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CASE REPORT

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A Rare Case of Charcot-Mari-Tooth Disease Type 2S in a 20-year-old Man

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Abstract

Charcot-Marie-Tooth disease type 2 (CMT2S) is rare form of Charcot-Marie-Tooth disease (CMT) that is characterized by a mutation in the *IGHMBP2* gene. This gene encodes a helicase superfamily member that binds a specific DNA sequence from the region of the immunoglobulin mu chain switch. Mutation of this gene leads to spinal muscle atrophy with respiratory distress type 1 and CMT2S. This case report presents a 20-year-old male with genetically confirmed CMT2S having clinical respiratory involvement and symmetrically involved lower extremities. DNA sequencing revealed a previously unknown heterozygous mutation in the exone 2 of the *IGHMBP2* gene leading to the replacement of the amino acid in the 46 position of the protein (chr11q13.3: 68673587 G>C). These atypical features widen the clinical spectrum of CMT2S. This is the first described case of a previously unknown mutation in the Russian population with confirmation of its genetic study. In describing this clinical case, we also improve diagnostic management and try to increase the alertness of various doctors towards neuromuscular diseases, including CMT. **(International Journal of Biomedicine. 2017;7(4):324-326.)**

Key Words: Charcot-Marie-Tooth disease • hereditary neuropathy • chromosome 11q13.3 • heterozygous mutation

Abbreviations

CMT, Charcot-Marie-Tooth disease; **CMT2,** CMT type 2; **CMT2S**, CMT type 2S; **DNA**, deoxyribonucleic acid; **EMG**, electromyography; **HSMN2S**, hereditary sensory and motor neuropathy type 2S; **NCV**, nerve conduction velocity; **IGHMBP2**, immunoglobulin mu binding protein 2.

Introduction

Hereditary sensory and motor neuropathy (HSMN) is a group of common neuromuscular disorders with heterogeneous clinical presentations and genetic causes. Detailed neuromuscular evaluations, including nerve conduction studies, laboratory testing, and histopathologic examination, can assist in identification of the inherited component beyond family history. Neurophysiologic studies, including needle EMG, are very useful for distinguishing acquired from inherited mechanisms. Chronic motor unit potential changes on a needle EMG, characterized by amplitude >2 mV and duration >15–20 msec, can help establish the chronic nature of the inherited neuropathy.[1] However, genetic testing increasingly enables definitive diagnosis of a rare form of HSMN.

CMT is genetic heterogeneous form of HSMN. CMT2 is an axonal (non-demyelinnating) HSMN characterized by distal muscle weakness and atrophy. Nerve conduction velocities are usually within the normal range. However, occasionally they fall in the low-normal or mildly abnormal range (35-48 m/sec), where peripheral nerves are not enlarged or hypertrophic. CMT2 shows extensive clinical overlap with CMT1. However, in general, individuals with CMT2 tend to be less disabled and have less sensory loss than individuals with CMT1. A threshold of 38 m/sec for *n. medianus* conduction is often used clinically to distinguish CMT1 from CMT2.[2]

Molecular genetic testing is possible for pathogenic variants in numerous genes associated with CMT2 phenotypes.

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An alternative genetic testing strategy is the use of a multi-gene panel that includes genes associated with CMT and other genes of interest.[3] Panels exist for dominantly and recessively inherited CMT as well as demyelination and axonal forms. Larger (all-inclusive) panels may also be available. Most individuals diagnosed as having autosomal dominant CMT have an affected parent, although occasionally the family history is negative. However, CMT2S is extremely rare, so the prevalence among the population is unknown.[4]

Case Report

A 20-year-old male has been observed at the University Clinic since he was 18. He first applied in June 2016 because of snoring. There was no complaint of any major illness in the past. At the first visit, on examination a large number of subcutaneous hematomas on the lower extremities attracted attention. It turned out that he works as a loader and when lifting the load with his hands bent at the elbows, the cargo often falls out of his hands. This problem is not present if he lifts the cargo with outstretched hands. He was examined by a neurologist.

Detailed evaluations

When communicating, the patient was apathetic, the mood was low, and he carried out some commands very slowly. Results of psychological tests were that he has a depressive syndrome.

We found the reduced sensation with stocking-glove distribution in the distal limbs; his feet and lower third of the shins were pale by the type of high socks, with local hypothermia 2 degrees Celsius below the temperature of the proximal parts of the limbs and trunk. There were a distal hyperhidrosis of the hands and feet, dystrophic changes in the skin and nails of both feet with a local anthrite, thinning of the skin, and minor skin lesions covered with hemorrhagic crusts, mainly on the back of the feet and the front surface of the lower third of the tibia at compression sites when wearing shoes.

Cranial nerves: the adjusting horizontal nystagmus with gaze to the sides, the weakness of convergence on the left and the dysarthria of the 1st degree.

The motor sphere: the hypotrophy and hypotonia of the muscles of both hands, especially *m. hypotenari*. A decrease in their strength to 3-4 points. Bicepital reflexes were moderate on both sides, carporadial reflexes were low. There was moderate hypotension and hypotrophy of the muscles of the feet and the lower third of the shins, and clew toes of both feet. Knee reflexes were moderate, Achilles reflexes low (less on the right). Standing on the toes was possible, but without vision control there was a risk of falls. Standing on heels was difficult with the risk of falling and with the formation of postures to compensate balance. Execution of the heel-knee test was difficult due to a sensitive ataxia; it was performed by the patient slowly with mild bilateral dysmetry. In the Romberg position he was stable; without vision control, there was a disturbance of balance. Violations of pain sensitivity were not found.

