Brief Report

DOI: 10.5582/irdr.2023.01051

Re-survey of 16 Japanese patients with advanced-stage hereditary motor sensory neuropathy with proximal dominant involvement (HMSN-P): Painful muscle cramps for early diagnosis

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SUMMARY Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) is an intractable neurological disease with autosomal dominant inheritance, four-limb weakness, sensory impairment, and a slowly progressive course. HMSN-P patients develop four-limb paralysis at the advanced-stage, as in amyotrophic lateral sclerosis (ALS). There is a natural 20- to 30-year course from initial painful muscle cramps and four-limb paralysis to respiratory dysfunction. A delay in the diagnosis of HMSN-P occurs due to the 20- to 30-year span from the initial symptom(s) to typical quadriplegia. Its early diagnosis is important, but the involvement of painful muscle cramps as an early symptom has not been clear. Following our earlier survey, we conducted a re-survey focusing on painful muscle cramps, assistive-device use, and hope for specific therapies in 16 Japanese patients with advanced-stage HMSN-P. Fifteen patients presented painful muscle cramps as the initial symptom, and muscle cramps in the lower abdomen including the flank were described by 10 of the patients. The presence of painful muscle cramps including those in the abdominal region may be a clue for the early diagnosis of HMSN-P. Painful abdominal cramps have not described in related diseases, *e.g.*, ALS, spinal muscular atrophy, and Charcot-Marie-Tooth disease. Recent patient-welfare improvements and advances in assistive devices including robot-suit assistive limbs are delaying the terminal state of HMSN-P. Regarding specific therapies for HMSN-P, many patients choose both nucleic acid medicine and the application of induced pluripotent stem cells as a specific therapy for HMSN-P.

Keywords painful muscle cramp, abdominal cramp, hereditary motor sensory neuropathy with proximal dominant involvement, HMSN-P, nucleic acid medicine, induced pluripotent stem cell

1. Introduction

Okinawa-type neurogenic muscular atrophy, *i.e.*, hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) is an intractable neurological disease that shows autosomal dominant inheritance and proximal muscle dominant-limb paralysis, and it is slowly progressive over a period of approx. 30 years (*1–3*). Advanced-stage HMSN-P results in severe amyotrophic lateral sclerosis (ALS)-like quadriplegia. HMSN-P has recently spread not only in Japan's Okinawa and Shiga prefectures but around the world, including sporadic cases in India (*4–6*). In 2017, Fujisaki *et al*. analysed the natural history of 97 patients with HMSN-P in Okinawa whose cases had been documented since 1980, and they reported a natural course of 20 to 30 years from the initial painful muscle cramps and four-limb paralysis to respiratory dysfunction (*3*).

In 2020, we used a survey to investigate whether there is a difference in the disease name notification and acceptance of HMSN-P compared to ALS (*7*). The early diagnosis of HMSN-P is important, but details such as the site and the triggers of painful muscle cramps, which is an early symptom, have not been fully analysed. Following our earlier survey (*7*), we provided the present study's re-survey to 16 patients with advanced-stage HMSN-P regarding mainly the presence of painful muscle cramps, the patients' use of assistive devices including a robot-suit hybrid assistive limb (HAL), and their hope for specific therapy for their HMSN-P.

2. Patients and Methods

In April 2022–March 2023, 16 patients with advanced-stage HMSN-P in their 50–70s in Okinawa, Japan were enrolled in this study with the cooperation of the local Patient Association (*Nozomi no Kai*). The re-survey's 10 items included the patient's age at the onset of HMSN-P, painful muscle cramps, current major symptoms, assistive-device use, and hope for specific therapy. The re-survey (see the Supplementary Materials, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=153*) was approved by our Hospital's Ethics Committee (Gaku 22-1015).

The 16 patients' conditions corresponded to the advanced-stage of HMSN-P before the appearance of respiratory dysfunction described in the natural history of HMSN-P by Fujisaki *et al*. (*3*). The pairs of Patients 1 and 2, Patients 3 and 5, Patients 4 and 6, and Patients 7 and 8, and Patient 10 and 12 respectively had the same pedigree in which one parent had HMSN-P, and the remaining Patients 9, 14, and 15 each had one parent with HMSN-P. The result of genetic testing for TRK-fused gene (TFG) mutation (*8*) was positive in all 16 patients. The disease-onset age was defined as the patient's age at the onset of limb muscle weakness, and the onset age of muscle cramps similarly defined.

An upper-limb single-joint robot suit HAL had been used by six of the patients for ~3 years since 2017. As part of the regimen for the patient's familiarization with the HAL, both elbows were alternately flexed and extended for 5 min, and after a break, two similar sessions were performed as one set on 3 days; improvements were observed in the patients' hand-grip strength and finger-pinch forces (*9*).

The re-survey was sent to the Patient Association in Okinawa, which delivered the re-survey to the 16 patients for completion; the completed re-surveys were collected by the Patient Association. Ambiguous points in the patients' responses to the re-survey were resolved by a telephone inquiry, with some exceptions.

