

Proptosis in a family with the p16 Leuc-to-Prol mutation in the PMP22 gene (CMT 1E)

Proptose em uma família com a mutação p16 Leuc-to-Prol no gene PMP22 (CMT1E)

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Charcot-Marie-Tooth disease (CMT) is the most common neuromuscular disorder. The autosomal dominant and demyelinating type (CMT1) associated with duplication of the PMP22 gene (CMT1A) is the most prevalent subtype around the world, including Brazil¹, and is typically associated with mild or moderate neuropathy. Point mutations in the same gene (CMT1E) are extremely rare² and typically result in severe demyelinating neuropathies, including Dejerine-Sottas syndrome and congenital hypomyelinating neuropathy³. Interestingly, CMT1 patients harboring the same mutation may develop different manifestations, even in identical twins.

Herein, we present Brazilian siblings harboring a previously described point mutation in the PMP22 gene that manifested as an unexpected clinical phenotype.

CASE REPORT

Both patients, one female and one male, were observed at the Neuromuscular Outpatient Clinics, UNIFESP, at the ages of 29 and 38 years old, respectively. Their family history indicated that the father had similar manifestations. They reported normal development up to the age of 12 and 11 years old, respectively, at which point they developed dropped feet and began to trip and fall. Thereafter, their disease slowly progressed. A physical examination identified severe distal weakness and atrophy in both the lower and upper limbs. The pain, tactile and vibration senses were severely decreased distally, and tendon jerks were absent. The peripheral nerves were hypertrophic, and both patients had pes cavus. The sister had claw hands, while the brother had a hand tremor. Interestingly, both patients had bilateral proptosis with preserved ocular movements. No malformation, including craniostenosis, was detected. Nerve conduction studies were performed, and no sensory or motor potential was recorded in the limbs; the blink reflex demonstrated R1 and R2 responses with very

prolonged latencies. After obtaining informed consent, DNA analyses demonstrated that the PMP22 duplication was absent, but a point mutation was detected in both patients at position c.T47C, resulting in p16 Leuc-to-Prol in the protein.

DISCUSSION

The mutation found in these patients has been reported previously in a family with a disabling phenotype (Dejerine-Sottas), including severe distal weakness, marked proximal paresis, severe kyphoscoliosis and foot and hand deformities⁴. The nerve conduction velocities were extremely low, and pathology was more severe than typically observed for CMT1A.

The siblings described in our report had a typical CMT1 phenotype. Additionally, both had bilateral proptosis whose investigation for the known causes⁵ resulted negative, raising the possibility that it is related to the harbored mutation.

Familial bilateral proptosis is an extremely uncommon condition that typically appears in patients with hypertiriodism or cranial malformations. Rare reports of patients with proptosis associated with peripheral neuropathy have been described in the literature. However, they are typically part of a more complex neurological picture, such as that observed in mitochondrial disorders (e.g., due to OPA1 mutations) or genetic dysmorphic syndromes (e.g., Cardiofaciocutaneous syndrome).

To the best of our knowledge, proptosis has not been described in CMT1A or CMT1E, but variability in the CMT1 phenotype is a well-known phenomenon, even in identical twins. Unfortunately, the remaining members of this family were not available for examination. The function of PMP22 is still extremely unclear. Apparently, there is no significant function related to the eyes or orbita. If the proptosis observed in these patients is truly related to the detected mutation, PMP22 must have an unknown function.

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