Case Report

A Türkiye Case with a Newly Discovered *SORD* Gene Mutation as the Cause of Distal Hereditary Motor Neuropathy

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ABSTRACT

Sorbitol dehydrogenase gene (SORD) is inherited as autosomal recessive and its different type biallelic mutations have been defined as the cause of distal hereditary peripheral neuropathy (dHMN) and charcot marie tooth (CMT) disease in the last years. With the newly defined cases, electrophysiological, clinical and genetic features will become clear. Furthermore, ongoing studies to reverse the clinical outcome caused by the high sorbitol amount caused by this gene defect are promising in terms of treatment. In this study, we described a Turkish case, a male patient with a *SORD gene* homozygous novel *c.755G>T p.(Gly252Val)* missense mutation and positive symptoms.

Keywords: *SORD Gene, CMT Disease, Distal Hereditary Motor Neuropathy.*

ÖZ

Distal Kalıtsal Motor Nöropatinin Nedeni Olarak Yeni Keşfedilen SORD Gen Mutasyonunun Olduğu Bir Türkiye Olgusu

Sorbitol dehidrojenaz geni (SORD) otozomal resesif olarak kalıtılır ve farklı tiplerdeki biallelik mutasyonları son yıllarda distal kalıtsal periferik nöropati (dHMN) ve charcot marie tooth (CMT) hastalığının nedeni olarak tanımlanmıştır. Yeni tanımlanan olgularla birlikte elektrofizyolojik, klinik ve genetik özellikler de netleşecektir. Ayrıca bu gen defektinin neden olduğu yüksek sorbitol miktarının neden olduğu klinik sonucu tersine çevirmeye yönelik devam eden çalışmalar tedavi açısından umut vericidir. Bu çalışmada *SORD geninde* homozigot yeni keşfedilen *c.755G>T p.(Gly252Val)* missense mutasyonu ve pozitif semptomları olan bir Türk erkek hastayı tanımladık.

Anahtar Sözcükler: *SORD geni, CMT hastalığı, distal kalıtsal motor nöropati.*

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Distal hereditary motor neuropathy is a disease with many subtypes that mostly manifests in childhood and adolescence, shows slow progression, has a high amount of genetic heterogeneity and can show clinical similarities with other hereditary neuropathies, especially CMT axonal form (1-3). Although stated in some studies as a variant of CMT axonal form, it is distinguished by the absence or minimal of sensory involvement (2, 4). Sorbitol dehydrogenase is an enzyme that plays an important role in sugar metabolism by converting sorbitol to fructose (5). It was identified in 2020 that various biallelic mutations in the SORD gene can cause peripheral neuropathy. It is autosomal recessively inherited. The various SORD gene biallelic mutations are one of the common genetic causes of dHMN and CMT2 forms showing axonal nerve conduction findings (6-8). The homozygous c.755G>T p.(Gly252Val) mutation that is seen in a case described in this study is shown for the first time to the best of our knowledge. In this study, we tried to describe the clinical features, nerve conduction studies and disease type of a case with this mutation.

CASE REPORT

A 28 years old male patient applied to our clinic with the complaint of difficulty walking. He stated that the complaint history is about 11 years and it is progressing gradually. He stated that he has seven siblings and that there were no symptoms in his family. In his current examination, the proximal extremities are almost complete, the distal extremities are approximately 4+/5 in the upper extremity, the plantar flexion of the ankle is 4/5 in the lower extremities, the dorsal flexion is 3/5 on the left and 2+/5 on the right (drop foot), and deep tendon reflexes are mildly hypoactive in the upper extremities. Babinski's sign and Achilles reflex were absent in the lower extremities. The patient also descri-

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bed cramps and pain in the legs for a long time. There was peroneal atrophy and claw toes appearance in the lower extremities (Figure 1).

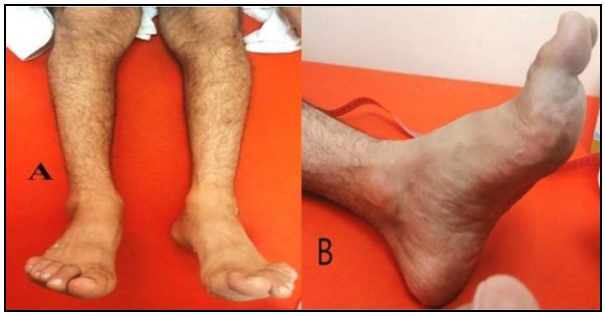

Figure 1. *Distal atrophy and foot drop (Bilateral but more prominent on the right) (**A**), pes cavus and claw toes on the left foot (**B**).*

Dermographism was found positive in the patient who described more than expected injuries after hard contact with his skin (Figure 2).

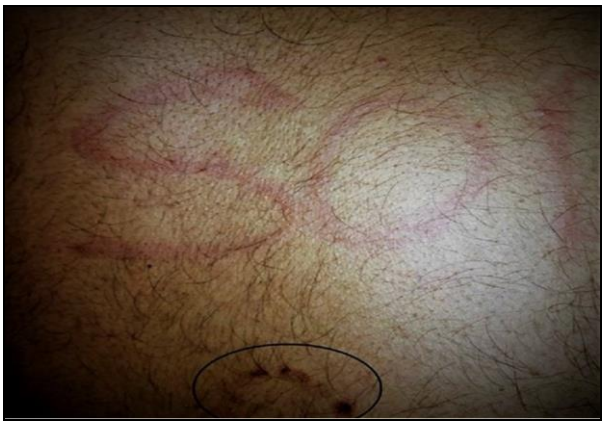

Figure 2. *Dermatographism and skin lesion due to sensitivity to previous trauma.*

In nerve conduction studies, findings consistent with distal prominent motor axonal neuropathy were observed (Table 1). The patient's cognitive functions and brain MR imaging are within normal limits.

