*Original Article*

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# The natural history of hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) in 97 Japanese patients

**Natsumi Fujisaki[1], Shugo Suwazono[1,2,*], Masahito Suehara[3], Ryo Nakachi[1], Miwako Kido[1], Yoshihisa Fujiwara[1], Saki Oshiro[1], Takashi Tokashiki[1], Hiroshi Takashima[4], Masanori Nakagawa[5]**

[1] *Department of Neurology, National Hospital Organization Okinawa National Hospital, Ginowan, Japan;*
[2] *Center for Clinical Neuroscience, National Hospital Organization Okinawa National Hospital, Ginowan, Japan;*
[3] *Department of Neurology, Fujimoto General Hospital/Fujimoto Medical System, Miyakonojou, Japan;*
[4] *Department of Neurology and Geriatrics, Kagoshima University, Graduate School of Medical and Dental Sciences, Kagoshima, Japan;*
[5] *North Medical Center, Kyoto Prefectural University of Medicine, Kyoto, Japan.*

**Summary** **Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) is a motor and sensory neuronopathy with autosomal dominant inheritance, adult onset, slowly progressive course, and is associated with *TRK-fused gene* (TFG) mutation. At advanced stages, respiratory failure and dysphagia becomes life-threatoning, and patients typically die by their 70s. Although there is currently no evidence for effective treatment, a therapy may be found by elucidation of the function of TFG. Recently its pathomechanism has been proposed to be associated with abnormalities in protein transfer from the endoplasmic reticulum. Such pathomechanisms might involve a similar process in amyotrophic lateral sclerosis; thus, its pathomechanisms and treatment strategy might make it a good model for neurodegenerative disorders. It is of great value to clarify the natural history of HMSN-P, in oder to judge the treatment effect. By evaluating 97 patients (79 out of 97 were examined and all confirmed with p.Pro 285 Leu mutation) in this study, it was confirmed that this disease follows a uniform course in the earlier stages, and there are individual differences in the onset between 20 and 30 years. Such uniformity might be due to the proposed single gene abnormality. At advanced stages, there are larger individual differences in the progression, but the reasons for these are unknown. Longer survival might be achieved with a better care for respiratory failure and dysphagia if such cares were undertaken at appropriate times.**

***Keywords:*** HMSN Okinawa type, natural history, TRK-fused gene

## 1. Introduction

Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN Okinawa type; HMSNO, OMIM # 604484, or HMSN-P used in the first detailed report (*1*), and this report uses the term HMSN-P) is a slowly progressive disease with autosomal dominant inheritance and adult onset. It is fatal and leads to a condition requiring support for swallowing/respiration in the 50s, which is more than 20 years after the first symptomatic painful muscle spasm. When patients present initial symptoms at around their late 30s, they have often had children. Thus, the disease passed to the next generation very easily.

Symptoms usually start with painful muscle cramping of limbs/trunk in the patients' 30s to 40s, followed by muscle weakness dominated by limb proximal muscles, and accompanied by elevated creatine kinase (CK) values (*2*). After their 50s,

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**Address correspondence to:*
Dr. Shugo Suwazono, National Hospital Organization Okinawa Hospital, 3-20-14, Ganeko, Ginowan, Okinawa 901-2214, Japan.
E-mail: zvb10512@nifty.ne.jp

swallowing/respiratory dysfunction could be a life-threatoning problem (*2*). Although HMSN-P is often compared with familial amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), there are features that differ from ALS or SMA, such as disappearance of the deep tendon reflex and obvious electrophysiological abnormalities of sensory nerve action potentials from early stages of the disease (*1,2*). Clinical diagnosis of HMSN-P has been conducted based on such characteristic clinical findings, detailed family history, and laboratory findings including blood examination and electrophysiological tests.

