



Case Report

Charcot-Marie-Tooth, Type 2, Caused by a MT-ATP6 Mutation, First Norwegian Case

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Introduction

The hereditary peripheral neuropathies are heterogeneous in nature and represent different forms of inheritance. Charcot-Marie-Tooth disease, CMT, may be autosomal dominant, autosomal recessive or x-linked. Neurophysiology may show severe demyelination with slow nerve conduction velocity, NCV, or axial forms with conduction velocities with normal range, the border between normal and slow NCV has traditionally been set to 38-40 m/s. Mitochondrial mutations usually cause myopathies and often affecting many other organs. These patients may have epilepsy, ataxia, headache, neuropathies or a spectrum of other symptoms. Recently, mutations in the mitochondrial DNA have been shown to cause peripheral neuropathies with CMT-like phenotype.

Case Report

A 20 years old female student was admitted to our outpatient clinic with a more than 10 years history of gait problems. She had 2 older brothers, both healthy as were both her parents. Around age 8 years old she started complaining of problems when running. This gradually progressed and when she became a teenager she had to stop down-hill skiing due to ankle weakness. She had been to several clinical tests in hospital and had been diagnosed with a CMT-like disorder with normal nerve conduction velocities. Her symptoms gradually progressed. On examination at age 20 years she appeared healthy with no ptosis or ophthalmoplegia and no retinopathy. The upper extremities had normal strength and sensations; there was no loss of sensation in the feet. She had no problems standing up from squat position. Talipes cavus and hammertoes were noted. She was able to walk on her toes but the anterior tibial muscles were severely affected and she was not able to walk on her heels. There was a slight increase in muscle tonus

when testing for spasticity in her lower limbs.

The deep tendon reflexes were normal except for the ankle reflexes which were absent as were the plantar responses. Her walking was characterized by the weakness of the pretibial muscles and a slight gluteal insufficiency was noted. A diagnosis of CMT-like neuropathy was made and a neurophysiological test was ordered: The Motor Nerve Conduction Velocities (MNCV) ranged from 35 to 40 m/s in the peroneal and tibial nerves, with low amplitudes and Sensory Conduction Velocities (SNCV) down to 35 m/s were subnormal indicating an axonal neuropathy. The muscle enzymes including CK were normal. Ophthalmological tests were all normal with no retinopathy. A brain MRI did not reveal any abnormalities, no cerebellar atrophy. In axonal CMTs most customized targeted NGS panels will not cover the regions of interest. A whole genome sequencing procedure identified a pathogenic MT-ATP6 variant; in nearly homoplasmic state, MT-ATP6, m.9185T>C p.ATP6: (Leu220Pro), consistent with a genetic diagnosis of an MT-APT6-associated disorder with mitochondrial inheritance, (Centogene AG, Rostock, Germany).

Discussion

This case presented with signs of a peripheral neuropathy and muscle weakness. It started in childhood and progressed during adolescence. A negative family history and almost normal nerve conduction velocities indicated one of the recessive and rare CMT variants. CMT and related disorders are a clinically and genetically heterogeneous group of disorders and over 100 genes have been identified. Mutations in the mitochondrial genes has traditionally been associated with muscle disorders but almost every organ may be affected. Neuropathies are common in most mitochondrial disorders but usually in combination with other signs and symptoms. MT-APT6-associated CMT was first reported in 2012 and seems to be found in ≈1 % of CMT2 patients carrying the mt9185T>C mutation [1]. This mutation has also been associated

several other mitochondrial disorders, including occurrence of a typical MELAS syndrome, (Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-Like episodes), in a single member of a large pedigree with episodic weakness [2].

The MT-ATP6 m.9185T>C is not uncommon in Leigh syndrome, LS, which is an early-onset progressive neurodegenerative disorder, associated with defects of mitochondrial oxidative phosphorylation [3]. In a large multicenter study in LS, 17 % of the cases had a MT-ATP6 mutation. In that study the majority of cases were associated with two mutations reported, the very severe mt8993T>C and the less severe mt8993T>G [4]. The pathogenic missense variant in the mitochondrial DNA MT-ATP6 gene, encodes the ATP6 subunit of the mitochondrial ATP synthase (OXPHOS complex V). This mutation was identified in several families presenting with early and late-onset LS [3]. It is not easy to explain the genotype/phenotype relationship of the m.9185 T > C variant to either of the phenotypes.

It causes familial neuropathy with a high proportion of this variant but less severe phenotypes, including CMT, cerebellar ataxia is some while other single cases develop LS. The most severe LS cases are related to high percentage heteroplasmy, usually above 95 % but lower heteroplasmy may also cause LS later in life [3]. The mean age at onset of LS with this mutation

is around 6 months of age [4]. This is to my knowledge the first Norwegian CMT2 case identified with the m.9185 T > C variant and the CMT phenotype. This case further broadens the clinical phenotypes associated with the MT-ATP6, m.9185T>C p.ATP6: (Leu220Pro), variant. It was missed on two muscle panels which emphasizes the necessity of upgrades. It may be important to know the underlying genetic cause of CMT2 since this is a potential risk both for the patients and for her children. Patients carrying genes which are potentially causing LS must indeed be referred to good genetic counselling.

References

1. Pitceathly RD, Murphy SM, Cottenie E, Chalasani A, Sweeney MG, et al. (2012) Genetic dysfunction of MT-ATP6 causes axonal Charcot-Marie-Tooth disease. *Neurology* 79: 1145-1154.
2. Aure K, Dubourg O, Jardel C, Clarysse L, Sternberg D, et al. (2013) Episodic weakness due to mitochondrial DNA MT-ATP6/8 mutations. *Neurology* 81: 1810-1018.
3. Takada R, Tozawa T, Kondo H, Kizaki Z, Kishita Y, et al. (2020) Early infantile-onset Leigh syndrome complicated with infantile spasms associated with the m.9185T>C variant in the MT-ATP6 gene: Expanding the clinical spectrum. *Brain Dev* 42: 69-72.
4. Sofou K, de Coo IFM, Ostergaard E, Isohanni P, Naess K, et al. (2018) Phenotype-genotype correlations in Leigh syndrome: new insights from a multicentre study of 96 patients. *J Med Genet* 55: 21-27.