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CASE REPORT

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Hereditary myopathy with early respiratory failure: case report

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Abstract

Background Hereditary myopathy with early respiratory failure (HMERF) is a rare myopathy that affects respiratory muscles in the early course of the disease leading to respiratory insufficiency. It is caused by mutation in titin (TTN) gene.

Case report At the age of 29, our female patient presented with a slowly progressive proximal lower limb and axial muscle weakness and respiratory issues. Her late mother had similar problems, she died at a young age and was never properly diagnosed. Patient's creatine kinase level was elevated up to three times above the upper limit of normal. Whole exome sequencing showed a pathogenic variant c.95372G>A in the TTN gene leading to the final diagnosis of HMERF. Cardiac examination was normal. Patient started to use a non-invasive nocturnal ventilation at age of 35.

Conclusions Our case is the first described case of HMERF in Serbian population. Multidisciplinary neurological and pulmonary approach is of great importance in HMERF and similar diseases. This case highlights the importance of considering early neuromuscular respiratory insufficiency as a distinctive syndrome leading to a challenging and broad differential diagnosis.

Keywords Hereditary myopathy with early respiratory failure (HMERF), Titinopathy, Respiratory failure

Background

Hereditary myopathy with early respiratory failure (HMERF) is an autosomal dominant myopathy, which is characterised by respiratory muscle weakness early in the disease course. HMERF is caused by mutation in the TTN gene that encodes sarcomere protein titin, that is necessary for normal functioning of the striated muscles. HMERF mutations are specifically located in the 119 fibronectin 3 (FN3) domain in the titin A-band, with the p.C30071R mutation being the most common [1]. HMERF affects lower more than upper extremities with early diaphragmatic weakness resulting in respiratory failure. Diagnosis is made by combining a clinical finding with specific genetic findings [2]. Mildly elevated levels of serum creatine kinase (CK), myopathic pattern on needle electromyography (EMG), and magnetic resonance imaging (MRI) of lower limb muscles can be also useful in diagnosis [3]. As there is no specific therapy, treatment consists of supportive measures with periodical neurological and pulmonary reassessments [4]. It is a very rare disease with an estimated prevalence of less than 1 in 1,000,000 [5], which is why the first Serbian case of this condition has gained importance.

Case report

We present a 35-year-old woman who was initially treated as polymyositis with prednisone because of feeling of heaviness in lower limbs and occasional joint pain that started at the age of 29. Since she had no

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improvement, she stopped the drug after 4 months of use. She noticed worsening at the age of 34 and she could not neither walk up the stairs nor get up from a low chair. At that time, she already noticed occasional breathing difficulties and night awakenings due to the shortness of breath. From the family history, her mother had similar symptoms and died at the age of 46, but she was never properly diagnosed, also her maternal grandfather had walking and breathing difficulties and died at the age of 69 due to pneumonia. Neurological examination at the age of 34 showed: high arched palate, mild atrophy and moderate weakness of the neck anteflexors, bilateral mild deltoid muscle atrophy with muscle strength 4 of 5 on a Medical Research Council scale, axial muscle weakness, mild lower limb proximal atrophy with muscle weakness of hip flexors and adductors 3, hip abductors and foot extensors 4, absent patellar reflexes and diminished Achilles reflexes. Muscle weakness slowly progressed, and she started to use a walker after six years from the disease onset. Serum CK was mildly elevated: from 350 to 513 U/l (reference range 0–171 U/l). ECG and echocardiography showed normal findings. Needle EMG indicated myopathic pattern, predominantly in deltoid and anterior tibial muscles. 1.5 T MRI of upper and lower legs showed no inflammation with fatty infiltration of adductors and posterior thigh muscles including semitendinosus muscle (Fig. 1).

Since acid alpha-glucosidase (GAA) activity was normal, and genetic testing for myotonic dystrophy type 2 (DM2) was negative, we decided to do whole exome sequencing (WES) and Sanger sequencing confirmation at the "3billion" laboratory in Seoul, Republic of Korea. Genetic testing showed that the patient had a pathogenic c.95372G>A (p.Gly31791Asp) mutation in a heterozygous state. The variant is in a 119 domain of A-band of titin where pathogenic variants associated with HMERF have been reported. Spirometry at the age of 35 showed *restrictive ventilatory disorder* (FEV1 54%, FVC 61% and FEV1/FVC ratio of 76.7%). Reduction in respiratory muscle strength was observed both in inspiratory and expiratory muscles (maximum inspiratory pressure—20.8% and maximum expiratory pressure—47.3%). Ultrasound examination showed reduced diaphragmatic movement during maximal inspiration. Polysomnography showed a mild obstructive sleep apnoea with apnoea–hypopnoea index (AHI) of 11 and aver*a*ge blood oxygen saturation (SatO2) of 93% (minimal recorded $SatO_2$ was 81%). Patient has been prescribed a non-invasive ventilation (NIV-BiLevel, IPAP 8cmH_2O; EPAP 4cmH_2O) during night.

