International Journal of Health Sciences
Available online at www.sciencescholar.us
Vol. 8 No. 3, December 2024, pages: 334-340
E-ISSN: 2550-696X
https://doi.org/10.53730/ijhs.v8n3.15252

Brief communication participation in social activities of six individuals with advanced-stage hereditary motor sensory neuropathy with proximal dominant involvement (HMSN-P)

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Manuscript submitted: 18 Aug 2024, Manuscript revised: 9 Sept 2024, Accepted for publication: 15 Oct 2024

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Keywords

hereditary motor sensory neuropathy with proximal dominant involvement;
HMSN-P;
motor neuron disease;
social activity;
welfare service system;

Abstract

The intractable neurological disease HMSN-P (hereditary motor and sensory neuropathy with proximal dominant involvement) includes four-limb paralysis and resembles amyotrophic lateral sclerosis (ALS). Although the long-term employment and social activities of individuals with severe neurological diseases have increased with improvements in medical/welfare services, those of individuals with HMSN-P have not been reported. We analyzed the long-term outcomes of six individuals with advanced-stage HMSN-P treated in 2018–2023; one exhibited proximal dominant quadriplegia in 2018 and was using an electric wheelchair with full assistance. He had continued to attend *Sanshin* concerts for 5 years and organized a music festival for the local handicapped population. The other patients similarly exhibited quadriplegia; three were using electric wheelchairs with full assistance, and two were using pushchairs. Four attended music festivals for the handicapped, and all have completed 20–35 years' continuous employment, attended public meetings about HMSN-P, and actively participated in the meetings' discussions.

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Contents

1 Introduction

The long-term employment and social activities of many individuals with severe neurological diseases have both increased in recent years with the improvements in their medical and welfare services. Among the neurological diseases, Okinawa-type neurogenic muscular atrophy, which is also known as hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P), has shown autosomal dominant inheritance with a *tropomyosin-receptor kinase* (*TRK)-fused gene* (TFG) pGly269Val missense mutation on chromosome 3 and muscle atrophy that is predominant in proximal muscles. HMSN-P is slowly progressive over ~30 years; at the terminal stage, individuals with HMSN-P require respiratory equipment (Takashima et al. 1997, Ishiura et al. 2012, Fujisaki et al. 2018). The term 'HMSN-P' is used in Japan but also in Brazil, Italy, India, South Korea and other countries (Nakagawa, 2009, Fabiniak et al., 2023).

Regarding the increased participation of individuals with neurological diseases in society, it is notable that an individual with amyotrophic lateral sclerosis (ALS), Mr. Yasuhiko Funago, was elected to Japan's House of Councilors in 2019 (Funago, 2019); his statements in the assembly have been provided by his representatives through eye-movement dialogue. In addition, Ms. Saou Ichikawa, who has congenital myopathy and uses respiratory equipment with total assistance, received the *Akutagawa Prize* literary award in 2023 for her novel *Hunchpack* (Ichikawa, 2023).

We conducted the present study to analyze the long-term outcomes of six individuals with advanced-stage HMSN-P who were treated in 2018–2023 in Okinawa, Japan. We determined each individual's onset age, job(s), social activities, major symptoms, use of assistive device(s), and complications. As an example, a representative of the HMSN-P Society who uses full assistance, Mr. Seiken Ganeko, organized the yearly *Anela* Music Festival Okinawa (for handicapped individuals) from 2014 to 2021, calling on people with disabilities to "love music and join society." He has also lobbied for progress and funding in HMSN-P research.

In 2023, our research group identified and described painful muscle cramps including abdominal regions as a specific early symptom in HMSN-P (Shoji et al., 2023). The present article is our response to an invitation from *International Journal of Health Sciences* to produce a short summary of that paper.

2 Materials and Methods

We enrolled six patients with advanced-stage HMSN-P (three pedigrees) who were examined at *Anela House* in Okinawa during the period April 2018–March 2023 in this study, and we analyzed their jobs, social activity, major symptoms, assistive device use, and complications. The study was conducted in accord with the principles of the Declaration of Helsinki and was approved by our Hospital's Ethics Committee (approval no. 24-0801).

