CASO CLÍNICO/CASE REPORT

A Family with Subclinical Charcot-Marie-Tooth Disease Associated with a Mutation in the *MPZ* Gene

Uma Família com Doença de Charcot-Marie-Tooth Subclínica Associada a uma Mutação no Gene *MPZ*

Beatriz Madureira [1,*], Isa Correia [2], Hildeberto Correia [2,3], Simão Cruz [1]

1-Serviço de Neurologia, Hospital Prof. Dr. Fernando Fonseca, EPE, Amadora, Portugal
2-Laboratório de Genética Médica, Joaquim Chaves Saúde, Lisboa, Portugal
3-Departmento de Genética Humana, Dr. Ricardo Jorge National Health Institute, Lisboa, Portugal

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Abstract

Charcot-Marie-Tooth (CMT) disease is an inherited neuropathy characterized by progressive motor and sensory impairment. Mutations in the myelin protein zero (*MPZ*) gene are the second most common cause of CMT and are often associated with severe clinical presentations. We describe the case of a 31-year-old woman who had an incidental diagnosis of an intermediate neuropathy on nerve conduction studies, without any symptoms or clinical signs. Genetic analysis identified a novel *MPZ* mutation, c.275dup [p.(Thr94Aspfs*28)], predicted to produce a truncated, non-functional protein. Over a follow-up period of seven years the patient remains asymptomatic. The patient's father, also asymptomatic and without findings relevant to observation, presented similar alterations in nerve conduction studies, but did not undergo genetic studies. This case broadens the known phenotypic spectrum of *MPZ*-related neuropathies and suggests that additional genetic or epigenetic factors may influence disease expression.

Resumo

A doença de Charcot-Marie-Tooth (CMT) é uma neuropatia hereditária caracterizada por défices sensitivos e motores lentamente progressivos. Mutações no gene da proteína zero da mielina (*MPZ*) constituem a segunda causa mais comum de CMT e estão frequentemente associadas a apresentações clínicas graves. Descrevemos o caso de uma mulher de 31 anos que teve um diagnóstico incidental de neuropatia com desmielinização uniforme nos estudos de condução nervosa. Não apresentava quaisquer sintomas ou sinais clínicos associados. A análise genética identificou uma nova mutação no gene *MPZ*, c.275dup [p.(Thr94Aspfs*28)], que provavelmente resulta numa proteína truncada e disfuncional. No decorrer do período de seguimento de sete anos, a doente permaneceu assintomática. O pai da doente, também assintomático e sem achados relevantes à observação, apresentou alterações semelhantes nos estudos de condução nervosa, mas não realizou estudo genético. Este caso aumenta o espectro fenotípico conhecido das neuropatias associadas a mutações no gene *MPZ* e sugere que fatores genéticos adicionais ou epigenéticos podem influenciar a expressão da doença.

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***Autor Correspondente / Corresponding Author:**
Beatriz Isabel Esteves Madureira
IC19 276,
2720-276 Amadora, Portugal
beatriz.e.madureira@gmail.com

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Introduction

Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy[1–4] and consists of a slowly progressive motor and sensory neuropathy, which usually includes clinical findings such as distally predominant muscle weakness and atrophy, especially in the lower limbs, pes cavus and large fibre sensory loss.[2,3,5]

From an electrophysiological standpoint, it is possible to classify CMT into demyelinating, axonal or intermediate, according to the median or ulnar motor nerve conduction velocity (NCV).[3,6,7]

Currently, more than 130 genes are known to cause CMT. Duplication of *PMP22* gene is responsible for approximately 70% of demyelinating CMT cases.[1,5,10] Mutations in the myelin protein zero (*MPZ*) gene are the second most common cause of CMT. This gene encodes myelin protein zero, a major component of the myelin sheath in the peripheral nervous system, which serves as an adhesion molecule between myelin lamellae.[7,10–12] Over 200 different pathogenic mutations have been identified in this gene and, besides "classical" CMT, they might also be associated with more severe phenotypes, such as congenital hypomyelinating neuropathy (CHN2) and Dejerine-Sottas syndrome (DSS).[10,13,14] Mutations in this gene are also the cause of CMT2I, an adult-onset neuropathy with normal NCV.[2,7,15,16]

In this report, we describe a family with subclinical neuropathy associated with a novel mutation in the *MPZ* gene.

