Neurology Asia 2025; 30(3) : 947 – 949

A rare case of proximal dominant hereditary motor and sensory neuropathy with TFG mutation

[1]Betül Özenç, [2]Damla Erimhan Çevik, [2]Mustafa Yurtdaş, [3]Aydan Topal

[1]Gaziantep City Hospital, Neurology Department, Gaziantep, Turkey; [2]Ankara Etlik City Hospital, Neurology Department, Ankara, Turkey; [3]Samsun Education and Research Hospital, Neurology Department, Samsun, Turkey

Abstract

Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) or Okinawa type is a rare neuromuscular disorder characterized by proximal dominant neurogenic atrophy and distal sensory changes with an autosomal dominant pattern of inheritance. The disease is characterized by adult-onset proximal weakness and atrophy, muscle cramps, fasciculations, areflexia, elevated creatine kinase, hyperlipidemia, and diabetes and is similar to Kennedy's disease, but differs in that the mode of inheritance is autosomal dominant. We present a 53-year-old male patient with symmetrical proximal weakness, fasciculations, absent patellar tendon reflexes, and a positive family history for the same symptoms suggestive of HMSN-P, as well as his clinical, electrophysiological, and genetic features. These findings led to a genetic test that identified a variant in the TFG gene (c. 854C>T (p.Pro 285Leu)) and confirmed the diagnosis of HMSN-P. This case demonstrates the importance of considering this rare differential diagnosis in patients with proximal muscle weakness and distal sensory deficits with progressive muscle cramps.

Keywords: Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P), autosomal dominant, TRK-fused gene (TFG), Okinawa-type neurogenic muscular atrophy

INTRODUCTION

Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) has the features of a motor neuronopathy involving the spinal motor neurons, characterized by adult onset, a slowly progressive course and an autosomal dominant inheritance that has been linked by exome analysis to a TRK-fused gene (TFG) mutation.[1]

The disease usually begins in the 40s and has a slowly progressive course. In the early stages, patients often suffer from painful muscle cramps and numerous fasciculations. While other hereditary motor and sensory neuropathies (HMSNs) present with predominantly distal motor weakness reflecting axonal length dependence, the clinical presentation of HMSN-P is unique in that it presents with predominantly proximal weakness with widespread fasciculations as seen in amyotrophic lateral sclerosis (ALS).[2]

We present the rare case of a patient with a heterozygous p.P285L mutation in the TRK-fused gene (TFG) who developed proximal dominant muscle weakness in his 40s that gradually evolved into a phenotype resembling motor neuron disease.

CASE REPORT

A 53-year-old male patient presented with complaints of painful muscle cramps, difficulty climbing stairs, and difficulty carrying weights that began 5 years ago. The cramps were widespread, especially in the proximal muscles of the four limbs, and were usually worse at rest and with stretching. After 5 years, the patient's cramps partially resolved but were replaced by progressive, asymmetric, proximal-onset muscle weakness and atrophy. Over time, he noticed twitching movements in the extremities and facial muscles. There were no respiratory, autonomic or sphincter defects.

There were no consanguineous marriages in the patient's family. He had an uncle in his family history who had similar complaints at a similar age and died at the age of 63 years. Examination

Address correspondence to: Betül Özenç, Gaziantep City Hospital, Neurology Department, Gaziantep, Turkey. Tel: 0554 307 14 62, email: betulozenc01@gmail.com

Date of Submission: 1 April 2025; Date of Acceptance: 2 May 2025

https://doi.org/10.54029/2025ewr

revealed weakness of the proximal muscles of the four limbs, which was slightly more pronounced on the right (Medical Research Council [MRC] grade 3/5 right, 4/5 left). The distal muscles (MRC grade 4) and the small muscles of the hands were also weak. Examination of the cranial nerves revealed fasciculations of the tongue, fasciculations of the face, and perioral myokymia. Postural tremor was observed in the hands. The tendon reflexes were symmetrically weakened everywhere, while the plantar reflexes were flexor. Muscle atrophy was observed in both shoulders, in the anterior compartment of the thighs, and in the distal muscles of the hands. There was no Romberg's sign.

Lipid levels, fasting blood glucose and glycosylated hemoglobin levels were normal. The serum creatine kinase level was 1620 IU/l (normal 50–170 IU/l). Nerve conduction studies (NCS) showed the absence of sensory nerve action potentials in the bilateral median and sural nerves. The amplitudes of the sensory action potentials of the bilateral ulnar nerve were small and the sensory conduction velocity was slightly slowed. Motor NCS and minimum F-wave latencies were normal in the muscles innervated by the peroneal and tibial nerves, with no signs of conduction block or temporal dispersion. Needle electromyography revealed widespread positive sharp waves, fibrillation potentials and fasciculations. Widespread chronic remodeling of motor unit action potentials (MUAP) with high amplitude, wide duration, and polyphasia was noted in all muscles examined.