Since TRK-fused gene (TFG) was identified as a gene related to the cause of HMSN-P in 2012 (*3*), HMSN-P patients having the same mutation have been reported in several regions of the world (*4-6*), but the disease with the TFG p.Pro 285 Leu mutation is documented only in patients with HMSN-P. On the other hand, another TFG mutation, that is different from the mutation found in HMSN-P, has been reported in ALS patients (*7*). The relationship between TFG and motor neuron degeneration has been discussed, and the possibility of treating motor neuron disease has been suggested (*7*), drawing attention widely from the neurodegeneration research field. In 2016, p.Gly269Val was reported as a second genetic mutation of HMSN-P (*8*), which is identical to the mutation found in autosomal dominant Charcot-Marie-Tooth disease Type 2 (CMT2) families (*9*). Careful consideration and further examination will be needed to determine whether the phenotype differs between two different mutations within a gene.

Recent studies on TFG abnormalities involved in the pathomechanisms of HMSN-P have suggested impaired protein transfer from the endoplasmic reticulum (ER) to the Golgi body due to the localization of the product protein. Although induced pluripotent stem cells have also been prepared and proteasome disorders were also described (*10*), detailed mechanism that specifically causes nerve cell degeneration is still unclear. There are many diseases that may be involved in ER stress, and ALS may be involved in the same way (*11*). HMSN-P could serve as a disease model in which the causative gene mutation is clear and may contribute to the elucidation of the pathomechanisms of many neurodegenerative diseases.

Under these circumstances, it is important to clarify the natural history of HMSN-P in order to better maintain the patient's quality of life, predict the prognosis of each case, and consider new treatments that will become available in the future. It is difficult to describe the whole disease course because of its length, therefore, there are few reports focusing on clinical status at advanced stages in which swallowing/respiratory abnormalities affect the clinical course.

We reviewed the detailed clinical course from more than 130 cases from 28 families of HMSN-P patients in the medical records at our hospital during a 30-year period, and tried to clarify the characteristics of the clinical course of HMSN-P, particularly the long-term disease progression.

## 2. Materials and Methods

In National Hospital Organization Okinawa National Hospital (Okinawa hospital), among more than 130 patients examined as HMSN-P since 1980, the clinical course of 97 patients whom we could confirm detailed medical records retrospectively were evaluated (a typical family tree is presented on Figure 1). Evaluation items were as follows: age at first visit, symptom onset age (regardless of subjective or objective) for painful muscle spasm, upper and lower limb muscular strength, sense, standing, walking, swallowing, respiration, age at death, the CK value at the first visit, and the type of TFG mutation. For the analysis of the advanced stage, we confirmed the onset/start age of dysphagia, respiratory failure, tube feeding and tracheotomy, age of death, and situation at the time of death (presence of tube feeding/tracheostomy, cause of death). We summarized the age at which each symptom was first recognized (Figure 2). The ratio of the number of the patients with each symptom at each age (every 5 years) to the total number of patients was calculated (Figure 3). The onset age of each symptom in each case that was confirmed for respiratory failure, tracheostomy, dysphagia, tube feeding and death was further examined especially in the advanced stage after age 50 (Figure 4). The age at first visit and the CK values measured at that visit were examined (Figure 5).

This study was discussed and approved by the ethics committee at Okinawa Hospital (# 29-8).

## 3. Results

An example of a family tree of HMSN-P (Figure 1) shows more than half of the brothers and sisters were afflicted and the penetration rate is high. Similar penetration rates are found in other families in this study. The progression details of 55 men and 42 females were analyzed. TFG mutation was confirmed in 79 cases (81.4%), all of which were p.Pro 285 Leu. Genetic testing was not possible in all cases because 5 patients died before the test, 9 patients moved to different hospitals, 2 could not be examined due to sample defect, and 2 patients dropped out before the exam. The average of age at the initial visit was 49.1 years, and the median was 48.5 years (17-74 years). The median of each symptom was 38.0 years (13-59 years) for painful muscle spasm, 47.0 years (25-60 years) for muscle weakness in upper limbs, 48.0 years (31-60 years) for muscle weakness in lower limbs, 50.0 years (40-68 years) for sensory disturbance, 53.0 years (43-69 years) for inability to stand, 58.0 years (44-74