3. Results and Discussion

The results of the re-survey are summarized in Table 1. The average age of the 16 patients (9 males and 7 females) was 62.2±5.7 (SD) years. All of the patients reported experiencing painful muscle cramps; the clinical characteristics are described in Table 2. The muscle cramps began at the average age 34 years in lower legs, often ascending to the thigh and abdomen, and recurring intermittently for 10–20 years. In 10 patients, painful muscle cramps preceded limb weakness, and five patients had painful muscle cramps simultaneously with the onset of weakness of limbs. Conversely, Patient

Table 1. Re-survey of 16 Japanese patients with advanced-stage hereditary motor and sensory neuropathy with proximal dominant involvement (April 2022–March 2023)

Patient No.	Age/Sex Educ.	Genetic testing onset age+	Onset age of painful muscle cramps	Current major symptoms, use of aids, HAL use	Job, yrs	Hoped for therapy 1: Nucleic acid Medicine 2: iPS
1	66/m Univ.	35	20, lower-leg, thigh, abdomen	Prox. dominant quadriplegia* dyspnea, elec. wheelchair	40 continuing	1,2
2	72/m HS	40	20, calf cramps, ascending abdomen	Prox. dominant quadriplegia* elec. wheelchair	25	1,2 HAL no response
3	66/f HS	50	45, calf cramps, thigh, abdomen	Prox. dominant quadriplegia* dysphagia, elec. wheelchair	20	Early development 1,2
4	67/f HS	30	28, lower-leg, ascending abdomen	Muscle cramps, quadriplegia* elec. wheelchair	20	Specific therapy 1,2
5	73/m HS	65	15, lower-leg, thigh, abdomen	Quadriplegia*, cane, walker	35	Unknown
6	64/f HS	43	40, calf cramps	Quadriplegia*, cane, wheelchair, walker	10	2
7	66/m HS	50	10, lower-leg, abdomen(flank)	Quadriplegia, dysphagia, elec. wheelchair	40 continuing	1,2 HAL no response
8	72/f HS	50	40, calf cramps, abdomen	Dysphagia, quadriplegia wheelchair, death at 72 yrs	10	Not clear
9	53/m HS	35	30, lower-leg, ascending abdomen	Upper-limb paralysis, → lower-limb paralysis	30 continuing	2 HAL no response
10	60/f HS	43	43, calf cramps, finger	Muscle cramps, quadriplegia, cane, wheelchair	20	Early development 1,2
11	57/f HS	40	40, calf cramps, abdomen, neck	Muscle cramps, quadriplegia, cane, wheelchair	20	Specific therapy 1,2
12	50/m HS	38	38, calf cramps	Dyspnea, quadriplegia, cane, elec. wheelchair	24	1
13	53/m HS	30	30, calf cramps	Lower-limb paralysis	20 continuing	Not clear
14	57/f HS	40	40, lower-leg	Quadriplegia, cane, wheelchair	14	Specific therapy 2
15	60/m HS	40	50,lower-leg	Quadriplegia, cane, → wheelchair	25	Specific therapy 2
16	59/m Univ.	38	34, calf cramps, abdomen	Quadriplegia, cane, → wheelchair	30	Early development 2

+: The genetic testing and onset age are stated in the text. Educ.: education, elec: electric, f: female, HS: high school graduate, HAL: hybrid assistive limb, *: HAL use, iPS: induced pluripotent stem cell, m: male, Univ.: university graduate.

Table 2. Clinical characteristics of the HMNS-P patients with painful muscle cramps (*n*=16)

Age, yrs; mean ± SD, gender	62.2 ± 5.7 yrs 9 males, 7 females
Onset age of limb weakness, yrs; mean ± SD (range)	41.7 ± 6.1 (30-65)
Onset age of painful muscle cramps, yrs; mean ± SD (range)	32.7 ± 8.9 (10-50)
Sites:	
Lower-leg, *i.e.*, calf cramps	5 (31.3%)
Lower-leg, thigh, ascending to painful abdominal cramps	9 (56.3%)
Calf cramp, abdomen with neck	1 (6.3%)
Calf cramps, finger	1 (6.3%)
Triggers:	
Falling asleep, sleeping	5 (31.3%)
Changes in position	5 (31.3%)
Fatigue	1 (6.3%)
Sneezing	1 (6.3%)
Unknown	4 (25%)

15's painful muscle cramps started after weakness of the extremities.

Two patients described neck or finger cramps together with lower-leg or abdominal cramps. The triggers included fatigue, falling asleep during the day or at night, changes in posture, and sneezing. These were relieved by stretching the lower legs, lightly tapping the abdomen, or standing up. In a few patients in their 50–60s, occasional muscle cramps still occur. Regarding medications for HMSN-P, some of the patients had received clonazepam or taurine (data not shown).

