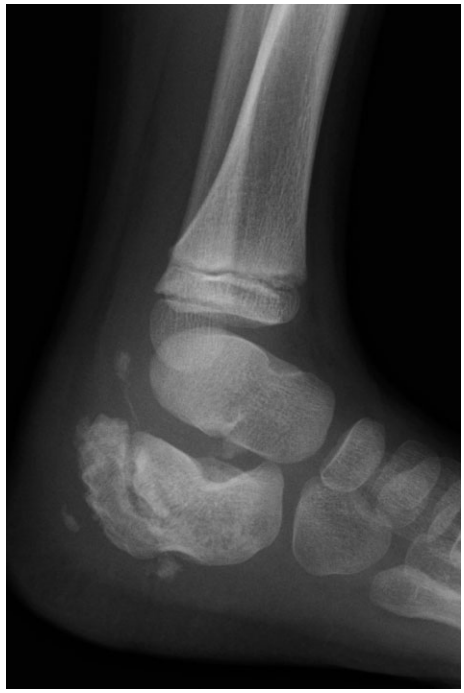

Fig. 1 Calcaneal fracture. A male patient with hereditary sensory and autonomic neuropathy type IV developed calcaneal fracture without any apparent trauma at 6 years old.

Management of musculoskeletal complications is extremely difficult. In conservative treatments, such as cast fixation and traction for fractures and dislocations, maintaining an appropriate position and avoiding weight bearing are difficult because of loss of pain sensation and intellectual disability. These may also lead to development of pressure sores. Even after surgical treatment, some patients cannot maintain non-weight bearing status, and the fixation of fractures or reduction of dislocations can break down. Because surgical and conservative treatment has drawbacks, prevention of trauma is important in HSAN-IV and-V, although few comments on injury prevention have appeared in the literature. The authors recommend that patients wear high-top sneakers with shoe-inserts of shock-absorbing material and knee pads. Some parents cover the floor in their house with soft-material sheets to prevent injuries.

Oral and dental complications

Oral self-mutilation, including autoextraction of teeth and biting injuries of the tongue, lip, and buccal mucosa, are common in patients with HSAN-IV (Fig. 3a).[23] In infants, trauma of the incisal edge of erupting mandibular primary incisors during sucking or nursing causes ulcers on the ventral surface of the tongue. Oral self-mutilation decreases with age and with intellectual, social, and/or emotional development. Treatment and prevention of glossal injuries and tooth luxation include tooth extraction, elimination of sharp edges of teeth, and use of a protective plate (Fig. 3b).[23]

