FOLIA MEDICA CRACOVIENSIA
Vol. LXIII, 4, 2023: 57–61
PL ISSN 0015-5616
DOI: 10.24425/fmc.2023.148758

HSPB1 mutation causing distal Hereditary Motor Neuropathy type 2B in a Polish family

Katarzyna Homa[1], Kamila Żur-Wyrozumska[2,3]

[1]Department of Neurology, The Gabriel Narutowicz Specialist Municipal Hospital, Kraków, Poland
[2]Department of Neurology, The Józef Dietl Specialist Hospital, Kraków, Poland
[3]Department of Medical Education, Jagiellonian University Medical College, Kraków, Poland

Corresponding author: Katarzyna Homa, M.D.
Department of Neurology, The Gabriel Narutowicz Specialist Municipal Hospital, Kraków, Poland
Phone: +48 12 257 84 52; E-mail: katarzynaanna.homa@gmail.com

Abstract: The heat-shock protein beta-1 (HSPB1) is one of small heat-shock proteins that play an important role in cell functioning by promoting correct folding of other proteins. The HSPB1 mutations are known to cause distal Hereditary Motor Neuropathy type 2B (dHMN2B) and Charcot-Marie-Tooth disease type 2F (CMT2F). More than 30 different mutations in the HSPB1 have been found in patients with CMT2F and dHMN2B. There are cases of the Thr151Ile HSPB1 mutation described in 4 countries: Croatia, Japan, France and Poland. In this paper we present a Polish family with p.Thr151Ile mutation causing distal hereditary motor neuropathy. A 48-year-old male patient presented progressive bilateral lower limb weakness and gait difficulty of typical onset. The presentation of the disease in his daughter, who carries the same mutation is yet uncertain. She has currently no clinical symptoms of the disease but registered mild muscle damage in EMG with correct conduction parameter in EMG.

Keywords: HSPB1 mutation, dHMN, distal Hereditary Motor Neuropathy 2B.

Submitted: 02-Oct-2023; **Accepted in the final form:** 30-Nov-2023; **Published:** 30-Dec-2023.

The HSPB1 gene encodes a small heat-shock protein beta-1. It belongs to the large family of small heat shock proteins, ten of which are expressed in human tissues. Among them HSPB1 is expressed in almost all human tissues. This protein is made up of three domains: poorly ordered N-terminal domain, conservative α-crystallin domain and predominantly disordered C-terminal domain. Small heat shock proteins participate in various intracellular and extracellular processes [1]. They act as a molecular chaperone that promote correct folding of other proteins and in this way control many molecular processes such as senescence and apoptosis, cell signaling or protec-

tion of cytoskeleton. Mutations in four of small heat-shock proteins including HSPB1 have been associated with human neuromuscular diseases such as distal hereditary motor neuropathy, Charcot-Marie-Tooth disease, Amyothophic Lateral Sclerosis and even some forms of myopathies. The majority of small heat-shock protein mutations are missense mutations, mostly associated with a dominant disease phenotype, high penetrance and late onset of symptoms [2].

Inherited peripheral neuropathies are a very complex and genetically diverse group of peripheral nervous system diseases [3]. They are classified as the Charcot-Marie-Tooth disease (CMT) also known as hereditary motor-sensory neuropathy if both, motor and sensory, systems are affected or distal hereditary motor neuropathy (dHMN) if motor deficit is predominant. Further subdivisions depend on observed nerve conduction [1, 4].

Mutations in HSPB1 can cause a group of length-dependent axonal neuropathy, which includes distal hereditary motor neuropathy type 2B (dHMN2B) and Charcot-Marie-Tooth disease type 2F (CMT2F). There are also mutations in HSPB1 reported in patients with amyotrophic lateral sclerosis and in one case with myopathy, which suggest overlap of these diseases [5, 6].

DHMN2B and CMT2F are mostly autosomal dominantly inherited and characterized by a progressive distal muscle weakness and atrophy predominantly in lower limbs. Electrophysiological studies show a length-dependent axonal motor neuropathy in dHMN2B or length-dependent motor-sensory neuropathy in CMT2F [7], though there are described forms of dHMN2B that have minor sensory involvement [5]. Usually the first symptoms of dHMN2B occur in 4th decade however, it can range from the 2nd till 6th decade [8]. The progression of the disease is slow [9].

Currently more than 30 mutations in the HSPB1 have been found in patients with CMT2F and dHMN2B. The mutations in HSPB1 were the most common cause of dHMN2B with a frequency of 8–14% [10]. In the families with HSPB1 mutation described in different countries, male predominance was found but the significance of the sex difference requires further investigation [5].