Fifteen patients described painful muscle cramps as the initial symptom, and muscle cramps in the lower abdomen, including the flank were described by 10 of the patients. Notably, painful abdominal cramps seemed to be specific to HMSN-P. Painful abdominal cramps have not described in related diseases, *e.g.*, ALS, spinal bulbar muscular atrophy (SBMA), or Charcot-Marie-Tooth (CMT) disease (*10–13*). Fasciculation in the face during tongue thrust has been observed in ALS and SBMA patients but not HMSN-P, and CMT disease shows findings of lower-extremity predominance.

Takashima *et al*. reported that muscle cramps occurred intermittently in the extremities and abdominal regions of their series of 23 patients with HMSN-P, and there was an interval ranging from 0 to 22 years between the muscle cramps and four-limb weakness (*1*). In our series of 16 patients, the corresponding interval ranged from 0 to 50 years; 10 patients had prodromal signs 3–50 years before limb weakness, and five patients had coexisting limb weakness with the onset of muscle weakness. In both types of patients, the presence of painful abdominal cramps in the present history may be a clue for the early diagnosis of HMSN-P.

Regarding the pathology of HMSN-P, Suehara described the loss of anterior horn cells throughout the spinal cord, marked atrophy of the dorsal column, and a loss of nerve fibers (*2*). The pathophysiology of abdominal muscle cramps appears to originate in the lumbar spinal anterior horn. On the other hand, muscle weakness in the upper extremities is always observed in HMSN-P, and it is presumed that muscle cramps frequently occur in the upper extremities of HMSN-P patients; however, only two patients in our present series described experiencing muscle cramps in the neck or fingers.

In six of our patients in their 60s, their current main symptoms were proximal dominant quadriplegia, and they needed an electric wheelchair and full assistance. However, they had maintained their cognitive ability, speech, and swallowing, and the painful muscle cramps were reduced in three of the six patients. They had an average of 24 years of work experience, and their jobs varied from company representative, nurse, sales worker, US military base driver, and clerical workers. Almost all of the patients had been obliged to stop working due to progressive limb weakness, but Patients 1, 7, 9, and 13 had maintained sufficient hand muscle strength to continue clerical work.

Compared to the responses to the same survey completed by the patients 2 years earlier, Patient 1 had developed dyspnea, Patient 3 had mild dysphagia, and Patient 6 was hospitalized for a hip fracture. Patient 8 had died of aspiration pneumonia. Patient 12's condition had progressed to quadriplegia, and he needed an electric wheelchair.

The present study's re-survey revealed that an upper-limb single-joint robot suit HAL was used intermittently by six patients for 3 years; Patient 1 experienced an immediate effect for 2–3 weeks in the evaluation items of hand-grip and finger-pinch forces at distal upper-limb muscles (*9*). Regarding the re-survey questions about the usefulness of an upper-limb single-joint robot suit HAL, two patients with mild disability and one patient with severe disability described the HAL as helpful; two patients with severe disability chose to maintain the HAL, and one patient with severe disability answered 'no' to the question about the HAL's helpfulness.

Comparing the patient group of 65–70 years old reported by Fujisaki *et al.* (*3*) with the seven present patients of the same age, we observed that > 50% of the patients in the Fujisaki series were using a respirator or had died, but six of our patients in that age group remained without respirator use, which shifted the terminal stage by several years. The improvement in the patients' welfare and the progress that has been made in the design of assistive devices are considered to have greatly contributed to a delay in the onset of terminal-stage HMSN-P. The hoped-for therapy in the survey we provided 2 years ago (*7*) resulted in the same number of specific therapies desired, *i.e.*, nucleic acid medicine and induced pluripotent stem cell (iPS) application. In the present study's re-survey, one patient chose nucleic acid medicine, and five patients selected iPS application. Seven patients chose both options, and

three patients' responses were unclear or not given.

A limitation of this study is that it enrolled only patients with advanced-stage HMSN-P who belonged to the Okinawa Patient Association. In addition, all of the patients are Japanese, and our findings may not be applicable to patients with other backgrounds. A wide range of investigations, including patients from outside Okinawa prefecture, are awaited.

In conclusion, we conducted a re-survey for 16 Japanese patients with advanced-stage HMSN-P concerning mainly painful muscle cramps as an early symptom of this disease. Of particular note, the presence of painful muscle cramps including the abdominal region may be a clue for the early diagnosis of HMSN-P. Recent improvements in patients' welfare and advances in assistive devices including robot-suit assistive HALs have postponed the terminal state of HMSN-P by several years. Many of our patients chose both nucleic acid medicine and iPS application as their hoped-for HMSN-P therapy.

Acknowledgements

We sincerely thank Mr. Seiken Ganeko, the *Nozomi no Kai* representative, for his cooperation and assistance.

Funding: This study was supported by a Health Labour and Welfare Science Research Grant (no. 21FC1006) and by the Research Program for Conquering Intractable Diseases from the Japan Agency for Medical Research and Development (AMED) (no. JP22ek0109616h).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received June 25, 2023; Revised August 7, 2023; Accepted August 15, 2023.

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Released online in J-STAGE as advance publication August 18, 2023.