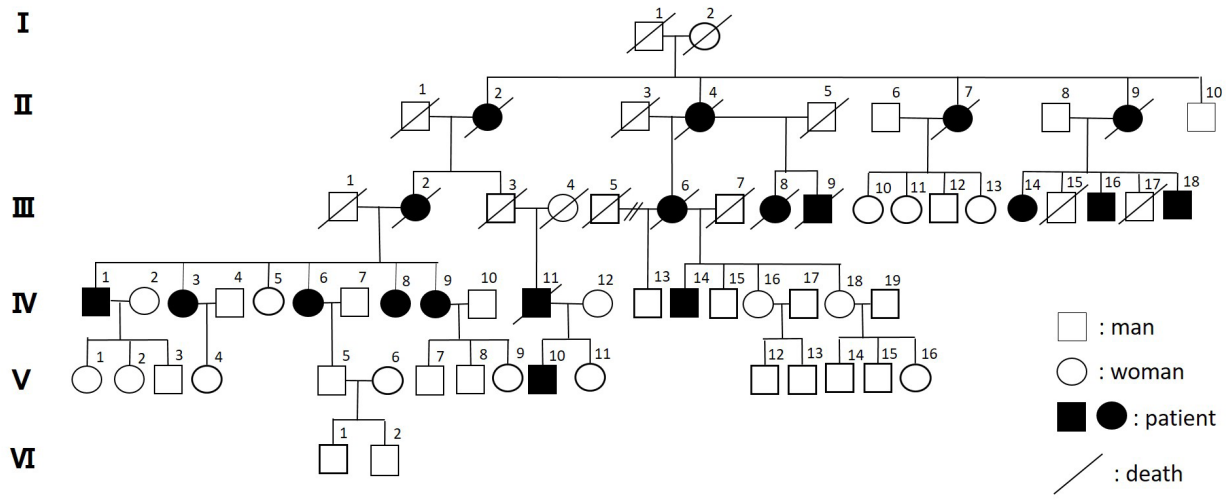


**Figure 1. A family Tree of HMSN-P.** Autosomal dominant inheritance is shown.

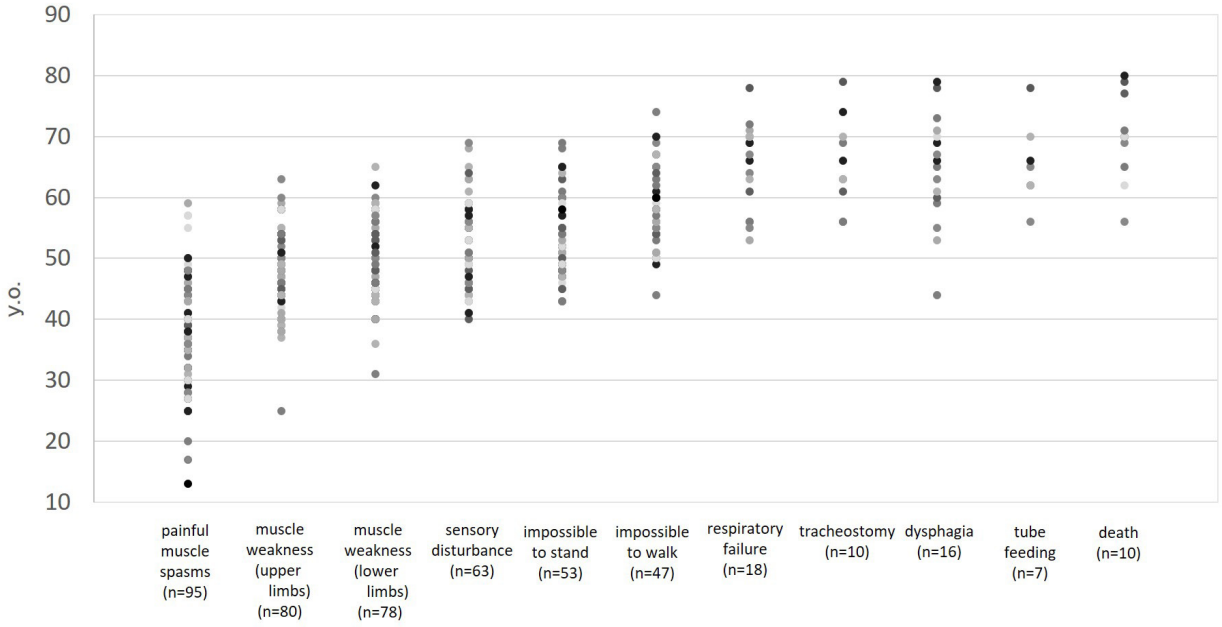


**Figure 2. Natural history of HMSN-P.** There is a specific order in the appearance of symptoms. There are individual differences in the period of disease onset between 20 and 30 years.

years) for inability to walk, 66.5 years (53-78 years) for respiratory failure, 64.5 years (56-79 years) for tracheostomy, 65.5 years (44-79 years) for dysphagia, 65.0 years (56-78 years) for tube feeding, and 70.0 years (56-80 years) for death (Figure 2 and Figure 3). There was a specific order to the appearance of symptoms (Figure 2). There are individual differences in the period of symptoms appearing between 20 and 30 years.

We further analyzed the disease progression at later stages as shown in Figure 4. There were 21 advanced stage patients who had impaired swallowing and respiration (Figure 4). Among them, 10 patients underwent tube feeding and tracheostomy; 3 had tracheotomy only, 0 had tube feeding only and 7 had both. Five patients had both tracheostomy and tube feeding at the same time or within one year. However, 3 patients, who had have been admitted for a long time in Okinawa hospital due to respiratory disturbance and had tracheotomy and respiratory management done soon after the occurrence of the problems, could extend the period with possible oral intake from 2 to 6 years after the tracheostomy. One patient died without tube feeding. Another patient, followed at a different clinic, was still orally ingestible even 7 years after tracheotomy. The death age was confirmed in 17 patients, including those who died at other hospitals. In 10 patients, the cause of death was aspiration/pneumonia or respiratory failure due to sudden deterioration of unexpected respiratory condition. Seven patienss died due to other causes: acute myocardial infarction ($n$ = 2), cancer ($n$ = 2), cerebral infarction ($n$ = 1), postoperative septicemia ($n$ = 1), and