In this study we present a 48-year-old male who was admitted to the hospital due to progressive bilateral lower limb weakness and gait difficulty. The onset of the disease took place 6 years before when the patient experienced difficulty while skiing. A year later damage of the right peroneal nerve occurred. The symptoms progressed causing lower extremities weakness and muscle slimming, mostly in distal parts. The family history revealed that gait problems affected his father, his father's brother and their mother (our patient's grandmother).

In neurological assessment the patient presented lower limb and gluteal muscle atrophy, mostly distal and with the right side predominance with decreased muscle tone in lower extremities (Fig. 1). We found absence of knee and ankle tendon reflexes bilateral and presence of fasciculations in thighs and calves. Sensory examination was

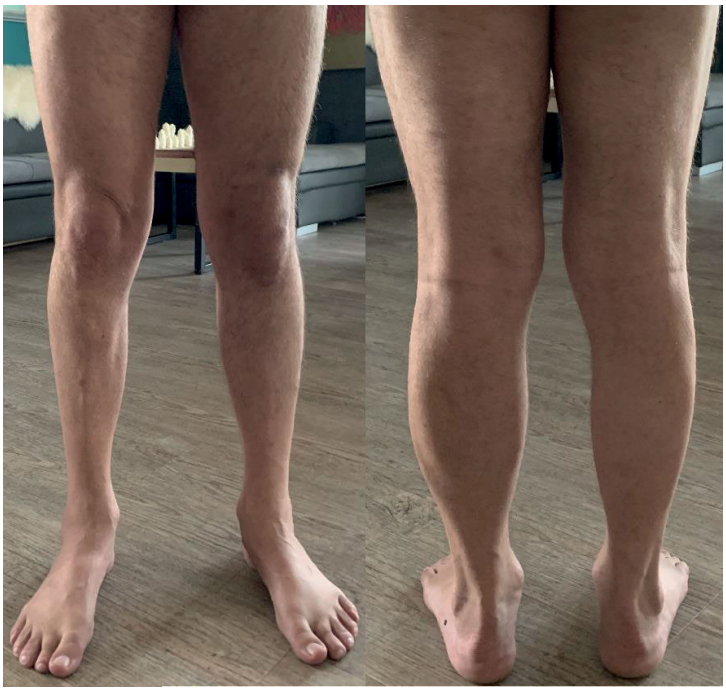

Fig. 1. Lower limb muscle atrophy.

normal. Babinski sign was absent. The examination of cranial nerves and upper extremities showed no abnormalities. He presented a waddling gait.

His electromiography revealed advanced demielinizating-axonal neuropathy of motor nerves and demielinization of medium sensory nerves, moreover active denervation and chronic neurogenic changes with reinervation covering one level of the spinal cord. In MRI of the thorasic spine nothing significant was found. In cerebrospinal fluid examination the level of protein was slightly elevated as well as serum creatine kinase level.

A genetic test was performed in the course of further diagnosis. A heterozygous HSPB1 gene mutation in c.452C>T; p.Thr151Ile was found. It was reported previously and classified as pathogenic with autosomal dominant hereditary. The diagnosis of dHMN2B was confirmed. Following genetic counselling, predictive analysis for the patient's 25-year-old daughter was made showing the same variant c.452C>T; p.Thr151Ile of HSPB1 gene mutation. She is clinically asymptomatic yet, although she had mild muscle damage in EMG with still correct conduction parameters in the motor nerves.

The p.Thr151Ile mutation is a missence HSPB1 mutation that occur in α-crystallin domain, which is highly conservative among the human small heat-shock proteins. It is supposed to be mutation hot spot [5, 11]. There are cases of the Thr151Ile HSPB1

mutation described in 4 countries: Croatia, Japan, France and Poland. The family cases were found in Croatia (4 relatives) and in Poland (2 relatives). Four unrelated patients in Japan and one in France were diagnosed with this mutation [5, 9, 11, 12]. The previously described Polish family presented very late onset dHMN2B, with first symptoms occurring in 7th decade, and with pyramidal signs (positive Babiński sign), not very common in this disease [9].

In conclusion, we would like to report a Polish family with Thr151Ile HSPB1 gene mutation with diagnosed dHMN2B disease of typical time onset in a male patient and yet uncertain presentation of the disease in a younger female patient. It proved the observation that the clinical phenotypes caused by the same HSPB1 gene mutation have heterogeneity in symptoms and onset age. Finding another family in our country with the same point HSPB1 mutation could suggest the significance of active search of this mutation as a cause of dHMN2B in the Polish population.

Funding

This publication was prepared without any external source of funding.

Conflict of interest

None declared.

