NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

CASE REPORT

Arch Neuropsychiatry 2025;62:205–206
https://doi.org/10.29399/npa.28654

A Case of Distal Hereditary Motor Neuropathy with HSPB1 Mutation in Coexistence with Myotonia and Myopathy

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ABSTRACT

Distal hereditary motor neuropathies (dHMNs), also named as distal spinal muscular atrophy, are a group of disorders that cause degeneration of motor nerves. Currently, only 15% to 32.5% of patients with dHMN have been genetically identified. The most common cause of dHMNs gene mutations is HSPB1 mutation. In HSPB1 mutation, which is also one of the myopathogens via satellite cell pathology, dHMNS may coexist with neuromuscular junction disorder, motor neuron disease, satellite cell dysfunction and therefore myopathic findings. No case of myopathy and myotonia with HSPB1 mutation has been reported in the literature yet. We present a case with electrophysiologic findings in HSPB1 mutation by discussing the possible mechanisms underlying myotonic discharges and myopathic findings.

Keywords: distal hereditary motor neuropathy, heat shock protein, HSPB1 mutation, myopathy, myotonia

Cite this article as: Uzunçakmak-Uyanık H, Tan E, Temuçin ÇM. A Case of Distal Hereditary Motor Neuropathy with HSPB1 Mutation in Coexistence with Myotonia and Myopathy. Arch Neuropsychiatry 2025;62:205–206.

INTRODUCTION

Distal hereditary motor neuropathies (dHMNs) are a group of disorders that cause degeneration of motor nerves. They usually present symmetrical and length-dependent motor polyneuropathy. Currently, only 15% to 32.5% of patients with dHMN have been genetically identified (1). The most common cause of dHMNs gene mutations are HSPB1 (10.4%), GARS1 (9.8%) and BICD2 (8%) (1). In HSPB1 mutation, which is also one of the myopathogens via satellite cell pathology, dHMNs may coexist with neuromuscular junction disorder, motor neuron disease and satellite cell dysfunction. Herein, we present a patient with motor axonal polyneuropathy accompanied by myotonia and myopathy with HSPB1 missense mutation.

Highlights

- **HSPB1 mutation is associated with satellite cell dysfunction and therefore myopathic findings.**
- **No case with both HSPB1 mutation and myopathy-myotonia has been reported before.**
- **The electrophysiological findings were presented along with possible mechanisms.**

CASE

A 74-year-old male patient was admitted to hospital with complaints of weakness that first started in lower extremities and then spread to upper extremities for two years. It was learned that her mother had similar complaints at his age. The upper extremity proximals were symmetrical 5-/5, the lower extremity proximal and distals were symmetrical 4+/5 muscle strength. There was atrophy of the calves. Deep tendon reflexes were widely hypoactive. No clinical myotonias or fasciculations were detected. There was no facial weakness or facial dysmorphic appearance. Laboratory tests revealed keratin kinase (CK): 440 U/L (normal ranges: 22–198 U/L.) Nerve conduction studies revealed low compound muscle action potential (CMAP) amplitudes in the lower extremities. Upper and lower extremity sensory nerve conduction study results were within normal limits for the patient's age. There were severe myotonic discharges (Figure 1) as well as denervation potentials in all examined muscles. Myopathic motor unit action potentials (MUAPs) and early recruitment pattern in proximal muscles were observed. Moreover, 15 Hz repetitive stimulation of the right ulnar nerve revealed a decremental response as 26.5% in the amplitude and 36.1% in the area that can be observed in myotonia (Figure 2). Electromyography (EMG) was reported as "compatible with diffuse myotonia accompanied by mild myopathy with axonal polyneuropathic involvement prominent in motor fibers and lower extremities". Left biceps muscle biopsy reported "nonspecific myopathic changes". No pathology was detected in the molecular genetic analysis performed for diseases with myotonia. The whole exome sequencing (WES) analysis report of the patient resulted as "the presence of HSPB1 gene c. 610G >A (p. A204T) (heterozygous) missense

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Received: 28.10.2023, **Accepted:** 03.12.2023, **Available Online Date:** 08.06.2025

