



**Epidemiology of Hereditary Sensory and Autonomic  
Neuropathy Type IV and V in Japan**

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**ABSTRACT**

Hereditary sensory and autonomic neuropathy (HSAN) refers to a group of rare congenital disorders characterized by loss of pain sensation and other sensory or autonomic abnormalities. Among them, a relatively large proportion of patients with HSAN type IV, which is accompanied by anhidrosis and mental retardation, are reported from Israel and Japan. HSAN type V, with normal sweating and mental development, is rarely reported in Japan. In 2009, we founded a research group for congenital insensitivity to pain and performed the first epidemiological survey of HSAN type IV and V in Japan. Questionnaires were sent to a total of 3488 certified training institutions of five nationwide medical societies comprising pediatricians, neurologists, orthopedic surgeons, and dentists. Answers were obtained from 1610 institutions, and 192 HSAN patients (152 with type IV and 28 with type V) were reported from 105 institutions. After excluding duplicated patients, we identified a total of 62 current, 36 past, and five deceased patients for HSAN-IV, and a total of 14 current, 13 past, and 0 deceased patients for HSAN-V. Using these figures, we estimated that the number of Japanese patients with HSAN type IV and V as 130-210 and 30-60 patients, respectively. We identified no gender differences, and patients with a 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 or older.

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Key words: congenital insensitivity to pain; hereditary sensory and autonomic neuropathy; epidemiology;  
prevalence

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## INTRODUCTION

Congenital insensitivity to pain (CIP) comprises a group of disorders manifesting in a congenital loss of pain sensation that stems from peripheral neuropathy. Dyck and colleagues named these disorders as hereditary sensory and autonomic neuropathies (HSAN), and classified them into type I to V [Dyck et al., 1983; Nagasako et al., 2003]. Recently, HSAN type VI was added to the list [Edvardson et al., 2012]. Among them, type III is most common, with a relatively high incidence of 27 among 100,000 live births is reported for Israel [Maayan et al., 1987]. Several hundred patients with HSAN type IV (HSAN-IV) have been reported [Feldman et al., 2009], but its prevalence has not been estimated. Other types are considered less common.

HSAN-IV, also called congenital insensitivity to pain with anhidrosis (CIPA), is an autosomal recessive disorder manifesting in a generalized loss of pain and thermal sensation, a lack of sweating, and is associated with variable degrees of mental retardation and/or learning deficits. CIPA results from loss-of-function mutations in the *NTRK1* gene encoding TrkA (tropomyosin-related kinase A), a receptor tyrosine kinase for nerve growth factor (NGF) [Indo et al., 1996]. Articles written in English on more than 10 patients are only from Israel [Shatzky et al., 2000] and Japan [Amano et al., 1998; Amano et al., 2006; Iijima et al., 2010]. Although additional case reports indicate a relatively high prevalence of CIPA among the Japanese population [Hasegawa et al., 1990; Hiura et al., 2002; Ishii et al., 1988; Iwanaga et al., 1996; Ohto et al., 2004; Okuno et al., 1990; Uehara et al., 2001; Yotsumoto et al., 1999], no epidemiological study of CIPA in Japan has been conducted to date.

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4 Similarly, the prevalence of HSAN-V amongst the Japanese population is unknown, with only one  
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7 English article reporting a Japanese patient with HSAN-V was found [Miura et al., 2008]. HSAN -V is also  
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10 an autosomal recessive disorder characterized by a loss of pain and thermal sensation. Contrastingly,  
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13 sweating and mental development are usually normal in these patients. In northern Sweden, a large family  
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16 with six members affected by HSAN-V has been reported, with mutations in the *NGFB* (nerve growth  
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19 factor, beta subunit) gene detected [Minde et al., 2004].