References

1. *Muranova L.K., Sudnitsyna M.V., Strelkov S.V., Gusev N.B.*: Mutations in HspB1 and hereditary neuropathies. Cell Stress Chaperones. 2020 Jul; 25 (4): 655–665. doi: 10.1007/s12192-020-01099-9. Epub 2020 Apr 16. PMID: 32301006; PMCID: PMC7332652.
2. *Benndorf R., Velazquez R., Zehr J.D., et al.*: Human HspB1, HspB3, HspB5 and HspB8: Shaping these disease factors during vertebrate evolution. Cell Stress and Chaperones. 2022; 27: 309–323. https://doi.org/10.1007/s12192-022-01268-y.
3. *Almeida-Souza L., Goethals S., de Winter V., Dierick I., Gallardo R., Van Durme J., et al.*: Increased monomerization of mutant HSPB1 leads to protein hyperactivity in Charcot-Marie-Tooth neuropathy. J Biol Chem. 2010 Apr 23; 285 (17): 12778–12786. doi: 10.1074/jbc.M109.082644. Epub 2010 Feb 23. PMID: 20178975; PMCID: PMC2857091.
4. *Bucci C., Bakke O., Progida C.*: Charcot-Marie-Tooth disease and intracellular traffic. Prog Neurobiol. 2012; 99: 191–225. https://doi.org/10.1016/j.pneurobio.2012.03.003.
5. *Tanabe H., Higuchi Y., Yuan J.H., Hashiguchi A., Yoshimura A., Ishihara S., et al.*: Clinical and genetic features of Charcot-Marie-Tooth disease 2F and hereditary motor neuropathy 2B in Japan. J Peripher Nerv Syst. 2018 Mar; 23 (1): 40–48. doi: 10.1111/jns.12252. Epub 2018 Feb 14. PMID: 29381233; PMCID: PMC5873406.
6. *Lewis-Smith D.J., Duff J., Pyle A., Griffin H., Polvikoski T., Birchall D., Horvath R., Chinnery P.F.*: Novel *HSPB1* mutation causes both motor neuronopathy and distal myopathy. Neurol Genet. 2016 Oct 31; 2 (6): e110. doi: 10.1212/NXG.0000000000000110. PMID: 27830184; PMCID: PMC5089436.
7. *Greenbaum L., Ben-David M., Nikitin V., Gera O., Barel O., Hersalis-Eldar A., et al.*: Early and late manifestations of neuropathy due to HSPB1 mutation in the Jewish Iranian population. Ann Clin

Transl Neurol. 2021 Jun; 8 (6): 1260–1268. doi: 10.1002/acn3.51362. Epub 2021 May 11. PMID: 33973728; PMCID: PMC8164855.

8. *Rossor A.M., Morrow J.M., Polke J.M., Murphy S.M., Houlden H., INC-RDCRC, et al.*: Pilot phenotype and natural history study of hereditary neuropathies caused by mutations in the HSPB1 gene. Neuromuscul Disord. 2017 Jan; 27 (1): 50–56. doi: 10.1016/j.nmd.2016.10.001. Epub 2016 Oct 8. PMID: 27816334; PMCID: PMC5260843.
9. *Spławski M., Broniarek K., Bonek R.*: Late onset distal hereditary motor neuropathy type IIB (dHMN IIB) — case reports. Aktualności Neurologiczne. 2018; 18: 144–147.
10. *Shen X., Zhang J., Zhan F., Tian W., Jiang Q., Luan X., Zhang X., Cao L.*: Heterogeneous Clinical Phenotypes of dHMN Caused by Mutation in HSPB1 Gene: A Case Series. Biomolecules. 2022 Sep 27; 12 (10): 1382. doi: 10.3390/biom12101382. PMID: 36291591; PMCID: PMC9599773.
11. *Evgrafov O.V., Mersiyanova I., Irobi J., Van Den Bosch L., Dierick I., Leung C.L., et al.*: Mutant small heat-shock protein 27 causes axonal Charcot-Marie-Tooth disease and distal hereditary motor neuropathy. Nat Genet. 2004 Jun; 36 (6): 602–606. doi: 10.1038/ng1354. Epub 2004 May 2. PMID: 15122254.
12. *Echaniz-Laguna A., Geuens T., Petiot P., Péréon Y., Adriaenssens E., Haidar M., et al.*: Axonal Neuropathies due to Mutations in Small Heat Shock Proteins: Clinical, Genetic, and Functional Insights into Novel Mutations. Hum Mutat. 2017 May; 38 (5): 556–568. doi: 10.1002/humu.23189. Epub 2017 Feb 25. PMID: 28144995.