© Aktualn Neurol 2018, 18 (3), p. 144–147
DOI: 10.15557/AN.2018.0020

Received: 08.08.2018
Accepted: 15.11.2018
Published: 30.11.2018

Mateusz Spławski, Katarzyna Broniarek, Robert Bonek

Late onset distal hereditary motor neuropathy type IIB (dHMN IIB) – case reports

Dystalna dziedziczna neuropatia ruchowa typu IIB o późnym początku – opisy przypadków

Department of Neurology and Clinical Neuroimmunology, Regional Specialist Hospital in Grudziadz, Grudziądz, Poland
Correspondence: Mateusz Spławski, Department of Neurology and Clinical Neuroimmunology, Regional Specialist Hospital in Grudziadz, Rydygiera 15/17, 86-300 Grudziądz, Poland, tel.: +48 56 641 44 51, +48 661 239 593, e-mail: mateusz.splawski87@gmail.com
Mateusz Spławski, Oddział Neurologii i Neuroimmunologii Klinicznej RSS w Grudziądzu, ul. Rydygiera 15/17, 86-300 Grudziądz, tel.: +48 56 641 44 51, +48 661 239 593, e-mail: mateusz.splawski87@gmail.com

Abstract

Distal hereditary motor neuropathies are a heterogeneous group of rare, genetically determined neuromuscular disorders. Distal hereditary motor neuropathy type IIB is an autosomal dominant disorder, and the onset of symptoms is observed in adulthood. Mutation refers to heat shock protein 27, also known as heat shock protein beta-1. The main symptoms of distal hereditary motor neuropathy type IIB are muscular atrophy and paresis of distal limb muscles. In this article, we present the first Polish case of familial late onset distal hereditary neuropathy type IIB with a T151I mutation (p.Thr151Ile) in one allele of the heat shock protein 27 gene. The first symptoms of the disease in our patients began around the age of 60.

Keywords: dHMN, late onset dHMN IIB, *HSP27* gene, T151I mutation

Streszczenie

Dystalne dziedziczne neuropatie ruchowe to heterogenna grupa rzadkich, uwarunkowanych genetycznie schorzeń nerwowo-mięśniowych. Dystalna dziedziczna neuropatia ruchowa typu IIB dziedziczy się autosomalnie dominująco, a początek objawów obserwujemy w wieku dorosłym. Mutacja dotyczy genu dla białka szoku cieplnego HSP27, zwanego również białkiem szoku cieplnego beta-1. Głównymi objawami dystalnej dziedzicznej neuropatii ruchowej typu IIB są zanik mięśni i niedowład mięśni dystalnych kończyn. W niniejszej pracy pragniemy przedstawić pierwszy w Polsce przypadek rodzinnego występowania dystalnej dziedzicznej neuropatii ruchowej typu IIB z wykrytą mutacją T151I (p.Thr151Ile) w jednym allelu genu *HSP27*. Pierwsze objawy choroby u naszych pacjentów pojawiły się w wieku około 60 lat.

Słowa kluczowe: dHMN, dHMN IIB o późnym początku, gen *HSP27*, mutacja T151I

INTRODUCTION

Distal hereditary motor neuropathy type IIB (dHMN IIB) is an inherited autosomal dominant condition (Reilly, 2007). The mutation is related to heat shock protein HSP27 encoded by the *HSPB1* gene which is located on the long arm of chromosome 7 (7q11.23) (Nefedova et al., 2015). The first symptoms of the disease usually appear around the age of 30 (4^{th}–6^{th} decade of life) (Rossor et al., 2017), but, in rare cases, they can also occur after the age of 60 – as late as 63 (James et al., 2008; Rossor et al., 2012). There are also reports stating that the symptoms of the disease may start around 10 years of age and earlier (Rossor et al., 2012). According to other publications, the average age of the disease onset is between 21 and 54 (Houlden et al., 2008). The frequency of distal hereditary motor neuropathies (dHMNs) is estimated at 2.14/100,000 inhabitants (1.62–2.66) (Bansagi et al., 2017). According to the European CMT Consortium, the main symptoms of the disease include atrophy and paresis of distal limb muscles (initially asymmetrical, then symmetrical), with more frequent involvement of the lower limbs (beginning with the peroneal and foot muscles) and less frequent involvement of the upper limbs. Additional symptoms include hollowed feet, calf hypertrophy, progressive hearing loss, vocal cord paralysis, arthrogryposis, and tremor. The exclusion criteria are: predominant proximal muscle involvement, sensory disturbances, significant central nervous system involvement, including pyramidal pathways, metabolic causes of muscle weakness, and an elevated creatine kinase level (2^{nd} Workshop of the European CMT Consortium, 1998). In the differential diagnosis of dHMNs, we take into account the amyotrophic lateral sclerosis (ALS), i.e. a form of selective lower motor neuron damage, spinal muscular atrophy (late SMA 4q), spinobulbar muscular atrophy (Kennedy's disease), multifocal motor neuropathy with conduction block, post-polio syndrome, chronic inflammatory demyelinating polyneuropathy with dominant motor symptoms, toxic polyneuropathy (e.g. lead poisoning), polymyositis, and lumbar root syndrome (Capponi et al., 2011; Garg et al., 2017; Rossor et al., 2012). The disease progresses slowly. The mutation of the same gene is observed in Charcot–Marie–Tooth disease type 2F (CMT 2F) (Capponi et al., 2011; Rossor et al., 2012). *HSPB1* also plays a neuroprotective role in another motor neuron disease, i.e. ALS (Heilman et al., 2017; Lupo et al., 2016), and may cause distal myopathy (Lewis-Smith et al., 2016). It has been shown that the frequency of the *HSPB1* mutation for dHMN was about 8% and for CMT2 about 4% (Capponi et al., 2011). In our article, we would like to present descriptions of the first Polish familial occurrence of late onset dHMN IIB caused by a T151I mutation (p.Thr151Ile).