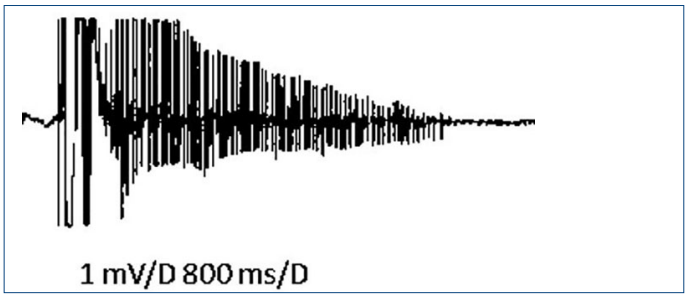

Figure 1. Myotonic discharge recorded from the right tibialis anterior

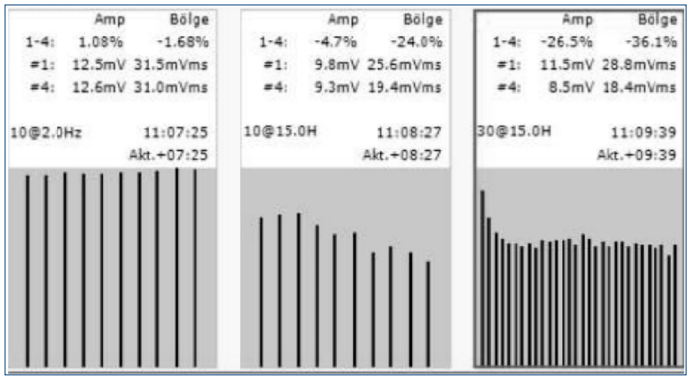

Figure 2. 2 and 15 Hz repetitive stimulations of the right ulnar nerve on the abductor digiti minimi muscle. 15 Hz repetitive stimulation of the right ulnar nerve revealed a decremental response as 26.5% in the amplitude and 36.1% in the area that can be observed in myotonia.

mutation". It was stated in the report that no other known mutations causing myopathy and/or myotonia were detected. Informed consent was obtained from the patient for publication.

DISCUSSION

The minimum prevalence of dHMN is 2.3 per 100 000 (1). Besides classical motor or motor-dominant neuropathy with onset in lower extremities presentation, dHMN may also have some additional features, such as pyramidal findings. In the majority of cases, symptoms first begin in the fourth or fifth decade of life and progress slowly.

Various cellular mechanisms such as interactions between neurons and non-neuronal cells and seeding of misfolded proteins by prion-like propagation are involved in motor neuron degeneration. HSPB1, a molecular chaperone, has a role in repair function of some proteomes. 'HSPB1 variant' is an ALS-like entity that generally has no family history and has an elevated CK.

In our case, besides diffuse motor axonal polyneuropathy in lower extremities, we also detected diffuse myotonia with mild myopathic findings as remarkable and unusual findings. Coexistence of motor axonal polyneuropathy and myotonia with myopathy accompanied by HSPB1 mutation has not been reported in the literature yet. HSPB1 (heat shock protein B1) is a chaperone (2); cardiac muscle, skeletal muscle, neurons and lens show high expression of HSPBs. "Satellite cells" serving as muscle stem cells, are important structures that contribute to growth and regeneration of skeletal muscle. Loss of function in genes involved in satellite cell function may lead to neuromuscular disorders. Ganassi and Zammit stated "There are 34 myopathogenic genes that regulate satellite cell activation and they may cause motor neuron disease" (3). In HSPB1 mutation, which is one of these myopathogens, distal hereditary motor neuropathy may coexist with neuromuscular junction disorder, motor neuron disease and satellite cell dysfunction (3). Because of satellite cell dysfunction HSPB1 mutation may also be responsible for myopathic findings.

In skeletal muscle, most of the repolarization is mediated by chloride (Cl^-) conductance via ClC-1 channels (4). Myotonia which is the inability of muscle fibers to relax, is caused by mutations in the gene encoding ClC-1 by a lower Cl^- conductivity. If T-tubular Cl^- channels do not work effectively, the conductivity of Cl^-deteriorates. So depolarizing high K^+ values lead to repetitive action potentials firing and myotonia. HSPB1 expression level correlates with functional Cystic Fibrosis Transmembrane Conductance Regulator Protein (CFTR) level (2). CFTR gene responsible for cystic fibrosis; encodes the Cl^- channel protein in structures such as airways and sweat glands. HSPB1 promote degradation of CFTR mutants (2). On the other hand, another pathogenic HSPB mutation at HSPB8 gene is associated with myotonia (5).

We discussed the possible mechanisms underlying myotonia and myopathic findings in HSPB1 mutation, which is more commonly known to play a role in the etiopathogenesis of distal hereditary motor neuropathy and motor neuron disease. Based on this information, it can be suggested that a defect in HSPB1 gene expression may cause myopathy via satellite cell pathology and myotonia by affecting the skeletal muscle T-tubule and sarcolemma Cl^- channels.

Informed Consent: Informed consent form was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- HUU, ÇMT; Design- HUU, ÇMT, ET; Supervision- HUU, ÇMT; Resource- HUU, ÇMT, ET; Materials- ÇMT, ET; Data Collection and/or Processing- HUU, ÇMT, ET; Analysis and/or Interpretation- HUU, ÇMT; Literature Search- HUU; Writing- HUU, ÇMT, ET; Critical Reviews- HUU, ÇMT.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: Authors declared no financial support.

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