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Case Report

Report of a Patient with Multiple Mutations Leading to Charcot-Marie-Tooth Disease and Distal Spinal Muscular Atrophy: A Case Report

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Abstract

The Charcot-Marie-Tooth disease is a group of progressive disorders that affects the peripheral nerves and results in loss of sensation and atrophy of muscles in lower limbs. There are several types of Charcot-Marie-Tooth and multiple genes are associated with this disease. Distal spinal muscular atrophy is an extremely rare disorder characterized by progressive pure lower motor neuron involvement. A 24 yr old woman using wheelchair referred to Farhud Genetic Clinic, Tehran, Iran in 2019, with progressive muscular atrophy, pain and Electromyography test suggesting Charcot-Marie-tooth. Both feet and hands were involved. Whole exome sequencing was performed on extracted DNA from her blood sample. We report the first case of a patient with different types of Charcot-Marie-Tooth and distal spinal muscular atrophy simultaneously, which are as a result of mutations in multiple genes; this case is very uncommon.

Keywords: Charcot-marie-tooth; Distal spinal muscular atrophy; Neuropathy

Introduction

Charcot-Marie-Tooth disease is a group of progressive disorders and the most common inherited neuropathy that affects peripheral nerves. It is also known as hereditary sensory and autonomic neuropathy. Initially, it was described by Charcot and Marie in Paris and Tooth in London in 1886 (1, 2). CMT prevalence is estimated at about 1 in 2500 individuals with three different inheritance patterns: autosomal dominant, autosomal recessive and X-linked (3-5). At least 40 genes/loci have been identified in relation to this disease (4-6). CMT is classified by its clinical symptoms, neurophysiological and genetic patterns to different types (CMT1, CMT2, CMT3, and CMT4) (5-7).

CMT2 has an autosomal dominant inheritance and is delineated by abnormalities in axons (non-demyelinating). The nerve conduction velocity in CMT2 is normal, but the strength of impulses is restricted. CMT4 effects either the axon or mye-

lin and has an autosomal recessive inheritance pattern. The nerve impulses are both slowed and reduced in strength, probably due to abnormalities in both axon and myelin (5-9).

CMT is identified by slowly progressive weakness and atrophy of muscles and distal extremities, loss of distal neural sensors and skeletal deformities. Clinical features include early onset especially within the two first decades of life, familial occurrence, reduction or loss of tendon's reflexes, scoliosis or foot abnormalities such as pes cavus and hammertoes and Later, hands could be involved too (1-5, 7). Some patients show more severity of the disease, leading to being limited to a wheelchair (about 5%) or bed and respiratory insufficiency occurrence. although their quality of life is almost always at risk, they have a reproductive life (5, 8).

Clinical diagnosis is based on symptoms found by the physician, electromyography (EMG) and nerve conduction velocity (NCV) tests and sometimes sural nerve biopsy is needed. Family history would be considered too. It is also possible to do molecular genetic tests that help to find variants matched with the presented phenotype (10-12).

The most frequently detected mutation is duplication of PMP22 gene located on chromosome 17p11.2-p12. GJB1, MPZ, INF2, DNM2, YARS, GNB4, NEFL, MFN2, GDAP1, KARS, LMNA, GARS, PRX, SH3TC2 are some of the genes that mutations of them is associated with a specific type of CMT (5, 7, 8, 13).

Spinal muscular atrophies are a heterogeneous group of motor system disorders characterized by progressive pure lower motor neuron involvement. Distal spinal muscular atrophy is an extremely rare and slowly progressive disorder that presents in adults involving the lower limb muscles. Research is on to use gene therapy to treat this otherwise untreatable entity (14, 15).

Case presentation

A 24 yr old woman suffering from muscular atrophy referred to Farhud Genetic Clinic, Tehran, Iran in 2019. She was able to run until age 10 and to walk without any help until 15 yr old. Ankle deviation presence began at age 10 and correction by surgery was performed at age 16, so the feet appearance is normal.

Based on an EMG/NCS test through the first diagnosis it was suggested that she has Charcot-Marie-tooth disease. Taking a molecular genetic test was recommended, but she denied. There was the ability to walk by cane and crutch in her until 20 yr old. Hands are involved too. Moderate joint construction, claw-shaped hands, and scoliosis are evident. She can use her hands to do her personal stuff.

There was no loss of hands or foot sensation or sleep problem but, she had a feeling of pain especially in shoulders and back. No similar case in her family was present. As the disease was getting worse and she was born out of a second-degree consanguineous marriage. The whole-exome sequencing (WES) assay was performed on the DNA extracted from her blood sample to identify disease type and mutations by her permission.

Ethical approval

This report is conducted with full respect for ethical issues and with the consent and permission of the patient.

Results

EMG/NCS tests showed low amplitude compound muscle action potentials of both tibia, DPN and median N, absent sensory nerve action potentials (SNAP) of low amplitude at upper limbs (Tables 1-4).