Table 1. *Nerve conduction studies at the first admission of the patient.*

Motor nerves conductions				Sensory nerves conductions		
	Amplitude (mV)	**Velocity (m/s)**	**Distalmotorlatency (ms)**		**Amplitude (µV)**	**Velocity (m/s)**
Median nerve (right)	11.65	54.7	3.54	Median nerve (right)	10.80	55.9
Ulnar nerve (right)	8.59	50.3	3.04	Ulnar nerve (right)	9.30	42.7
Peroneal nerve (right)	1.26	36.7	6.15	Sural nerve (right)	28.60	55.6
Tibial nerve (right)	3.28	35.2	4.35	Sural nerve (left)	34.20	52.4
Peroneal nerve (left)	6.99	37.8	4.35			
Tibial nerve (left)	3.33	39.6	4.50			

Genetic Evaluation

DNA extraction was performed according to instructions (Maxwell RSC Blood DNA kit, Promega, USA). The concentration of DNA samples was determined using Qubit 3.0 (Thermo Fisher Scientific). The libraries for sequencing were constructed following the instructions of Twist Human Core Exome Kit protocol (Twist Bioscience, USA). Next-gene sequencing was performed on a Novaseq system (Illumina, USA). Sequence data analysis using Sophia DDM (Switzerland). The analysis revealed a homozygous variation (*c.755G>T p.(Gly252Val))* in the *SORD* gene. On the other hand, *silico* prediction data bases, such as MetaRNN, BayesDel, PROVEAN, CADD, SIFT indicated that the variation was classified as 'pathogenic.' In addition, this variant has not been observed as homozygous in the healthy population according to Genome Aggregation Database (gnomAD). According to the American College of Medical Genetics (ACMG) 2015 criteria (Richards S, Aziz N, Bale S, et al. Standards and Guidelines for the Interpretation of Sequence Variants: a Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May; 17 (5): 405-24.), the variant was classified as class 3 clinical significance. Our opinion that given the similarity between the patient's clinical presentation and the expected findings of the "sorbitol dehydrogenase deficiency" phenotype caused by homozygous pathogenic variant features, the patient in the similar variant has the expected findings of the "sorbitol dehydrogenase deficiency with peripheral neuropathy".

DISCUSSION

It has been understood that the recently discovered autosomal recessive SORD mutation is a significant cause of dHMN and CMT2 (axonal). In our study, the pathogenic variant was found to be homozygous novel c.755G>T p.(Gly252Val) missense mutation. In a previous study in China, a homozygous mutation of c.757 delG (p.A253Qfs∗27) was detected in two of the five cases. In the other 3 cases, besides the heterozygous c.757 delG (p.A253Qfs∗27) allele, the second possible pathogenic variant was C>T (p.P244L), c.776 C>T (p.A259V) or c.851T>C (p.L284P) was found. In this

study, two cases with episodic pain, numbness and a positive pinprick test were considered as minor sensory deficits and defined as CMT2, and the other three cases were accepted as dHMN with pure motor involvement. There was mild upper extremity distal involvement in two cases, which were also considered as CMT2 (6). In the study of Cortese et al. (9), just as in our case, 69% of the cases were sporadic and had no family history. In the 45 cases included in this study, 23 were compatible with axonal CMT and 18 with dHMN. In this study, c.753delG (p.Ala253GlnfsTer27) allele was the most common mutation as missense homozygous or compound heterozygous. In this study, it was stated that the use of aldose reductase inhibitors could be a safe and effective treatment for SORD-associated inherited neuropathy. In the study of Yuan et al. (7), three cases were identified and two cases had c.757delG (p.A253Qfs*27) homozygous mutations, and one case had c.757delG (p.A253Qfs*27) and c.625C>T (p.R209X) compound heterozygous mutations. In this study, pinprick test was found positive in two cases, glove-sock-like sensory defect was observed in one patient and these three cases were defined as axonal CMT. The known c.757delG (p.Ala253GlnfsTer27) homozygous mutation was seen in three of the 4 families reported in the study of Dong et al (8). In the other family, as a new mutation c.908 + 1 G > C and c.404 A> G (p.His135Arg) was reported. Walking difficulty, distal motor neuropathy seen in nerve conduction study and distal muscle atrophy were observed in these cases. These 4 cases were reported as dHMN (8). In a study conducted in the Czech Republic, a homozygous c.757del(Ala253Glnfs*27) mutation was found in nine of 18 cases from 16 different families, and in the other 9 cases the compound heterozygous second allele was 6×c.458C>A p.(Ala153Asp), 1×c.218C>. T p.(Ser73Leu), 1×c.503G>A p.(Gly168Asp), and 1×c.553G>A p.(Gly185Arg) were seen. Two of these 18 cases were reported as dHMN, 14 cases as CMT2 and two cases as CMT intermediate type (10). SORD is one of the two enzymes that causes intracellular oxidative stress caused by hyperglycemia by converting sorbitol to fructose via polyol pathway using the NAD cofactor. The other enzyme is aldose reductase (AR). AR, which uses the NADPH cofactor, it converts glucose to sorbitol and participates in the polyol pathway (11). SORD defect causes synaptic degeneration and progressive motor impairment (9). It has been observed that aldose reductase inhibitors can be effective in SORD defective cell models and it has been stated that they increase the climbing ability in these patients (12, 13). Just like aldose reductase inhibitors, many hopeful genetic studies are in progress in clinical trials (12, 14).

DISCLOSURE

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Consent Form: Informed voluntary consent form was taken from the patient.

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