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21 In 2009, we founded a research group for CIP in Japan to establish treatment and support guidelines for  
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24 HSAN-IV and V. We chose these two conditions because members of this group had experienced  
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27 diagnosing and treating many patients with these two types and only a few with other types of HSAN. The  
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30 purpose of this study is to reveal the epidemiological data on the Japanese patients with HSAN-IV and V.  
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## 36 MATERIALS AND METHODS

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39 The present research included a questionnaire that was sent to pediatricians, neurologists, orthopedic  
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42 surgeons, and dentists who were believed to deal with CIP patients. Questionnaires were sent to a total of  
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45 3488 certified training institutions of the Japan Pediatric Society (520 institutions), the Japanese Society of  
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48 Neurology (734 institutions), the Japanese Orthopaedic Association (1994 institutions), the Japanese  
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51 Society of Pediatric Dentistry (47 institutions), and the Japanese Society for Disability and Oral Health  
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54 (193 institutions, excluding duplication with those of Japanese Society of Pediatric Dentistry). These  
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57 questionnaires were sent in November and December 2009, and the answers were gathered and analyzed in  
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7 The questionnaire included the experiences of examining or treating patients with HSAN-IV and V. The  
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10 diagnosis was based on the clinical findings, physiological tests, and sometimes nerve biopsy and/or gene  
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13 analyses. Because we did not ask which of these the diagnosis of each patient was based on, we could not  
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16 find out how many patients had molecular confirmation of the diagnosis. If the institution had experiences  
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19 with these patients, the questionnaire asked the initials of the patient's name, gender, date of birth, the  
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22 prefecture where the patient lives, and the presence or absence of a family history of the disorder.

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24 Physicians were also asked to detail the status of the patients with respect to the clinic: current patients,  
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27 past patients (those no longer attending the clinic), and deceased patients.

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30 This study was approved by the Ethics Committee, Faculty of Medicine, The University of Tokyo, Japan  
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33 (approval number 2769).

## 34 35 36 37 38 **RESULTS**

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41 Of the institutions targeted for our study, 1610 institutions answered the questionnaire, providing an  
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44 answer rate of 46.2%. Of these, 105 institutions reported the identification of 192 patients with HSAN-IV  
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47 or V, among which 152 patients were characterized as having HSAN-IV, and 28 patients with HSAN-V  
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50 (Table 1). Twelve patients with unknown diagnoses were excluded.

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53 To avoid patient duplication, we determined patients with overlapping demographic details: the same  
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56 initials, gender, date of birth, and the place of residence. After exclusion of suspected duplications, a total  
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4 of 62 current, 36 past, and five deceased patients were identified for HSAN-IV. For the five deceased  
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7 patients, the ages at death were 1, 2, 7, 18, and 22 years. For HSAN-V, a total of 14 current, 13 past, and 0  
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10 deceased patients were identified.

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12 To estimate the number of patients in Japan, we set the minimum number of patients by dividing the  
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14 number of current patients by the answer rate of the questionnaire and the maximum number by dividing  
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16 the sum of the current and past patients by the answer rate of the questionnaire. These results led to  
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18 estimations of 130-210 patients with HSAN-IV, and 30-60 patients with HSAN-V. Using the Japanese  
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20 population statistics from 2010 of approximately 127,522,000 people, we calculated the prevalence of  
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22 HSAN-IV and V as 1 in 600,000-950,000 and 1 in 2,200,000-4,200,000, respectively.  
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30 For the current patients, we analyzed patient gender, heredity, and age distribution at the time of the  
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32 questionnaire. Patients with HSAN-IV included 27 males and 35 females; patients with HSAN-V included  
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34 eight males and five females (the gender of one patient was not described). No apparent gender difference  
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36 existed in both HSAN-IV and V. Fifteen out of 46 patients with HSAN-IV, and seven out of 14 patients  
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38 with HSAN-V had a positive family history for the disorder, all of whom were siblings, including several  
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40 sets of twins. As for the age distribution (Figure 1), most patients with HSAN-IV were under 40 years,  
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42 with those under five years of a relatively smaller number. Comparatively, the age distribution of patients  
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44 with HSAN-V was relatively equal, with half of them aged 40 years or older.  
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## 56 DISCUSSION