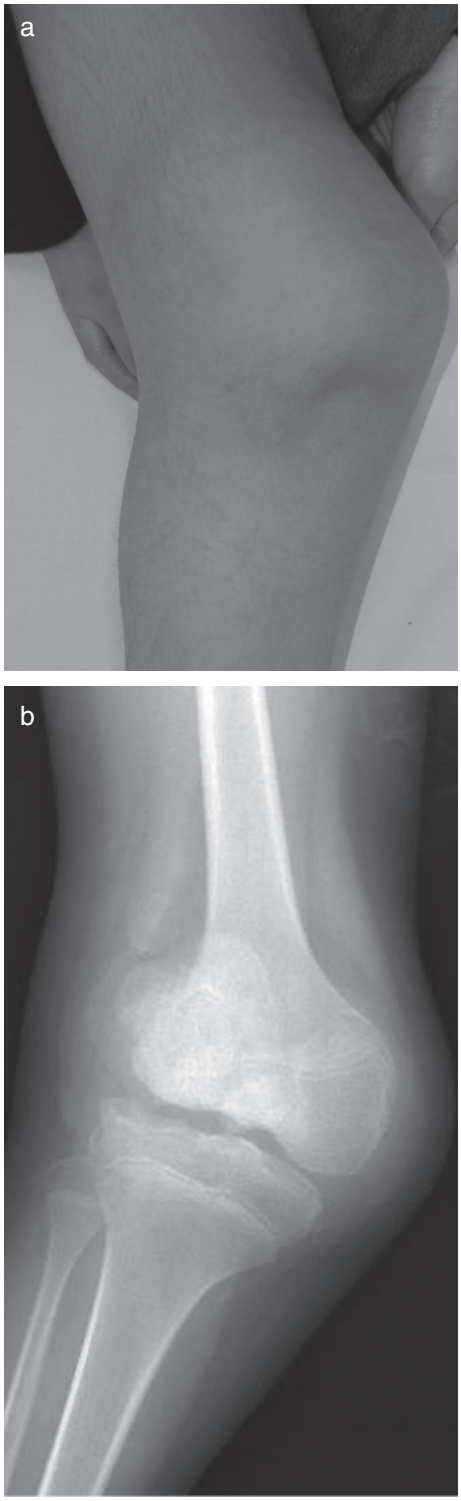

Fig. 2 (a) Photograph and (b) X-ray of Charcot's knee joint. A male patient with hereditary sensory and autonomic neuropathy type IV aged 10 years developed a Charcot joint with knock-knee deformity following avascular necrosis in the lateral femoral condyle.

We tested the threshold of pre-pain sensation of dental pulp of anterior teeth with the electric pulp test in patients with HSAN-IV and -V. Patients with HSAN-IV did not feel any sensation, but those with HSAN-V felt pre-pain sensation similar to

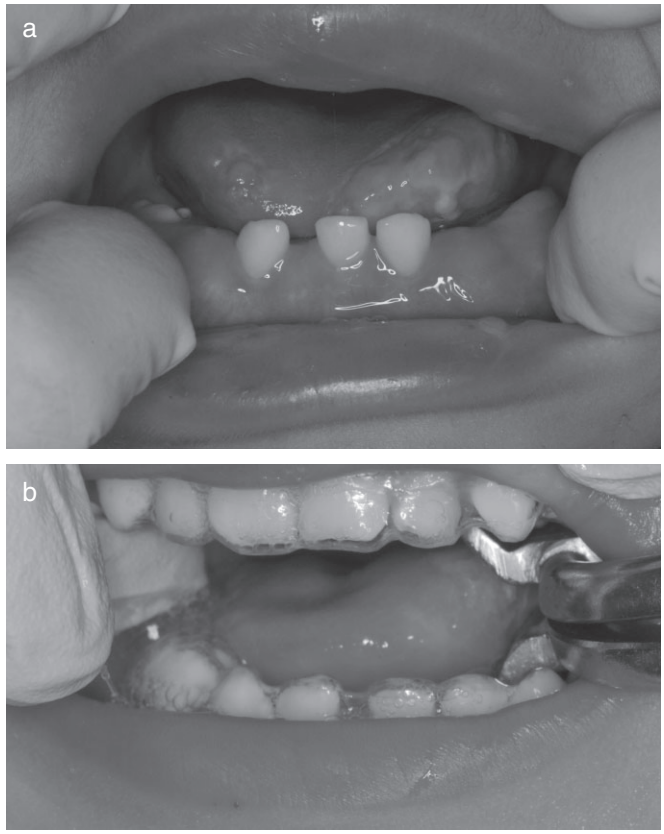

Fig. 3 Oral and dental complications. A female patient with hereditary sensory and autonomic neuropathy type IV aged 1 year 4 months developed (a) biting injuries of the tongue and lip, and autoextraction of a deciduous tooth. (b) She was using a protective plate at the age of 2 years.

a normal person. We also observed only a few myelinated fibers in the dental pulp of patients with HSAN-IV. With regard to oral sensation of taste, we found that the ability to taste and smell in patients with HSAN-IV is not impaired (Z. Miwa *et al*.; unpubl. data, 2012).