Case Report

A 31-year-old female, with no relevant past medical or family history, first presented to an orthopedic surgeon due to recent-onset numbness in a small area of skin in the dorsal region. Nerve conduction studies were initially requested in this setting.

As further discriminated in **Table 1**, sensory nerve

Table 1. Nerve conduction studies of the proband. The numbers on bold are nerve conduction parameters above the upper limit of normal but not fulfilling electrophysiological criteria for demyelination. The numbers on red are on the demyelinating range.

Motor NCS						
Nerve	**Latency (ms)**	**Amplitude (mV)**	**Conduction Velocity (m/s)**	**Duration (ms)**	**Persistency F waves (%)**	**Minimum F wave latency (ms)**
Right Motor Peroneal						
Ankle - EDB	5.98	2.3		6		
Bellow knee – Ankle	16.8	2	**26.3**	6.1		
Above knee – Bellow knee	18.6	1.91	**36.1**	6.6		
Right Motor Tibial						
Ankle – Above hallux	**7.35**	3.6		6.5	85	**72.5**
Knee - Ankle	20.4	1.54	**29.5**	6.1		
Right Motor Median						
Wrist - APB	**4.29**	12.9		4.8		
Elbow - Wrist	11	11.3	**35**	5.2		
Right Motor Ulnar						
Wrist - ADM	**3.43**	10		5.2	100	**37.7**
Bellow Elbow - Wrist	8.83	9.2	**39.8**	5.8		
Above Elbow – Bellow Elbow	10.9	9	**36.2**	5.7		
Sensitive NCS						
Nerve	**Initial Latency (ms)**	**Peak Latency (ms)**	**Amplitude (uV)**	**Conduction Velocity (m/s)**	**Duration (ms)**	
Left Sural						
Mid. lower leg - Lat. Malleolus	2.15	3.25	11.5	**34.9**	2.2	
Right Sensory Ulnar						
Wrist - Dig V	2.8	3.85	26.9	**39.3**	2.8	
Right Sensory Radial						
EPL tendon - Wrist	2.05	2.83	29.1	**43.9**	1.72	

conduction studies (NCS) showed decreased velocities in all studied sensory nerves, with preserved amplitudes of sensory nerve action potentials (SNAPs). Motor NCS revealed mildly increased distal motor latencies, uniform slowing of NCV across motor nerves and prolonged F wave latencies, with preserved amplitudes of compound muscle action potentials (CMAPs). In the lower limbs CMAP velocities were decreased to a demyelinating range (<35 m/s), whilst in the upper limbs they fell within the intermediate interval (35-45 m/s). No temporal dispersion or conduction blocks were found. NCS were therefore highly suggestive of a hereditary demyelinating or intermediate polyneuropathy.

The patient denied any sensory symptoms or weakness in the limbs or imbalance issues. Physical examination was unremarkable: no weakness, muscle atrophy, or pes cavus were found (**Fig. 1**); vibration and postural sensation in the toes were normal and tendon reflexes were preserved and symmetrical throughout.

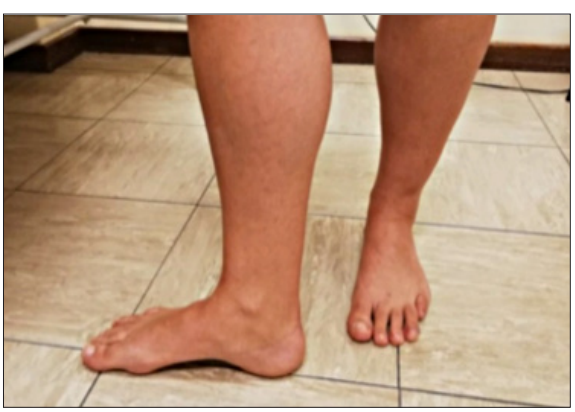

Figure 1. Normal foot morphology and leg muscle bulk.

The patient's father, also asymptomatic and without any remarkable findings on physical examination, underwent NCS (as detailed in **Table 2**) and similar abnormalities were found.