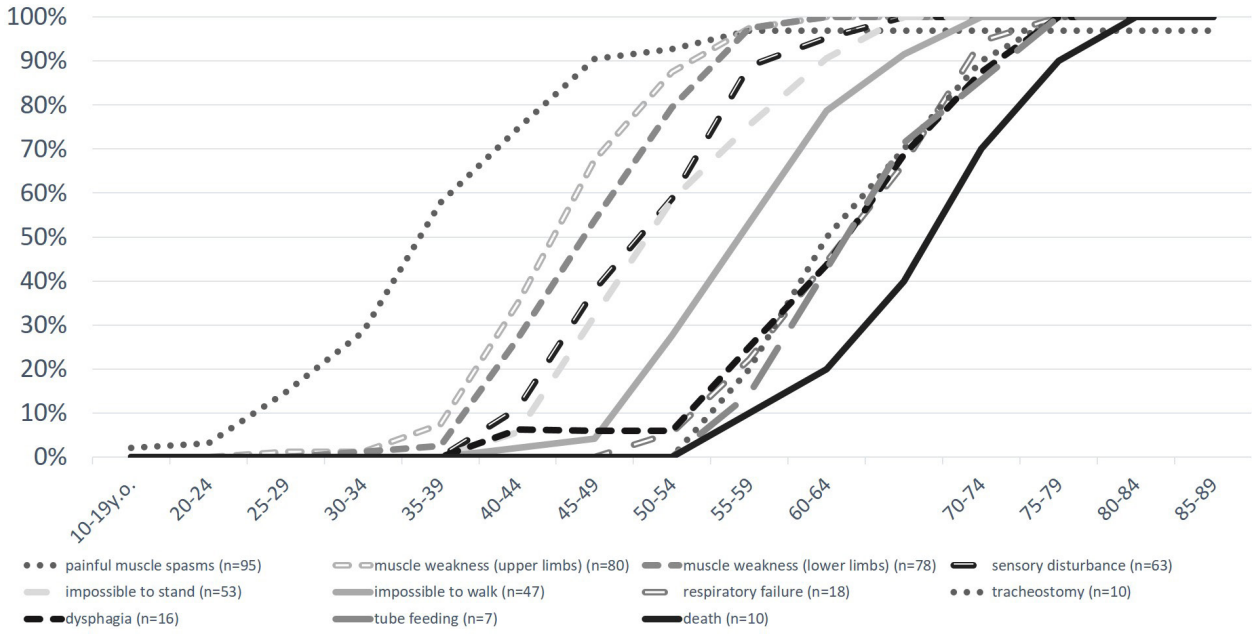


**Figure 3. Natural history of HMSN-P.** Observed symptom frequency in 5 bins (see Materials and Methods for calculation). Dysphagia and breathing disorders begin to increase after the patients' 50s.

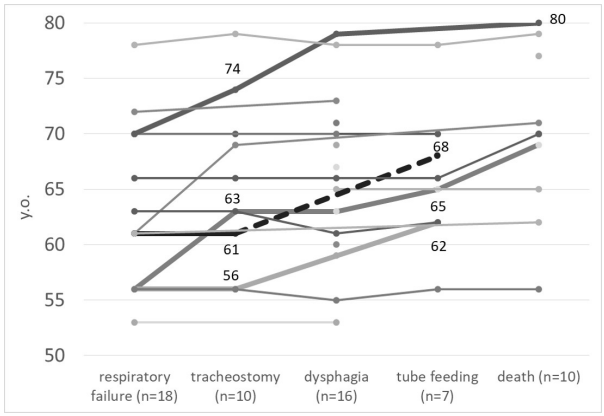


**Figure 4. Natural history (advanced stage).** Natural history of several cases with detailed course information at advanced stages.

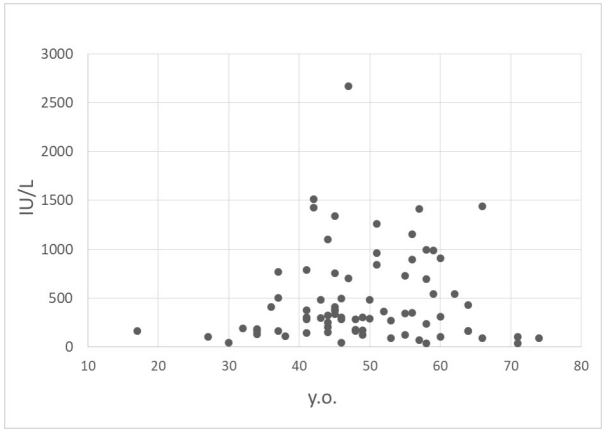


**Figure 5 CK value (first visit).** The CK value tends to be high in the 40s and 50s, and decrease from the late 50s when walking becomes impossible.

unknown cause ($n$ = 1).

Painful muscle spasms that appears early in the disease tended to decrease at later stages. Three out of 97 cases did not show painful muscle spasm during the entire course. CK also tended to decrease after the age of 60 (Figure 5).

## 4. Discussion

Disease progression, in terms of the order of the appearance of each symptom, is usually variable within a neurodegenerative disease entity, including Alzheimer disease, ALS, and Parkinson's disease. However, the current study confirmed that the clinical course of HMSN-P is extremely uniform with slow progression, *i.e.*, the order of symptom appearance is almost identical in every patient for long after the onset (Figure 2 and Figure 3), although the onset age varied 20-30 years. This fact might be attributed to the proposed pathophysiological mechanisms that HMSN-P is caused by single gene abnormality. As a disease model for neurodegenerative disorders of protein metabolism failure based on a single gene abnormality, HMSN-P provides a suitable example with some hope to plan treatment strategies.