Hereditary anamnesis

There were no manifestations of this disease in the first- or second-degree relatives.

Laboratory testing

Biochemical analysis: the level of creatine kinase and lactate dehydrogenase was normal.

EMG/NCV tests: low speed of motor conduction on *n. medianus* 29.8 m/sec and *n. peroneus* 43.8 m/sec and decrease of M-response *n. medianus* 2.22 (-75.3%), *n. peroneus* 2.3 (-34.4%).

Esthesiometry: From the distal sections of the lower limbs (ankles), there was a significant asymmetric (more to the left) decrease in vibration sensitivity at frequencies 8, 16, 32, 63, 125, 250, and 500 Hz, with a tendency to fall out at high frequencies.

Cardiorespiratory monitoring: there are no data for sleep apnea syndrome. Podography: high arch, claw toes.

DNA sequencing data

The search for pathogenic mutations associated with hereditary neuromuscular diseases was carried out in the laboratory of molecular pathology, the GENOMED laboratory (Moscow, Russia). The search revealed a previously unknown heterozygous mutation in the exone 2 of the gene *IGHMBP2* leading to the replacement of the amino acid in the 46 position of the protein (chr11q13.3: 68673587 G>C).

Discussion

The term “CMT” includes a clinically and genetically heterogeneous group of disorders, which are the most common inherited neuromuscular disorders with an estimated prevalence of one in 2,500 individuals.[5] Not only does CMT present with a significant genetic heterogeneity but it may also segregate with different Mendelian patterns: autosomal-dominant (AD), autosomal-recessive (AR) or X-linked.[6]

Previously it was believed that the described variant of the genetic mutation in the *IGHMBP2* gene leads to the emergence of only spinal muscular atrophy with diaphragm paralysis (OMIM: 604320).[7] However, in 2014, cases of patients from England, America, Serbia, Poland, Italy, Korea, and Vietnam were first described with a mutation in the same gene leading to the clinical presentation of HSMN2S (OMIM: 616155).[8]

The young man turned to the doctor with complaints of a breathing disorder, which is typical for the clinical picture of spinal muscular atrophy with diaphragm paralysis. However, the conducted examinations showed no significant deviations from the norm. To clarify the diagnosis, DNA sequencing was recommended.

Exome sequencing techniques have non-standardized, highly variable coverage; of particular note are regions of the exome refractory to accurate sequencing by this method (including genes with pseudogene, highly repetitive coding regions, and large deletions and duplications). It is for this reason we use this method.

DNA sequencing revealed a previously unknown heterozygous mutation in the exone 2 of the gene *IGHMBP2* leading to the replacement of the amino acid in the 46 position of the protein (chr11q13.3: 68673587 G>C). Homozygous and compound heterozygous mutations in this gene are described in patients with CMT axonal form 2S type disease. In spite of

the fact that in this clinical case the mutation is heterozygous, the clinical picture corresponds to CMT2S. This type has been described quite recently; the clinical picture is not yet fully formed. Presenting this case, we are replenishing the world database. The boy was admitted to the University Clinic at the age of 18 with an extensive clinical picture. Earlier he had undergone routine medical examinations in educational institutions and in various private clinics, but none of the doctors suspected the disease. He never went for additional examinations or consultations with outside doctors. In describing this clinical case, we also improve diagnostic management and try to increase the alertness of various doctors towards neuromuscular diseases, including CMT.

Conclusion

The data from clinical and EMG/NCV tests of the patient, as well as the presence of a mutation in the heterozygous state in the *IGHMBP2* gene, revealed by the targeted sequencing, has allowed us to establish the final diagnosis: CMT2S (OMIM: 616155), heterozygous carrier of the mutation 68673587 G>C in the exon 2 of the *IGNMBP2* gene, a sporadic case first identified; distal peripheral upper paraparesis with predominant involvement of ulnar nerves and the ulnar group of muscles of both hands of 1 degree of severity, with moderately pronounced atrophy and hypotension of the hypotenor muscles (forming a "flat" hand), the initial signs of angiotrophoneuritic syndrome at the level of the hands; distal peripheral lower paraparesis in the predominant lesion of the tibial nerves and the tibial muscle group, with deformity of both feet as hollow, sensory dinamostatic ataxia of 1 degree of severity and angiotrophoneurotic syndrome at the level of the feet and lower third of the tibia with trophic changes in the skin and its derivatives, cornflowers on the rear of the foot.

While visiting a neurogeneticist, the patient received explanations about the disease, prognosis of life, ability to work, about the methods of habilitation and way of life. With the help of psycho-correction techniques, the depressive syndrome regressed. At the time of the last admission, the young man was going to college to become an electrician. He plans to enter the university, marry and take care of his health. This is the first described case of a previously unknown mutation in the Russian population with confirmation of its genetic study.

Competing interests

The authors declare that they have no competing interests.

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