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4 This study describes the prevalence of Japanese patients with HSAN-IV and V as 1 in 600,000-950,000  
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7 and 1 in 2,200,000-4,200,000, respectively. While these figures are small, the estimated number of  
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10 130-210 HSAN-IV patients from institutions across Japan seems large considering the number of reported  
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12 patients from non-Israeli and non-Japanese populations.  
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15 Mutation in the *NTRK1* and *NGFB* genes are linked with HSAN patients who had consanguineous  
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17 parents and in families with a history of consanguineous marriages [Minde et al., 2004, Shatzky et al.,  
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19 2000]. The present results reported that the family history only consisted of affected siblings, which is  
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21 consistent with the autosomal recessive inheritance of HSAN-IV and V; however, the consanguinity in the  
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23 family was not asked in our questionnaire. Though Japanese may have higher frequency of *NTRK1*  
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25 mutation, more precise investigation of pedigrees in Japanese patients is mandatory. An article from  
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27 Sweden reports a pedigree in which patients with heterozygous mutation of *NGFB* shows a milder  
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29 phenotype of HSAN-V [Minde et al., 2004].  
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39 The age distribution of patients may be affected by the age at diagnosis, follow-up conditions, and the  
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41 life expectancy. In HSAN-IV, the relatively small number of patients under the five years of age indicates  
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43 the difficulty of diagnosis in young patients. It is unknown if the decline in patient numbers after adulthood  
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45 is caused by decreased visits to a medical facility or shorter life expectancy, although the reported ages of  
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47 death in this study indicates a shorter life expectancy for these patients with HSAN-IV. In HSAN-V, the  
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49 lack of such a decline in adult patient numbers suggests a longer life expectancy for these patients.  
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56 The diagnostic criteria for both HSAN-IV and -V have not been established. As such, this study was  
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4 limited by the diagnoses based on the clinical findings, physiological tests, and sometimes nerve biopsy  
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7 and/or gene analyses from institutions across Japan. In addition, Carvalho and colleagues recently  
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10 identified a homozygous loss-of-function mutation in the *NGFB* gene in a consanguineous Emirati  
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12 Bedouin family with lack of pain sensation, mild mental retardation and anhidrosis [Carvalho et al., 2011].  
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15 This finding indicates the phenotypic overlap between HSAN-IV and V due to changes in the NGF/TRKA  
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18 signaling pathway and may indicate further difficulty in accurately diagnosing patients with these  
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21 disorders.  
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24 There are various methods to estimate a prevalence of a rare disorder. One of such methods is the  
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27 protocol established by the Research Committee on the Epidemiology of Intractable Diseases funded by  
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30 the Ministry of Health, Labour and Welfare of Japan [Kawamura et al., 2006]. This protocol recommends  
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33 sampling hospitals to which questionnaires are sent, and asking the presence of patients during a limited  
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36 term of years in the preliminary screening. In preparation for the present research on HSAN-IV and V, we  
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39 estimated that the number of patients would be extremely small and each patient could be visiting multiple  
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42 clinical departments in different large hospitals. So we did not follow the above-mentioned protocol, but  
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45 sent questionnaires to certified training institutions of medical societies comprising pediatricians,  
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48 neurologists, orthopedic surgeons, and dentists. We also tried to gather information on all current and past  
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51 patients, and exclude duplicated reports.  
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53 In conclusion, the present study revealed estimations for the number of Japanese patients with HSAN-IV  
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56 and V. We identified no gender differences and noted that patients with a family history of the disorder  
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4 were limited to affected siblings for both conditions. Most patients with HSAN-IV were 5-40 years of age,  
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7 whereas half of the patients with HSAN-V were 40 years or older.  
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21 the Health and Labour Sciences Research Grants for Research on Intractable Diseases, the Ministry of  
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24 Health, Labour and Welfare.  
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27 The authors declare that they have no conflict of interest with regard to this study.  
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For Peer Review