Considering the results of the NCS, the diagnosis of CMT disease was suspected. Initially, duplication of the *PMP22* gene was sought but turned out negative. Subsequently, a gene panel for hereditary neuropathies was requested and identified the c.275dup [p.(Thr94Aspfs*28)] variant in heterozygosity in the *MPZ* gene. This is a frameshift variant which presumably results in a premature stop codon, thus encoding a truncated, non-functional protein. This specific variant has not been previously reported in dbSNP or gnomAD databases and was classified as likely pathogenic. After a follow-up of seven years, both the index patient and her father remain asymptomatic.

Discussion

To the best of our knowledge, this is the first report of *MPZ* gene-associated neuropathy without any symptoms or clinical signs. This case thus broadens the phenotypical spectrum of neuropathies associated with the *MPZ* gene.

It has been speculated that most of the phenotypic variation in patients with *MPZ* mutations is due to the nature of the specific mutations, but a precise genotype-phenotype correlation is yet to be fully established.[2,7] In a cohort of 787 patients with CMT, half of those with *MPZ* gene mutations presented with an adult-onset phenotype, often ensuing after the age of 40.[5] In an observational study that included 103 patients with neuropathies caused by mutations in the *MPZ* gene, 47 different mutations were identified. These were associated with either infantile, childhood, or adult-onset phenotypes. Only two mutations were found in more than one of these age groups, which could indicate a fairly homogeneous genotype-phenotype correlation in *MPZ* gene-associated neuropathies.[17] Further evidence seems to support a general correlation between specific mutations and the severity of their phenotype.[3] However, it is still not possible to predict the age of onset and the phenotype severity based on a specific mutation in the *MPZ* gene and it is also not yet clear whether modifier genes, inflammation or environmental factors might play a role in defining the phenotypic expression of a given mutation.[17]

In the case herein reported, there is a striking discrepancy between the expected effect of the mutation on the protein synthesis and the clinical phenotype. The abnormal NCS findings in a pattern compatible with a mild CMT neuropathy argue in favour of a pathogenic role for this mutation. However, the absence of clinical findings and the mild severity of the NCS abnormalities are intriguing, as this mutation should result in a truncated and non-functional protein. This extreme example of a genotype-phenotype mismatch supports the hypothesis that the phenotypic expression of *MPZ* gene mutations might be

Table 2. Nerve conduction studies of the proband's father. The numbers on bold are nerve conduction parameters above the upper limit of normal but not fulfilling electrophysiological criteria for demyelination. The numbers on red are on the demyelinating range.

Motor NCS	Latency (ms)	Amplitude (mV)	Conduction Velocity (m/s)	Duration (ms)	Persistency F waves (%)	Minimum F wave latency (ms)
Nerve						
Right Motor Peroneal						
Ankle - EDB	**6.06**	3.7		4.1	-	-
Bellow knee – Ankle	16.9	2.2	**27.7**	4.7	-	-
Above knee – Bellow knee	20.5	2.5	**30.6**	4.4	-	-
Left Motor Peroneal						
Ankle - EDB	**7.17**	2.7	-	-	-	-
Bellow knee – Ankle	17.5	2.4	**30.0**	6.2	-	-
Above knee – Bellow knee	20.9	2.1	**32.4**	6.6	-	-
Right Motor Median						
Wrist - APB	**4.88**	8.8	-	5.1	-	-
Elbow - Wrist	10.9	7.2	**36.5**	5.3	-	-
Right Motor Ulnar						
Wrist - ADM	**3.54**	8.3	-	5.4	-	-
Bellow Elbow - Wrist	8.79	7.7	**43.8**	5.9	-	-
Above Elbow – Bellow Elbow	11.5	7.4	**44.3**	5.6	-	-
Sensitive NCS						
Nerve	**Initial Latency (ms)**	**Peak Latency (ms)**	**Amplitude (uV)**	**Conduction Velocity (m/s)**	**Duration (ms)**	
Left Sural						
Mid. lower leg - Lat. Malleolus	3.02	3.53	5.6	-	1.10	-
Right Sensory Radial						
EPL tendon - Wrist	2.26	3.11	17.9	-	-	-

co-determined by other genetic or epigenetic factors, yet to be determined. ■

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