Figure 1 depicts the pedigree of Patients 1 and 2. Many of their descendants, especially the fourth generation, have not yet shown symptoms and have not undergone genetic testing. Nevertheless, they face both the possibility of the onset of HMSN-P and the present lack of specific treatments for this disease.

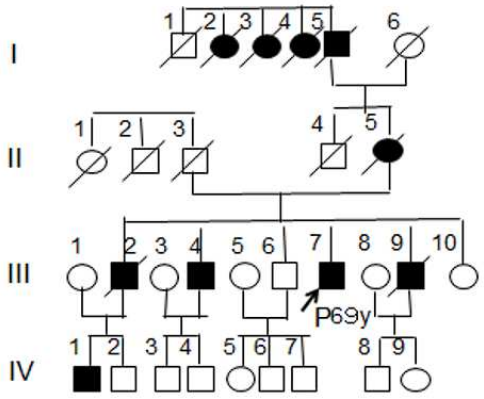

Figure 1. The hereditary motor and sensory neuropathy with proximal dominant involvement (HSMN-P) appeared over two generations and showed autosomal dominant inheritance, maternal founder. III-7 (Proband; Patient 1) has six siblings, and III-2 (the eldest brother of Patient 1) and III-9 (the younger brother) died in their 60s from different illnesses. *Squares* represent males and *circles* do females, *oblique slash*: death, *filled symbol* mean affected person with HMSN-P.

3 Results and Discussions

Table 1
Clinical characteristics of six patients with advanced-stage HMNS-P (n=6)

Age, yrs; mean±SD, gender	69.3 ± 2.1 yrs 3 males, 3 females
Onset age of limb weakness, yrs mean±SD (range)	43.8 ± 9.1 (30-65)
Major symptoms Prox. quadriplegia Dyspnea Dysphagia	 6 1 1
Employment,yrs, mean±SD (range) Construction, Nurse, Driver, Deli	28±6.7 (20-40)
Assistive devises Cane,Walker Elect. Wheelchair Respirator	 2 4 1
Degree of physical disability Level 1,or 2	 5
Social activities *Sanshin* concert, yrs Representive of HMSN-P Society Attendance of public meeting	 1 (5yrs) 1 (10yrs) 4
Complications Hypertension Hip & foot fracture Diabetes Hyperlipidemia	 3 3 1 1

HMNS-P= hereditary motor sensory neuropathy with proximal dominant involvement

Table 1 summarizes the six patients' employment, major symptoms, social activities, and complications. The patients (three males, three females) were aged 69.3 ± 2.1 years (mean ± SD); the mean age at the onset of HMSN-P was 43.8 ± 9.1 years. All six patients' results were positive on the genetic test for *TFG-fused gene* mutation. They had held occupations such as nurse, driver, and construction, and they left their jobs when they were in their late 50s–60s. Four of the patients were at physical disability level 1 and one patient was at level 2; the level of the remaining patient was uncertain.

Among the six patients, proximal predominant quadriplegia with sensory impairment was present in their four limbs; four patients used an electric wheelchair and full assistance, and two patients used a cane or pushchair. Full assistance care was provided by Japan's 'severe nursing care' insurance level 4 or 5. Compared to individuals with related diseases such as ALS, spinal and bulbar muscular atrophy (SBMA), or Charcot-Marie-Tooth disease (CMT), the distal upper-limb muscle strength is preserved in people with HMSN-P, and thus individuals with HMSN-P can continue working in office jobs and participating in social activities for relatively long periods of time (Shoji et al., 2023).

We next provide the details of each of the patients.

Patient 1

A 69-year-old male. At age 30, he noticed muscle cramps in calf-to-abdominal areas. He was diagnosed with HMSN-P at age 40, and at age 61 (in 2017), he became a representative of an HMSN-P patient association. At that time, his brain function, speech, and swallowing were normal. He required 10 hr/day total assistance by helpers, but he continued to attend five yearly *Sanshin* concert activities in Tokyo, Osaka, and Okinawa. He organized a music festival for handicapped individuals in February 2020, and in December 2021, his fingertips' strength was maintained and he could use a smartphone freely.