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5 **Figure Legends**  
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11 **Figure 1: Age distribution of patients.**  
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14 Black bar indicates patients with HSAN-IV and white bar indicates patients with HSAN-V.  
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17 One patient with HSAN-IV and two with HSAN-V with unknown ages are not included in this graph.  
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Table 1. Raw results of the questionnaire according to the medical department

	Pediatrics	Neurology	Orthopedics	Dentistry	Total
Questionnaires sent	520	734	1994	240	3488
Questionnaires answered	257	312	919	122	1610
Answer rate (%)	49.4	42.5	46.1	50.8	46.2
Institutions with patients	28	7	51	19	105
Total No. of patients	44	7	86	55	192
No. of HSAN-IV patients	31	1	70	50	152 (62 / 36 / 5)*
No. of HSAN-V patients	8	6	12	2	28 (14 / 13 / 0)*
No. of unknown diagnosis	5	0	4	3	12

\*: Figures in the parentheses indicate the actual numbers of the current / past / deceased patients after excluding suspected duplication of patients.

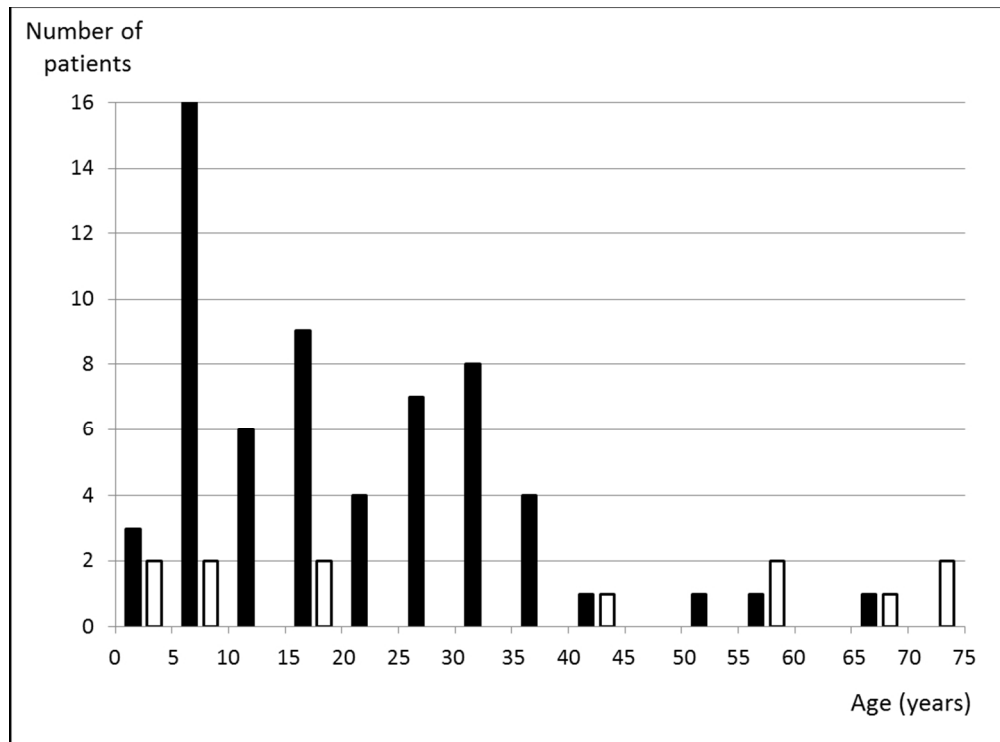


Figure 1: Age distribution of patients.  
 Black bar indicates patients with HSAN-IV and white bar indicates patients with HSAN-V.  
 One patient with HSAN-IV and two with HSAN-V with unknown ages are not included in this graph.  
 184x136mm (150 x 150 DPI)

Review