Recently many interesting observations are accumulating about the role of TFG protein, which belongs to the coat protein complex II transportation system from the endoplasmic reticulum (ER) to the ER-Golgi intermediate compartment (ERGIC), and plays a very important role in maintaining the efficacy of the vesicles (*12*), in various areas of basic cellular biology

(*13*), insulin metabolism (*14*), and in a discussion of future cancer therapy (*15*). It is very important with this background to shed lights on the detailed clinical facts and the natural history in patients with HMSN-P.

In 2016, p.Gly269Val was reported as a second genetic mutation of HMSN-P (*8*), which is identical to the mutation found in autosomal dominant Charcot-Marie-Tooth disease Type 2 (CMT2) families (*9*). Although careful consideration and further examination will be needed to determine whether the phenotype differs between two different mutations within a gene, the clinical manifestation in their reports might be different from our experience on HMSN-P.

The factors causing individual differences in disease onset could not be elucidated in the current study. It has been reported that HMSN-P patients have many complications of diabetes and dyslipidemia (*1*), and the treatment of such complications may change the clinical course. Since the effects of those factors on the survival rate were not analyzed in this survey, differences in prognosis due to the presence or absence of those complications are subjects for the future analysis.

Another feature of the current study is the detailed clinical descriptions of the advanced stage of HMSN-P. The life-threatening risks for the patients with advanced stage HMSN-P may be comparable to those for the patients with ALS. However, because HMSN-P progresses more slowly than ALS, the period for which careful attention to risk management is needed can be much longer than that for ALS. It is necessary to carefully observe symptom progressions of HMSN-P patients from the age of 50, when fatalities begin to increase due to impaired swallowing and respiration (Figure 3).

Compared to the circumstances for the patients 30 years ago when the HMSN-P study was initiated, many medical situations have dramatically changed, including managements of nutrition and respiratory failure, owing to development of medical technology and equipment. The clinical course of HMSN-P may be further improved by providing advanced medical treatment with higher quality and developing new treatments in the future. Today, if a patient visits the hospitals, the swallowing/respiratory state can be regularly evaluated, and tracheotomy and tube feeding can be performed at an appropriate time if needed. It is noteworthy that there exist HMSN-P patients who can survive beyond the age of 70 if optimal care is provided with optimal timing. This fact also suggests that providing detailed and precise information about natural history is crucial for optimal treatment for patients with HMSN-P.

When the current study was began, we expected that swallowing/respiration problems progress in this order; breathing earlier and swallowing later. However, there was no clear difference of the start time of disability between these two. This is one of the limitations of the current study. One possible explanation for this is that as symptoms progressed and activity of daily life declined, many patients had difficulty visiting the hospital, so they were changed to home care, or entered nursing home facilities. It could then be difficult to have a precise evaluation at such nursing homes.

At motor function declines in the advanced stages, some patients have fewer chances to walk, and they do not report particular problems of respiratory systems while resting. Some patients experienced "sudden" respiratory episodes (*e.g.*, sputum blocks, aspiration), following a very slight physical condition change like catching cold or mild dehydration. After such events, some patients deteriorated to a condition in which they needed to receive advanced respiratory care including tracheostomy. It is noteworthy that in advanced stages, the condition (especially respiratory function) easily deteriorates. Therefore, regardless of the presence or absence of subjective symptoms, regular respiratory function checks are highly recommended starting when patients are in their 50s. For swallowing, it is necessary to establish a better evaluation routine utilizing, for example, videofluorography or videoendoscopy for swallowing.

Clinical reports focusing on disease progression based on many patients with HMSN-P have not yet been published. The current survey provides detailed information that can be widely provided to patients and families who traditionally get information only from their relatives privately.

## 5. Conclusion

We surveyed medical records in detail from 97 patients with HMSN-P. Disease progression, in terms of the order of the appearance of each symptom, is extremely uniform with slow progression, *i.e.*, the order of symptom appearance is almost identical in every patient for long after the onset, although the onset age varied 20-30 years. At the later stages, the disease progression and prognosis varied among patients, and its reason is unknown yet. As a disease model for neurodegenerative disorders caused by protein metabolism failure at the ERGIC zone based on a single gene abnormality, HMSN-P may provide a suitable example to develop treatment strategies.

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