A robot-suit hybrid assistive limb (HAL) was intermittently used for mainly his upper limbs for 3 years, and a standing-assist electric wheelchair was temporarily used; these contributed to the preservation of his activities of daily living (ADLs) and quality of life (QOL) (Taniguchi et al., 2021; Fabiniak et al., 2023). He had continued working and participating in social activities for 40 years after his diagnosis. However, he was infected with COVID-19 in September 2022, and he gradually developed dyspnea due to probable long COVID-19. He had been on a respirator since October 2023, with repeated hospitalizations due to aspiration pneumonia. He died in January 2024.

Patient 2

The elder brother of Patient 1, Patient 2 was 73 years old at study enrollment. When he was 25 years old, painful abdominal muscle cramps developed, and but he worked in construction for 25 years. At the age of 40, he developed proximal muscle weakness and was diagnosed with HMSN-P. At 69 years old (in August 2020), he began to use an electric wheelchair and required full assistance by 2023. He has been receiving home treatment and visiting nursing care.

Patient 3

This 68-year-old female's HMSN-P onset occurred when she was 40 years old. The initial diagnosis was mitochondrial myopathy. She had worked as a nurse for 20 years. Under cold ambient temperatures, she experienced myotonia with pain, and proximal limb muscle weakness appeared with hypoesthesia. She currently she needs total assistance and uses an electric wheelchair. She is intermittently hospitalized ~4 times/year for HAL use/rehabilitation and attends rehabilitation sessions at a hospital 2 times/week.

Patient 4

A 72-year-old male. His mother died of HMSN-P. His symptoms, mainly proximal lower limb weakness, began to appear when he was 65 years old. After he reached 10 years old, mild muscle cramps including the trunk began, but he was able to continue working as a driver for the U.S. military 35 years. In August 2020 at 69

years old, he exhibited proximal quadriplegia in all four limbs, and his grip strength was 25 kg. He used a cane to walk.

Fabrizi et al. (2020) described a family with a TFG (p.Gly269Val) missense mutation that is different from the Okinawa type and exhibits muscle atrophy that is predominant in the distal upper limbs, which overlaps with CMT2. Our Patient 4 exhibited a late onset age at 65 years old, which is atypical, but the presence of proximal-predominant quadriplegia and a CMT mutation in his case seems to be an exception.

Patient 5

At the age of 50, this 68-year-old female noticed face tremor and muscle cramps. She had worked as a deli owner for 20 years, but quadriplegia with hypertension developed and progressed. The initial diagnosis was CMT disease, and she later acquired spinal muscular atrophy (SMA), which is designated an intractable disease in Japan. She uses an electric wheelchair with total assistance. She showed abdominal myoclonus. Her degree of physical disability has been level 1. The patient's rehabilitation and use of a HAL have continued.

Patient 6

This 66-year-old female stared experiencing calf muscle problems at the age of 40, and her HMSN-P onset age was 43 years. In her 50s, she worked as a cook in a hospital kitchen for 10 years, and she was diagnosed with SMA. At 62 years old (August 2020), she developed quadriplegia and started using a cane. When she reached the age of 66, she transitioned to the use of pushcart. She has participated in HAL use/rehabilitation 4 times/year.

4 Conclusion

Even people in electric wheelchairs who require 24-hour/day assistance are able to actively engage in social activities, as evidenced by the member of Japan's House of Councilors with ALS and a recipient of the *Akutagawa Prize*. Of the present six HMSN-P patients under follow-up, four use electric wheelchairs, but they participate in social activities, and Patient 1 in particular has organized the annual *Anela* music festival eight times as a representative of an HMSN-P patient association; he has also contributed to the research and development of specific treatments for HMSN-P disease.

Acknowledgments

This study was supported by Research on the Dissemination of the Best Practicable Care for Muscle Dystrophy (24FC1009) and by a grant from the Research Program for Conquering Intractable Diseases from the Japan Agency for Medical Research and Development (AMED) (no. JP22ek0109616h). We sincerely thank Ms. Kazuyo Ganeko for her cooperation and assistance.

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