

## Editorial

# Heterogeneous Prognosis for Hereditary Motor and Sensory Neuropathy with Proximal Dominance

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## EDITORIAL

Hereditary motor and sensory neuropathy with proximal dominance (HMSN-P) is a rare disease. Its clinical phenotype is characterized by adult-onset proximal muscular weakness with a very subtle sensory disturbance inherited in autosomal dominant manner. Bulbar palsy can develop, but the pyramidal tract is not involved clinically. Diabetes mellitus and hyperlipidemia might be complications [1].

HMSN-P was first reported by Takashima and Nakagawa et al. in 1997. They described the clinical and pathological features of 23 patients from 8 families in Okinawa Prefecture and mapped the gene locus to 3p14.1-q13 [2]. They later narrowed the gene locus to 3q13.1 [3]. Cardiomyopathy might develop in members of these families [4]. On the other hand, Takahashi et al. followed 8 patients from 2 families in Shiga Prefecture from 1984 [5]. Their vigorous work led to the discovery of the mutation of another type of Charcot-Marie-Tooth disease [6]. Their work was succeeded by that of Kaji et al. Maeda and Kaji et al. carried out a linkage study of Shiga families and identified its locus on 3q13.1 [7]. The pathological report of Shiga-type HMSN-P was published in 2011 by Fujita et al. [8] Until 2007, HMSN-P had been reported only in Japan. In 2006, I discovered one family affected by HMSN-P among Brazilians working in Japan. Their parents had originally emigrated from Okinawa to Brazil at the urging of the then Japanese government [9]. Another family noticed this paper and e-mailed me, which led to the discovery of the second Brazilian family with HMSN-P [10]. Nakagawa and I went to Brazil in 2009, and saw these two families on the spot with Brazilian doctors. We found that three additional siblings had developed HMSN-P in the first Brazilian family. In 2012, c. 854C>T (p. Pro285Leu) mutation in the TRK-fused gene (TFG) was identified as the causative mutation for HMSN-P. Cytoplasmic aggregation of TAR DNA-binding protein 43kDa (TDP-43) was observed in motor neurons in the spinal cord and cells expressing the mutant TFG [11]. HMSN-P was found in Kumamoto Prefecture in Japan, a different region from either Okinawa or Shiga [12]. Around the world, it has been discovered in Korea [13] and the United States [14], suggesting that HMSN-P is no longer an endemic condition,

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as I predicted in my paper [9]. Although this disease is classified as 'neuropathy', the pathological studies showing neuronal loss in the anterior horn and the dorsal root ganglion indicate that it is not 'neuropathy' but 'neuronopathy' [15].

I have worked as a neurologist at National Hospital Organization Higashi-ohmi General Medical Center (previously Shiga Hospital) since 2009. Here, I have seen several patients with Shiga-type (Kansai-type) HMSN-P. I had recognized that the clinical course of HMSN-P is slowly progressive, resembling that of adult-onset spinal muscular atrophy or bulbospinal muscular atrophy. In Okinawa-type HMSN-P, Takashima et al. described that "The patients became unable to walk 5 to 20 years and bedridden 10 to 25 years after disease onset" [2]. In Shiga-type HMSN-P, the patients also became bedridden in 10 to 20 years after onset [7]. The patient showing rapid progression was V4 in Family 2 [11]. His genotype of TFG was shown to be c. 854C>T. His age at onset was 38. Initial weakness appeared in his proximal upper extremities. There was no bulbar palsy or pyramidal tract sign. Fasciculation was observed in the greater pectoral muscles. Nerve conduction study showed no conduction block but decreased amplitude of the sensory evoked potentials in the median and sural nerves. Electromyography revealed giant spikes in some muscles, suggesting chronic denervation. Serum CK level was 204 IU/L (range, 62-287 IU/L). Neither diabetes nor hyperlipidemia was found. Within two years after onset, he could not elevate his arms at all. Grip power was also decreased. In the next two years, he complained of dyspnea during walking and even during conversation. He used his neck muscles for respiration. Arterial gas analysis showed pH 7.442, pCO<sub>2</sub> 42.4 mmHg, pO<sub>2</sub> 94.6 mmHg, HCO<sub>3</sub><sup>-</sup> 28.5 mM, and base excess 4.3 mM. He refused the use of ventilators or tracheotomy. His mother (IV7 [11]) also had HMSN-P, and died of respiratory failure in her forties. Takahashi et al. described a case series of Shiga-type HMSN-P. They noticed that some patients showed rapid disease progression like amyotrophic lateral sclerosis (ALS). They described two patients from different families showing four-year and seven-year survival time [5]. There are probably modifying factors affecting disease prognosis, such as genetic background or environmental factors.

As mentioned above, some patients with HMSN-P show rapid progression and death within ten years. In addition to the prognosis described, pathological study revealed alteration of cortical motor neurons [11]. These observations suggest that HMSN-P and ALS share some clinical characteristics. That is why I think that HMSN-P should be classified as familial ALS rather than hereditary neuropathy. In Japan, there are social resources available that patients with intractable neurological diseases can utilize. Especially, some diseases such as ALS, spinal muscular atrophy, and bulbospinal muscular atrophy are designated as intractable diseases by the Japanese government and patients can receive financial support to partially cover the medication. Unfortunately, HMSN-P is not widely recognized and is not designated as an intractable disease. Although HMSN-P is a rare disorder, I think that efforts should be made to provide relief for patients medically and socially.

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