CASE REPORT 1

A 64-year-old woman reported progressive muscle weakness (mainly distal, periodical right foot sag) and lower extremity muscle pain and cramps. The onset of the symptoms was at the age of 61. She presented no sensory loss or bowel and bladder dysfunctions. The patient had a history of hypothyroidism (euthyreosis, without treatment). Neurological examination revealed muscular atrophy of the lower limbs, mainly distal muscles, especially the extensors, weakness in the distal muscles of the lower limbs graded 3 on the MRC (Medical Research Council) scale (slightly more on the left side) and positive Babinski's symptom on the left side. Tendon reflexes were absent. Sensory examination was normal. Laboratory tests were normal, including complete blood count, electrolyte levels, C-reactive protein, creatine kinase, hepatic parameters, thyroid-stimulating hormone, triiodothyronine, thyroxine, parathyroid hormone, vitamin B_{12}, IgM and IgG antibodies against *Borrelia* as well as onconeural and anti-ganglioside antibodies. The examination of the cerebrospinal fluid (CSF) revealed cytosis of 7/mm^3, the protein level of 18.4 mg% and small erythrocyte sediment (blood contamination of the CSF). In electromyography (EMG), the right vastus lateralis and right tibialis anterior were neurogenic, with acute denervation and re-innervation (more severe changes in the distal muscle); the right biceps was normal. Additionally, significant symmetrical axonal damage of the motor nerve fibres of the lower limbs was found (Tabs. 1, 2). No damage to the

MNCS				
Patient	**1**		**2**	
Nerve	**Amp. – mV**	**CV – m/s**	**Amp. – mV**	**CV – m/s**
Peroneus left				
Ankle – EBD	-	-	0.26	No response
Fib. head – ankle	-	-	0.11	37.1
Knee – fib. head	-	-	0.10	37.9
Peroneus right				
Ankle – EBD	0.18	-	1.81	No response
Fib. head – ankle	0.032	42.6	1.80	44.1
Knee – fib. head	-	-	1.73	47.6
Tibialis left				
Ankle – abd. hal.	No response	No response	0.72	No response
Knee – ankle	No response	No response	0.18	47.8
Tibialis right				
Ankle – abd. hal.	0.81	No response	0.43	No response
Knee – ankle	0.25	39.2	0.30	50.6

MNCS – motor nerve conduction study; **amp.** – amplitude; **CV** – conduction velocity; **EBD** – extensor digitorum brevis; **fib. head** – fibula head; **abd. hal.** – abductor hallucis.

Tab. 1. Motor nerve conduction study

 DOI: 10.15557/AN.2018.0020

EMG						
Patient	**1**			**2**		
Muscle	**Amp. – µV**	**Dur. – ms**	**SI**	**Amp. – µV**	**Dur. – ms**	**SI**
Vastus lateralis	1315	18.4	2.3	1748	17.9	3.2
Tibialis anterior				1031	13.9	1.8
EMG – electromyography; **Amp.** – amplitude; **Dur.** – duration; **SI** – size index.						

