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Review Article

## Ocular Manifestations of Charcot-Marie-Tooth Disease: A Short Review -

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## ABSTRACT

Charcot-Marie-Tooth is the most common inheritable polyneuropathy. Even though it is characterized by length dependent nerve degeneration, cranial nerve involvement has also been reported. Ocular manifestations include pupillary anomalies, ophthalmoplegia and optic neuropathy. Visual field assessment, optical coherence tomography, visual evoked potentials, electroretinogram and molecular test are all useful to evaluate and diagnose ophthalmological manifestations of the disease.

**Keywords:** Charcot-Marie-Tooth Disease; Polyneuropathies; Neuromuscular diseases

## ABBREVIATIONS

CMT: Charcot-Marie-Tooth; CMT1A: Charcot-Marie-Tooth disease type 1A; CMT2A: Charcot-Marie-Tooth disease type 2A; CMT4: Charcot-Marie-Tooth disease type 4; CMTX: X-linked Charcot-Marie-Tooth disease; NCV: Nerve Conduction Velocity

## INTRODUCTION

Among polyneuropathies, Charcot-Marie-Tooth (CMT) disease is the most common inheritable polyneuropathy. Its prevalence ranges from 9.7 to 82.3 by 100,000 inhabitants, depending on the country [1-3]. It is a diverse group with common motor and sensory clinical manifestations, commonly classified into five categories: 1. CMT1 (demyelinating type), autosomal dominant with onset between 5 to 20 years and NCV < 38 meters per second; 2. CMT2 (axonal type), autosomal dominant with nerve conduction velocity > 38 meters per second and a variable onset; 3. Intermediate form, autosomal dominant with nerve conduction velocity > 25 meters per second and < 38 meters per second; 4. CMT4, autosomal recessive with variable presentations and phenotypes; and 5. CMTX, X-linked disease with axonal degenerations and myelin abnormalities. The main subtypes are CMT1 (representing 50%-80% of CMT cases) and CMT2 (representing 10%-15% of the CMT cases) [1].

## PATHOPHYSIOLOGY

CMT is caused by multiple mutations in structure protein codifying genes, such as myelin sheaths, Schwann cells and other varied structures related to mitochondrial metabolism and axonal transport. Most of these mutations are autosomal dominant [1] and the final phenotype is characterized by length-dependent nerve degeneration [4]. The electrophysiological differences among the subtypes are related to nerve conduction velocity, with the demyelinating type (CMT1, intermediate form and CMT4) characterized by a NCV < 38 meters per second, and the axonal type (CMT2) with a NCV > 38 meters per second.

## CLINICAL FEATURES

Considering multiple genetic mutations that can originate this disorder, a common phenotype emerges. Its pathological and genetic base is generalized damage to both motor and sensory nerves. Epidemiologically, the disease shows a peak in incidence during the first two decades of development, gradually slowing during the next developmental years [5].

Its main characteristic is length-dependent nerve damage, with unaltered psychomotor development, and progressive and symmetrical neural damage, that impairs both motor and sensory nerves [6].

Motor neuron function alterations begin with neural atrophy-dependent symptoms, such as high plantar arches, hammer toes,

and progressive and intrinsic foot-muscle weakness and fatigue. The atrophy slowly starts progressing, starting with the foot, advances to the peroneal territory, and then compromises the upper thirds of the thigh, leading to a lower extremity distal atrophy. Sensory function follows the same distal-to-proximal pattern, and while hands and foot-soles are the first sensory manifestations, more proximal structures start showing a decline in function. Main sensory manifestations include loss of vibration, touch and pain sensation, even leading to an ataxic gait. Reflexes are also affected, diminished or even suppressed [7,8].

Classical clinical findings include pes cavus, hammer toes and other lower extremity alterations that can lead to osteomuscular deformities [6], difficulty in running, walking clumsiness, hand coordination difficulties, tremors, diminished osteomuscular reflexes, muscular weakness, and fatigue. The most prominent sensory symptom is the presence of pain, and though CMT disease is classically described as a painless disorder, many patients, children and adults alike, do present it. Pain can be expressed as neuropathic, musculoskeletal or both [9].

Adult-onset (40 years and above), although rare, is a phenotype that must be considered, and it also manifests as a progressive polyneuropathy [6].

## OPHTHALMOLOGICAL FEATURES

CMT disease has a few ophthalmological manifestations that should be considered:

1. Pupillary anomalies, such as fixed myosis (unilateral or bilateral) with little to no response to light, cocaine or pilocarpine were the first reported symptoms. Therefore, the manifestations have been correlated to affection of sympathetic postganglionic fibers [10]. Patients have also been reported with Argyll-Robertson-like pupils in the early stages of the disease [5].
2. Oculomotility alterations. Considering the length-dependent progression of the disease, cranial nerves are rarely affected, but there have been case reports of myasthenia-gravis-like patients with fluctuating ptosis or ophthalmoplegia [11] and even patients whose main concern was cranial nerve involvement rather than distal weakness. Oculomotor palsy is more related to CMT1A [12].
3. Optic neuropathy has also been reported in both CMT1A and CMT2A patients. The latter group had retinal nerve fiber layer affection and reduction of the ganglion cell layer of the retina, leading to diminished visual acuity. Those patients with CMT1A did not present these signs, as the mutation (PMP22) involved in this subtype of CMT codes for Schwann cell proteins, whereas CMT2A mutation (MFN2) is implicated in mitochondrial structure and function, which leads to nerve atrophy [13].

Useful tests to both suspect and evaluate ophthalmologic manifestations of CMT include:

1. Computerized or Goldmann's visual field, which may reveal centrocecal scotomas;
2. Optical coherence tomography, which may reveal optic nerve atrophy, diminished retinal nerve fiber layer and ganglion cell layer thicknesses;
3. Visual evoked potentials, which may reveal increased latencies; and
4. Electroretinogram, which is able to measure diminished amplitudes in cone responses.

The final diagnosis is made upon characteristic genetic findings [1,2,4,13].

## CONCLUSION

CMT disease is the most frequent inherited polyneuropathy and has a diverse range of clinical features. Ophthalmologic involvement should always be considered as patients may present with pupillary anomalies, ophthalmoplegia, and optic neuropathy. In those patients who have been previously diagnosed with the disease, ocular involvement should be expected, and in those who debut with ocular symptoms, although rare, CMT should be considered as a differential diagnosis and studied accordingly.

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