All evidence was compatible with the progressive generalized non-myotomal neurogenic process at upper and lower limbs which was distally more than proximally. This condition involved mixed old and active ongoing axon loss findings. Such results mean heredity sensory-motor neuropathy such as Charcot-Marie-Tooth. The result of WES study indicated the presence of multiple mutations in LMNA, GARS, PLEKHG5, SH3TC2 and PRX genes. Table 5 shows all existing variants.

Table 1: Motor nerve conduction study

Side	*Nerve*	*D_latency (ms)*	*Amp (mv)*	*NCV (m/s)*	*F_wave (ms)*
R&L	Tibial	4.2	0.9	33	-
R&L	DPN/EDB	Unobtainable	-	-	Unobtainable
R&L	Median	4.2	2.6	44	25
R&L	ulnar	4	6	56	-

Table 2: Sensory nerve conduction study

Side	*Nerve*	*D_latency (ms)*	*Amp(mv)*	*NCV(m/s)*
R&L	Median	3.2	5	33
R&L	Ulnar	3.1	4	-
R&L	Sural	Unobtainable	-	44
R&L	SPN	Unobtainable	-	56

Table 3: Hoffmann's reflex

Side	*Nerve*	*Latency (ms)*
R	Median	Unobtainable
L	Median	Unobtainable
R	Tibial	Unobtainable
L	Tibial	Unobtainable

Table 4: Electromyography (EMG)

Side	*Muscle*	*IA*	*Fib*	*Psw*	*Fasc*	*Others*
R&L	Proneus Longus SPN L5,S1	N	2+	2+	1+	CRD
R&L	Gastrocnemious Tibial S1,S2	N	2+	2+	1+	CRD
R&L	Sural Tibialis. Ant DPN L4,L5	N	2+	2+	1+	CRD
R&L	Gluteus Maximus IGN L5-S2	N	2+	2+	1+	CRD
R&L	F.D.I Ulnar C8, T1	N	2+	2+	-	--
R&L	abductor pollicis brevis median C8,T	N	2+	2+	-	--

Table 5: Identified variants

No	*Gene*	*Variant*	*Change*	*Mutation type*	*Location*
1	LMNA	rs59885338	c.892C>T p.Arg298Cys	Missense	1q22
2	GARS	rs1049402	c.124C>G p.Pro42Ala	Missense	7p15
3	PRX	rs139624657	c.4077_4079delGGA p.Glu1361del	Inframe deletion	19q13.2
4	PRX	rs268674	c.3394G>A p.Gly1132Arg	Missense	19q13.2
5	PRX	rs268671	c.2645T>C p.Val882Ala	Missense	19q13.2
6	PLEKHG5	Rs113541584	c.2166_2168delGGA p.Glu723del	Inframe deletion	1p36
7	SH3TC2	rs6875902	c.1402G>T p.Ala468Ser	Missense	5q32

Discussion

This report shows a patient referred to the Farhud genetic clinic, which has different types of CMT with distal muscular atrophy simultaneously due to 7 mutations in 5 different genes, which is very uncommon.

There is 7 mutations in the studied patient of this report. c.892C>T (p.Arg298Cys) mutation in LMNA gene, c.124C>G (p.Pro42Ala) mutation in GARS gene, c2166_2168delGGA (p.Glu723del) mutation in PLEKHG5 gene, c.1402G>T (p.Ala468Ser) mutation in SH3TC2 gene and also c.4077_4079delGGA (p.Glu1361del), c.3394G>A (p.Gly1132Arg) and c.2645T>C (p.Val882Ala) mutations in PRX gene have been identified in this case.

Lamin A/C proteins are a class of intermediate microfilaments encoded by LMNA gene. These structural proteins have an important role in nuclei membrane and are associated with CMT type 2B. The c.89C>T (p.Arg298Cys) mutation in the LMNA gene leads to CMT2B1 (16).

The GARS gene codes for an enzyme called Glycyl-tRNA synthetase and is involved in some neuropathies. CMT2D and DSMA type V are caused by c.124C>G (p.Pro42Ala) mutation (17, 18). PLEKHG5 has a role in some nerve cells. There is only one phenotype identified for c.2166_2168delGGA (p.Glu723del) mutation which is distal spinal muscular atrophy (19). SH3TC2 encodes a protein with protein-protein interactions in Schwann cells. Researchers have found more than 30 SH3TC2 gene mutations that cause CMT4C. c.1402G>T p.Ala468Ser mutation is associated with CMT4 (20).

The PRX gene provides instruction for Periaxin, a protein that is necessary for the maintenance of myelin. The patient shows compound heterozygosity in three positions of c.4077_4079delGGA (p.Glu1361del), c.3394G>A (p.Gly1132Arg) and c.2645T>C (p.Val882Ala) that are all responsible for CMT4F (8, 21). All mutations are checked by Ensemble Gene browser, ClinVar-NCBI, and MedGen-NCBI databases.

Although some of these mutations are benign, the presence of these mutations which all lead to neuromuscular disorders in one person is interesting. Since the patient's family was not available, molecular genetic examinations were not achievable. Therefore, it can't be declared if these mutations are inherited from the parents or they are de novo.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interests

The authors declare that there is no conflict of interests.

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