Tab. 2. Electromyography

SNCS				
Patient	**1**		**2**	
Nerve	**Amp. – mV**	**CV – m/s**	**Amp. – mV**	**CV – m/s**
Peroneus superficialis right				
Calf – n. cutan. dor. med.	10.7	51.9	11.1	57.7
Medianus right				
Dig. II – wrist	17.4	58.2	19.5	58.0
Suralis right				
Shin centre – lat. malleolus	12.7	54.3	35.7	50.2
Ulnaris right				
Dig. V – wrist	13.4	60.6	7.8	63.9
SNCS – sensory nerve conduction study; **amp.** – amplitude; **CV** – conduction velocity; **n. cutan. dor. med.** – nervus cutaneus dorsalis medialis; **dig. II/V** – digitus II/V; **lat. malleolus** – lateralis malleolus.				

Tab. 3. Sensory nerve conduction study

sensory fibres was detected (Tab. 3). Magnetic resonance imaging of the brain and lumbosacral spine did not show any significant deviations from normal. Because of to the family history (walking problems in the patient's brother, mother, and maternal grandfather), genetic tests for *SMN1*, *SMN2*, *GARS*, *HSP22*, and *HSP27* for dHMN were ordered. A T151I mutation (also called p.Thr151Ile) was detected in one allele of the *HSP27* gene (heterozygous). The genetic tests for *SMN1*, *SMN2*, *GARS* and *HSP22* were negative. The diagnosis of dHMN IIB was established.

CASE REPORT 2

A 59-year-old patient (younger brother of the above-described patient) complained about progressive increasing weakness of the lower limbs, especially when straightening the feet, from the age of 55. He did not have any sensory disturbances or bowel and bladder dysfunctions, or no significant medical history. In the neurological examination, we observed muscular atrophy of the lower limbs, mainly distal, especially the extensors, muscle weakness in the lower limbs graded 3 on the MRC scale on the left side and 4 on the right side, both sides with positive Babinski's symptom. Tendon reflexes were absent and sensory examination was normal. As in the case of his sister, the laboratory studies revealed no significant deviations. EMG showed significant axonal damage to the motor nerve fibres of the lower limbs, especially on the left side (Tab. 1). The EMG record from the distal muscles of the upper limb was correct, while EMG of the proximal lower limb muscle showed features of chronic neurogenic changes with re-innervation, and EMG of the distal lower limb muscles revealed signs of active denervation and re-innervation (Tab. 2). Moreover, there was no damage to the sensory fibres (Tab. 3). Genetic tests for *HSP22* (*HSPB8*), *PMP22* and *BSCL2* were negative. In the study of the *HSP27* gene (*HSPB1*), by sequencing exons 2 and 3 with surrounding intron regions, a known pathogenic T151I mutation (p.Thr151Ile) was detected in one allele of the gene (heterozygous), confirming the diagnosis of dHMN IIB.

DISCUSSION

A group of dHMNs is a heterogeneous group of peripheral nervous system disorders in which the pathological process takes place in the motor cells of the anterior horn of the spinal cord (Harding and Thomas, 1980). The inheritance pattern of the disease is mainly autosomal dominant, rarely recessive or X-linked. At first, the symptoms of the disease relate to distal muscular groups of the lower limbs, but after about 5–10 years muscular atrophy and paresis may also involve the upper limbs. In 2016, there were 23 genes associated with dHMN (Heilman et al., 2017). The coding genes are divided into five subgroups (Rossor et al., 2012): associated with protein folding (*HSPB1*, *HSPB3*, *HSPB8*, *DNAJB2*, *BSCL2*), tRNA metabolism (*IHMBP2*, *SETX*, *GARS*), axonal transport (*DYNC1H1*, *DCTN1*), ion channel activity (*ATP7A*, *TRPV4*), and transcriptional control (*FBXO38*). Despite the advances in the field of medicine, about 80% of patients with dHMN have a mutation in an undiscoverable gene (Rossor et al., 2012). According to Bansagi et al. (2017), the diagnostic rate in the dHMN subgroup was 32.5%. The first cases of an

DOI: 10.15557/AN.2018.0020 AKTUALN NEUROL 2018, 18 (3), p. 144–147

HSPB1 gene mutation in dHMN IIB were described in 2004 in families in Russia, Great Britain, Croatia, Belgium and Austria (Evgrafov et al., 2004; Rossor et al., 2012).