Discussion

We present the first Serbian patient with HMERF. We initially thought about adult-onset Pompe disease. However, GAA activity was normal. Our second guess was myotonic dystrophy type 2 due to clinical presentation. However, genetic testing for DM2 was also negative. We also thought about myasthenia gravis and amyotrophic lateral sclerosis, but the clinical presentation of the disease was not convincing enough to make such a diagnosis. Since other diseases with similar presentation are rare, we ordered WES that identified a pathogenic variant in the TTN gene consistent with HMERF. HMERF is an autosomal dominant (AD) disease with variable expressivity. It

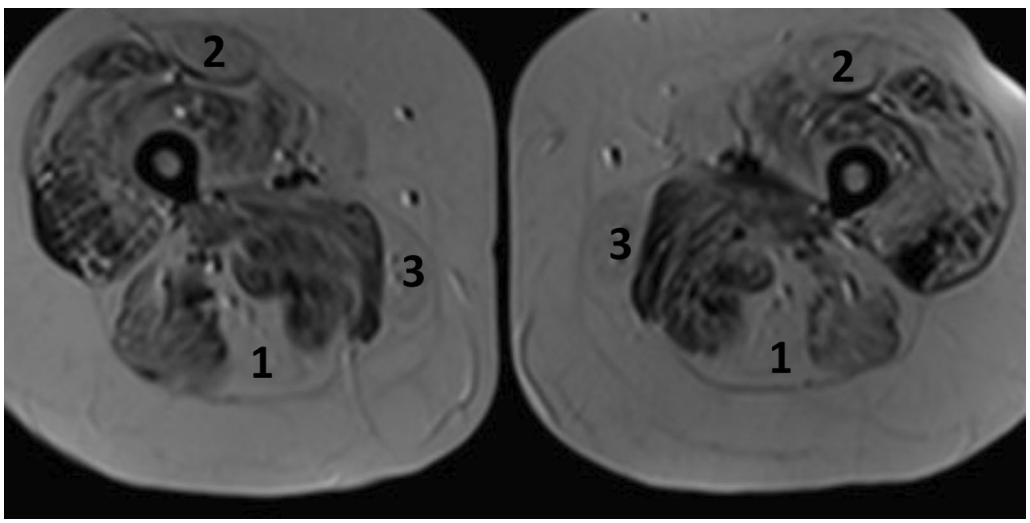

Fig. 1 Axial T2-weighted muscle MRI of the upper part of the lower limbs showing fat infiltration and fibrosis affecting all compartments with the most pronounced involvement of the semitendinosus and semimembranosus (1), rectus femoris (2) and gracilis (3) muscles

is a slowly progressive myopathy, which begins from the 3rd to the 5th decade of life as in our patient, with need of orthosis and walking aids later in the disease course [4]. It usually starts with affection of proximal lower limb muscles. Moderate rise of serum CK and chronic myopathic pattern on needle EMG are also seen in HMERF, as in our patient. Muscle MRI can be useful to make diagnosis early in the disease course when semitendinosus is already affected like in our patient. Normal cardiac findings in our patient are in line with the previous reports that heart is very rarely affected in HMERF [6]. Early diaphragmatic dysfunction of HMERF occurs while patients are still ambulant and is characterized by decreased FVC, with progressive restrictive respiratory distress [2]. Life expectancy is shortened, usually due to pulmonary complications such as respiratory infections [4]. According to the data available from the literature, the specific mutation of the titin gene in our patient belongs to the group of rare forms of this mutation, described so far in only a few people in two families in Japan and North America [7]. The average age at the onset of symptoms is 42 years (in our patient, symptoms began at the age of 29). Most affected individuals require walking aids within a few years of onset, many require ventilatory support in their 40 s (in the case of our patient at the age of 36) [4].

Conclusions

We described the first Serbian patient with HMERF, diagnosis that should be considered in patients with adult onset proximal or distal myopathy and early respiratory failure. Muscle MRI with fatty infiltration of semitendinosus and peroneus longus muscles may help in early diagnosis. Final diagnosis is made by genetic testing. Considering the early development of respiratory pathology, the evaluation of pulmonary function is of great importance. Early implementation of non-invasive ventilation can improve the quality of life of these patients.

Abbreviations

HMERF	Hereditary myopathy with early respiratory failure
MRI	Magnetic resonance imaging
WES	Whole exome sequencing
EMG	Electromyography

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Author contributions

MP and MR contributed to writing and interpreting patient data; SP was a significant contributor to writing the manuscript; RP drafted the manuscript; IC was the first one to come up with the idea and was a significant contributor to writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Since this is a case report, there is no need for ethical approval. Written informed consent was obtained from the patient to publish this case report and accompanying images.

Consent for publication

Written informed consent was obtained from the patient to publish this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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