Dermal complications

In HSAN-IV, diminished sweating leads to dry and exfoliated skin, and sometimes results in palmoplantar keratoderma.[24] Baba *et al*. measured the degree of hydration in the superficial layers of the stratum corneum, using the Moisture Checker (MY707S; Scalar, Tokyo, Japan). The degree of hydration was lower in HSAN-IV patients compared with normal subjects. Daily use of a moisturizing agent improved dermal complications (N. Baba *et al*.; pers. comm., 2014). In relation to the pathomechanism of diminished sweating, Nolano *et al*. demonstrated, on immunohistochemistry, a lack of unmyelinated and small myelinated nerve fibers in the epidermis, and only a few hypotrophic and non-innervated sweat glands in the dermis.[11] In HSAN-V, sweating is reported as normal.[6]

Multiple skin ulcerations and scars are observed in HSAN-IV and -V, and these can develop from painless injuries, and sometimes from self-mutilation.[25] Self-mutilation typically manifests

as biting of the lips, tongue, and fingertips. Biting of fingertips can lead to digital shortening, nail deficiency, and phalangeal osteomyelitis (Fig. 4).

Ocular complications

In patients with HSAN-IV, corneal opacity and corneal ulcer have been reported as ocular manifestations.[26] Amano *et al*. carried out ophthalmologic examinations in 18 Japanese patients with HSAN-IV. They observed superficial punctate keratopathy at the interpalpebral area in 64% and corneal opacity in 8.3% of the examined eyes. Tear breakup time was below the lower limit of the normal range in all of the examined eyes, and the Schirmer 1 test was above the lower limit of the normal range in most of the examined eyes.[27] Accordingly, they recommended care for dry eye, prevention of corneal infection, and daily observation of the ocular surface to maintain good visual function in patients. They also observed the morphology of corneal cells and the sub-basal nerve plexus in patients with HSAN-IV or -V on *in vivo* confocal microscopy, and found lower superficial epithelial cell density and a severe decrease in nerve fibers at the central cornea.[28]

Complications resulting from impaired thermal control

Impaired temperature perception in HSAN-IV and -V, and reduced sweating in HSAN-IV lead to difficulty in thermal control. Rosenberg *et al*. reported that death from hyperpyrexia occurs within the first 3 years of life in almost 20% of HSAN-IV patients.[29] Among 15 Japanese patients who had HSAN-IV and died, hyperthermia was recognized in six before death (Y. Awaya, pers. comm., 2010). We recently encountered an 8-year-old boy with HSAN-IV (he had the *NTRK1* mutation, R548fs) who developed acute encephalopathy with hyperthermia and prolonged convulsion following injection of diphtheria-tetanus-pertussis vaccine (M. Kubota *et al*.; unpubl. data, 2014). The pathomechanism of the development of acute encephalopathy is still unclear.

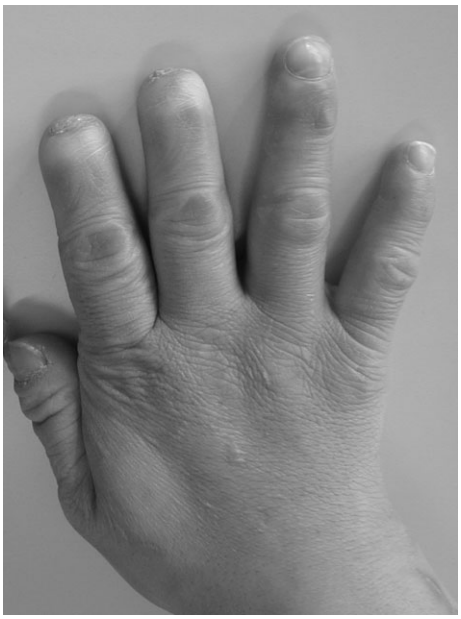

Fig. 4 Digital shortening and nail deficiency in an adult patient with hereditary sensory and autonomic neuropathy type IV.