The patient's cancer markers, serum electrophoresis and thoracoabdominal tomography revealed no significant pathology. Ultrasonography of the superficial tissues performed for gynecomastia revealed no changes attributable to gynecomastia.

The data was obtained with the next generation sequencing method using DNA from the patient's blood. It involves the selective capture and sequencing of the protein-coding regions of the genome/genes. The sequences obtained were analyzed using the GRCh37(hg19) reference genome. The detected variations were evaluated on the basis of 30-fold read depth (coverage) per allele (reference allele/alternative allele). The recommendations of the ACMG (American Collages of Medical Genetics) Standards and Guidelines 2015 were considered when evaluating the variations.

A heterozygous missense variation in the receptor kinase-fused gene (TFG) was detected, which leads to an amino acid substitution of leucine for proline at codon 285 (p. Pro285Leu; NM_006070.6). The observed variation is located in the P/Q-rich domain in the C-terminal region of the TFG protein and has been previously reported in patients with HMSN.

DISCUSSION

Okinawa-type neurogenic muscular atrophy, i.e. HMSN-P, is an autosomal dominant neurodegenerative disorder characterized by widespread fasciculations, proximal-predominant muscle weakness and atrophy followed by distal sensory involvement. Symptoms usually begin in the fourth to fifth decade of life. This disease was first described in 1997 by Takashima *et al*. based on the observation of affected patients in eight families from Okinawa, the southern archipelago of Japan.[3] The diagnostic criteria for HMSN-P were first established by Takashima *et al*. in 1997 after studying more than 100 patients in 15 families.[3,4]

The diagnostic criteria are based on Takashima *et al*. They were determined as follows: slowly progressive proximal dominant muscle weakness and atrophy first manifesting after the age of 30 years, autosomal dominance, fasciculations in the extremities and trunk, absence of deep tendon reflexes, and sensory disturbances including sensory nerve conduction abnormalities. If not all criteria were not satisfied, there should be a typical case in the patient's family. Pathogenic variants of the tropomyosin-receptor kinase fused gene (TFG) have been described in the context of neurological diseases with a broad phenotypic spectrum. The TFG protein is required for protein transport and secretion from the endoplasmic reticulum to the Golgi apparatus in various tissues. This protein contains three known domains, including a Phox-Bem1p (PB1) domain, a coiled-coil (CC) domain, and a proline and glutamine (P/Q)-rich domain.[5]

HMSN-P, which is due to a TFG mutation, has been observed not only in the Japanese prefectures of Okinawa and Shiga but also worldwide, including sporadic cases in India.[6] When the disorder occurs in other parts of the world due to spontaneous mutations, as in this case, clinicians should be aware of the clinical and electrodiagnostic features of the differential diagnosis (e.g. Kennedy's disease, spinal muscular atrophy, amyotrophic lateral sclerosis). Although there is currently no evidence for an effective treatment, elucidating the function of TFG and its pathomechanisms and treatment strategy could

make it a good model for neurodegenerative diseases.

DISCLOSURE

Ethics: Informed consents have been obtained from the patients for this publication.

Financial support: None

Conflict of interest: None.

REFERENCES

1. Ishiura H, Sako W, Yoshida M, *et al*. The TRK-fused gene is mutated in hereditary motor and sensory neuropathy with proximal dominant involvement. *Am J Hum Genet* 2012; 91(2), 320-9. https://doi.org/10.1016/j.ajhg.2012.07.014
2. Fujita K, Yoshida M, Sako W, *et al*. (2011). Brainstem and spinal cord motor neuron involvement with optineurin inclusions in proximal-dominant hereditary motor and sensory neuropathy. *J Neurol Neurosurg Psychiatr* 2011; 82(12), 1402-3. https://doi.org/10.1136/jnnp-2011-300783
3. Takashima H, Nakagawa M, Nakahara K, *et al*. A new type of hereditary motor and sensory neuropathy linked to chromosome 3. *Ann Neurol* 1997; 41(6):771-80. https://doi.org/10.1002/ana.410410613
4. Nakagawa M, Takashima H, Suehara M, *et al*. Hereditary motor and sensory neuropathy with proximal dominant involvement: clinical, pathological, and genetic features. *Ann N Y Acad Sci* 1999; 883: 449-52.
5. Johnson A, Bhattacharya N, Hanna M, *et al*. TFG clusters COPII-coated transport carriers and promotes early secretory pathway organization. *EMBO J* 2015; 34(6): 811-27. https://doi.org/10.15252/embj.201489032
6. Ansari AF, Jagiasi K, Ojha P, Ansari R, Nagendra S, Kharat S. Proximal dominant hereditary motor and sensory neuropathy with *TFG m*utation: First case report from India. *Neurol India* 2011;70(3): 1220-2. https://doi.org/10.4103/0028-3886.349586