The article presents cases of siblings with late onset dHMN IIB. In both situations, the onset of symptoms was not characteristic of dHMN IIB. According to the literature, the first signs of the disease appear around 30 years of age (Rossor et al., 2012), whilst in our patients they occurred around the age of 60 (61 and 55 years of age, respectively). Paresis and lower limb muscle atrophy were initially asymmetrical, and no sensory disturbances were observed, which is characteristic of dHMNs. We found pyramidal signs in our patients (positive Babinski's symptom), which is not typical of dHMN. The collected interview revealed the familial nature of the disease, inherited in an autosomal dominant way: walking disorders in the mother, siblings and maternal grandfather. Both patients presented a known pathogenic T151I mutation (p.Thr151Ile) in one allele of the gene (heterozygous). The same mutation in patients with dHMN is described by Evgrafov et al. (2004) in his article describing a family from Croatia. Genetic heterogeneity of distal hereditary motor neuropathies type IIA and type IIB, type VA and VB as well as type VII were observed. It has been shown that an *HSP22* mutation causes dHMN IIA and CMT type 2L (Reilly, 2007). dHMN IIB is an allelic disease with CMT 2F (Evgrafov et al., 2004). In 2016, Rossor et al. analysed the natural course of hereditary neuropathy caused by an *HSPB1* gene mutation (Rossor et al., 2017). The study involved 20 patients from 14 families. Among them, there was a case of a family of the Polish origin with CMT type 2F, in which the mutation of the *HSPB1* gene (Ser135Phe) was found in 4 persons.

In conclusion, we report the first Polish case of the familial occurrence of late onset dHMN IIB, caused by a T151I mutation.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could negatively affect the content of or claim to have rights to this publication.

References

2nd Workshop of the European CMT Consortium: 53rd ENMC International Workshop on Classification and Diagnostic Guidelines for Charcot-Marie-Tooth Type 2 (CMT2–HMSN II) and Distal Hereditary Motor Neuropathy (Distal HMN–Spinal CMT) 26–28 September 1997, Naarden, The Netherlands. Neuromuscul Disord 1998; 8: 426–431.

Bansagi B, Griffin H, Whittaker RG et al.: Genetic heterogeneity of motor neuropathies. Neurology 2017; 88: 1226–1234.

Capponi S, Geroldi A, Fossa P et al.: *HSPB1* and *HSPB8* in inherited neuropathies: study of an Italian cohort of dHMN and CMT2 patients. J Peripher Nerv Syst 2011; 16: 287–294.

Evgrafov OV, Mersiyanova I, Irobi J et al.: Mutant small heat-shock protein 27 causes axonal Charcot-Marie-Tooth disease and distal hereditary motor neuropathy. Nat Genet 2004; 36: 602–606.

Garg N, Park SB, Vucic S et al.: Differentiating lower motor neuron syndromes. J Neurol Neurosurg Psychiatry 2017; 88: 474–483.

Harding AE, Thomas PK: Hereditary distal spinal muscular atrophy. A report on 34 cases and a review of the literature. J Neurol Sci 1980; 45: 337–348.

Heilman PL, Song SW, Miranda CJ et al.: HSPB1 mutations causing hereditary neuropathy in humans disrupt non-cell autonomous protection of motor neurons. Exp Neurol 2017; 297: 101–109.

Houlden H, Laura M, Wavrant-De Vrièze F et al.: Mutations in the *HSP27* (*HSPB1*) gene cause dominant, recessive, and sporadic distal HMN/CMT type 2. Neurology 2008; 71: 1660–1668.

James PA, Rankin J, Talbot K: Asymmetrical late onset motor neuropathy associated with a novel mutation in the small heat shock protein HSPB1 (HSP27). J Neurol Neurosurg Psychiatry 2008; 79: 461–463.

Lewis-Smith DJ, Duff J, Pyle A et al.: Novel *HSPB1* mutation causes both motor neuropathy and distal myopathy. Neurol Genet 2016; 2: e110.

Lupo V, Aguado C, Knecht E et al.: Chaperonopathies: spotlight on hereditary motor neuropathies. Front Mol Biosci 2016; 3: 81.

Nefedova VV, Muranova LK, Sudnitsyna MV et al.: Small heat shock proteins and distal hereditary neuropathies. Biochemistry (Mosc) 2015; 80: 1734–1747.

Reilly MM: Sorting out the inherited neuropathies. Pract Neurol 2007; 7: 93–105.

Rossor AM, Kalmar B, Greensmith L et al.: The distal hereditary motor neuropathies. J Neurol Neurosurg Psychiatry 2012; 83: 6–14.

Rossor AM, Morrow JM, Polke JM et al.: Pilot phenotype and natural history study of hereditary neuropathies caused by mutations in the *HSPB1* gene. Neuromuscul Disord 2017; 27: 50–56.