Anesthetic considerations

Patients with HSAN sometimes need anesthesia to undergo surgery or examination, although they do not feel pain. Tomioka *et al*. carried out a questionnaire study on 45 surgical procedures under general anesthesia for 15 Japanese patients with HSAN-IV. Among them, four patients felt mild headache and nine felt mild abdominal pain. With appropriate temperature management and sufficient perioperative sedation, problems associated with the use of muscle relaxants and malignant hyperthermia did not occur. Two patients experienced postoperative nausea or vomiting, although no patients had clear autonomic nervous system dysfunction. They recommended consideration of the possible abnormalities in the autonomic nervous system.[30] Rozentsveig *et al*. reviewed 40 anesthesia records for 20 patients with HSAN-IV, and reported that cardiovascular events occurred in 15 patients, with one case of cardiac arrest. They recommended that attention should be paid to potential cardiovascular events when managing patients with HSAN-IV.[31]

Other complications possibly related to autonomic dysfunction

Kubota carried out a questionnaire study on 23 Japanese patients with HSAN-IV about sleep-wake rhythm, digestive symptoms, and development of locomotion. All the patients were noted to have muscle hypotonic tendency in the early infancy. Sixteen out of 23 patients had frequent nocturnal awakening (fragmented sleep) and crying at night in infancy, mainly in the summer season, and 14 had various digestive symptoms. All five patients who suffered from cyclic vomiting also had nocturnal waking in infancy, and in four of them, development of crawling was delayed.[32] Generally, sleep–wake rhythm, sleep stages and antigravity locomotion are controlled, at least in part, by the cholinergic and aminergic neurons of the brainstem.[33,34] Sobreviela *et al*. showed that raphe serotonergic neurons coexpressed TrkA in the brainstem.[35] Miyamoto *et al*. showed that integrative function of the serotonergic input to the basal forebrain/preoptic area via the excitatory action of 5-HT_2 receptors plays a critical role in the diurnal regulation of slow wave sleep and night-dominant locomotor activity.[36] We have noted the clinical efficacy of serotonergic modulating drugs including valproic acid, cyproheptadine or tandospirone for the treatment of cyclic vomiting in HSAN-IV patients. Together, although the underlying mechanism in sleep–wake rhythm disturbance, abnormal locomotion and cyclic vomiting is still unclear, some common causal system such as a serotonergic one could be postulated.

Abnormal mental development and behavior

Children with HSAN-IV are mentally retarded and sometimes have symptoms of attention-deficit–hyperactivity-disorder (ADHD), whereas mental and cognitive dysfunctions are rare in

those with HSAN-V. Levy Erez *et al*. examined 23 Arab Bedouin children with HSAN-IV. They found that these children had lower scores in the intelligence test and the adaptive behavior scale compared with their healthy siblings. IQ was significantly higher among children aged up to 7 years than among the older children.[37] In examinations of Japanese children with HSAN-IV, Shirakawa and Nihei found that development is variable in preschool children, and reduced interest in objects, a lack of communication, speech delay, autistic traits, and ADHD symptoms, are often observed. At school age, patients have difficulty in learning the concept of numbers and are weak in arithmetic. In adolescence, most patients have delayed mental development (K. Shirakawa and K. Nihei, pers. comm., 2012).

Guidelines of treatment and care

As mentioned here, the treatment and care for patients with HSAN-IV and -V require a wide range of knowledge and experience, and a multidisciplinary team approach. To provide information for medical specialists based on our knowledge and experience, our group planned and produced the "Guideline of Total Management and Care on Congenital Insensitivity to Pain (Ver.1)" in 2012. This guideline includes not only medical issues, but also descriptions of social participation and welfare. This can be downloaded from MHLW Grant System (http://mhlw-grants.niph.go.jp/) with the literature number 201128072B. Our group also collaborated with the Japanese Patients' and Supporters' Society to produce a book called "Congenital Insensitivity to Pain with Anhidrosis: Our Care Guide", and a DVD called "Congenital Insensitivity to Pain with Anhidrosis: Understanding this Disease and Support the Patients", for patients, families, and caregivers.

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