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Review article

# Hereditary sensory and autonomic neuropathy types 4 and 5: Review and proposal of a new rehabilitation method

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ABSTRACT

Although pain is unpleasant, it should serve as a reminder for individuals to avoid similar damaging incidents in the future. Hereditary sensory and autonomic neuropathy (HSAN) includes genetic disorders involving various sensory and autonomic dysfunctions. They are classified by the mode of inheritance, clinical features, and related genes. HSAN type 4 (HSAN-4) and type 5 (HSAN-5) are characterized by insensitivity to pain and thermal sensation. Further, HSAN-4 is accompanied by decreased sweating and intellectual disabilities. These characteristics of HSAN-4 and -5 result in many clinical features, such as pediatric, psychiatric, orthopedic, oral, dermatological, and ophthalmological problems. Orthopedic problems include destructive injuries such as multiple fractures and joint dislocation. Studies on gait have shown greater speed and higher heel contact angular velocity in HSAN-4 and -5 patients compared with controls. Studies on grasp-lift-holding tasks have shown higher grasp force and fluctuations in acceleration of the object. We believe that these findings represent outcomes of deficient motor learning. We propose a new rehabilitation method for patients with HSAN-4 and -5, with the aim of decreasing their destructive injuries.



**Contents**



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## 1. Introduction

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the International Association for the Study of Pain (Merskey and Bogduk, 1994). Although pain is unpleasant, it is necessary for individuals so that they will learn to avoid similar damaging experiences in the future.

Hereditary sensory and autonomic neuropathy (HSAN) consists of a group of genetic disorders involving various sensory and autonomic dysfunctions. These disorders are classified by the mode of inheritance, clinical features, and related genes (Table 1) (Dyck et al., 1983; Haga et al., 2015; Rotthier et al., 2012; Yuan et al., 2013). HSAN type 4 (HSAN-4) and type 5 (HSAN-5) are characterized by insensitivity to pain and thermal sensation. HSAN-4 (also called congenital insensitivity to pain with anhidrosis) is additionally accompanied by decreased sweating and intellectual disabilities.

In this article, we review the features of, and experimental studies on HSAN-4 and -5, and we discuss the findings regarding motor learning. We also propose a new rehabilitation method for HSAN-4 and -5.

## 2. Epidemiology

Although the prevalence of HSAN-4 and -5 has not been well established, they appear to be very rare, except in a few countries.

For HSAN-4, reports on more than 10 patients have come only from Japan and Israel (Haga et al., 2015; Shatzky et al., 2000). Half of the reported patients were offspring of consanguineous parents (Axelrod, 2002). We have previously collected epidemiological data from Japanese clinicians and estimated the number of Japanese HSAN-4 patients as 1 in 600,000–950,000. The prevalence of the disorders in the collected data showed no gender preference (Haga et al., 2013).

As for HSAN-5, a family from Sweden has been reported (Einarsdottir et al., 2004; Minde et al., 2004). This family had originated from a progenitor, and consanguinity was common in their community. Another report was from the United Arab Emirates regarding five patients with HSAN-5 (Carvalho et al., 2011). In Japan, we have estimated that the number of Japanese HSAN-5 patients is one in 2,200,000–4,200,000 (Haga et al., 2013).

## 3. Cause of the disease

In HSAN-4, mutations in *NTRK1* (*TRKA*) have been reported (Indo et al., 1996). NTRK1 encodes tropomyosin-related kinase A (TrkA), a receptor for nerve growth factor (NGF). TrkA normally exists in the target organs of NGF-dependent neurons. NGF is a neurotropic factor, and interaction between NGF and TrkA is essential for the survival and maintenance of NGF-dependent neurons (Reichardt, 2006). Therefore, patients with HSAN-4 have dysfunctions in NGF-dependent neurons (Indo, 2012).

NGF-dependent neurons include (1) NGF-dependent primary afferents and (2) sympathetic postganglionic neurons in the peripheral nervous system (PNS) (Indo, 2010). NGF-dependent primary afferents are defined as primary afferent neurons with a small diameter, thinly myelinated Aδ fibers, or unmyelinated C-fibers. NGF-dependent primary afferents detect noxious stimuli. They also transmit sensations from the body's interior; this is known as the "interoceptive sense" (Indo, 2009, 2012). The interoceptive system is a homeostatic afferent pathway representing the physiological status of all body tissues, including the mechanical, thermal, chemical, metabolic, and hormonal status of the skin, muscles, joints, teeth, and viscera (Craig, 2002). NGF-dependent primary afferents are therefore responsible for both nociceptive and homeostatic afferent pathways (Indo, 2014b).

Sympathetic postganglionic neurons innervate blood vessels, piloerector muscles, and sweat glands as well as other target organs in the body. These neurons contribute to homeostasis in the body, together with NGF-dependent primary afferents (Indo, 2012, 2014b).

In HSAN-5, mutations in *NGFB* have been reported (Einarsdottir et al., 2004). *NGFB* is the gene encoding the NGF protein. Therefore, patients with HSAN-5 also have dysfunction in the NGF system (Capsoni, 2014).

## 4. Features of HSAN-4 and -5

The main characteristics of HSAN-4 and -5 are insensitivity to pain and impaired thermal sensations. In addition, anhidrosis (loss of sweating), mental retardation, and other symptoms are observed in HSAN-4 and partly in HSAN-5. These characteristics result in many clinical features including pediatric, psychiatric, orthopedic, oral, dermatological, and ophthalmological problems (Haga et al., 2015; Indo, 2014a).

Severity varies among HSAN-4, Swedish HSAN-5, and Arabic HSAN-5 (Table 2) (Capsoni, 2014). In general, HSAN-4 and Arabic HSAN-5 seem to be more severe than Swedish HSAN-5. In Swedish HSAN-5, patients with homozygous NGF mutation seem to be more severe than patients with heterozygous NGF mutation.

In addition, severity varies among individuals. For example, Tomioka et al. reported a patient with HSAN-4 who complained of itching as a sequel to Herpes zoster infection; they suspected that this itching was a symptom of post-herpetic neuralgia (Tomioka et al., 2002). However, Indo noted that patients with HSAN-4 did not experience pain or itching sensations because of a lack of NGF-dependent primary afferents (Indo, 2010).

### 4.1. Pediatric problems

Impaired thermal sensations and anhidrosis lead to hyperthermia (Haga et al., 2015; Indo, 2002, 2014a). In HSAN-4, anhidrosis is present on the trunk and upper extremities in 100% of the patients, but is more variable in other areas of the body (Axelrod, 2002; Ismail et al., 1998). Recurrent hyperthermia is usually the first clinical sign of HSAN-4 and can begin in infancy or early childhood (Swanson, 1963). Febrile convulsions are also observed in patients. Rosenberg et al. reported that death from hyperpyrexia occurred within the first 3 years of life in almost 20% of HSAN-4 patients (Rosemberg et al., 1994). Among 15 Japanese HSAN-4 patients who died, hyperthermia was recognized in six of them (Haga et al., 2015). Therefore, clinicians should be aware of this life-threatening feature.

Swedish HSAN-5 patients were reported to sweat normally and not suffer from repeated fever during childhood (Einarsdottir et al., 2004).

Arabic HSAN-5 children have been reported as not being able to sweat and having no sense of temperature. These children could

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