Charcot-Marie-Tooth disease type 2S: Case report of a rare form associated with spinal muscular atrophy type IV

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ABSTRACT

Introduction: Charcot-Marie-Tooth disease (CMT) is one of the most frequent diseases of the peripheral nervous system, occupying the first place among hereditary neuromuscular disorders. In some patients, a better characterization of inheritance is possible, especially in those with large families. The presence of a sibling with a similar disease, in the absence of consanguineous parents, signals us as an autosomal recessive inheritance. In others, this distinction becomes more complex, requiring genetic evaluation when necessary.

Case Report: We report the case of a 40-year-old patient who started the first symptoms in childhood, with a Charcot-Marie-Tooth Disease phenotype, but findings of injury in the anterior tip of the spinal cord; including with diaphragmatic involvement. The way the disease evolved and, obviously, the early onset of the clinic and the motor disability drew our attention; she never walked. After a genetic panel to identify a possible overlap of two diseases, we obtained an alteration in the IGHMBP2 gene.

Conclusion: In our case, the patient presents an overlapping finding of suffering from the peripheral nerves and the second motor neuron. Genetic testing was extremely important in the present case, as it revealed two variants, expanding the phenotype of these conditions and warning about respiratory involvement.

Keywords: Genetics, Motor neuron diseases, Peripheral neuropathies, Respiratory muscles

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INTRODUCTION

Peripheral neuropathies with hereditary nature are classified based on different aspects as clinical, mode of inheritance and electrophysiological characteristics, metabolic defects, and genetic markers [1]. Charcot-Marie-Tooth disease (CMT) consists of a spectrum of disorders caused by mutations in several genes whose protein products are expressed in myelin, gap junctions, and/or axonal structures in peripheral nerves [2].

A variety of mutation types have been associated with CMT, including whole gene duplications and deletions, as
well as point mutations [3, 4]. For example, PMP22 gene duplication causes CMT1A, the most common subtype (approximately 40% in total). Charcot-Marie-Tooth is genetically heterogeneous with several causative genes identified to date [5, 6], but the vast majority of cases are attributed to mutations in only four genes: PMP22, MPZ, GJB1, and MFN2.

The estimated overall prevalence of CMT is 40 per 100,000 [7], ranging from 10 to 82 per 100,000 in different reports [8]. There is no known ethnic predisposition [9]. Charcot-Marie-Tooth types 1 and 2 represent by far the largest proportion of patients, as documented in several studies, including some from Russia [10] and France [11]. The most common initial presentation of CMT is distal weakness and atrophy that manifests with foot drop and flat feet. Later in the course, foot deformities such as hammer toes occur, along with hand weakness and atrophy [12].

Diagnostic evaluation, despite the wide availability of genetic tests, still focuses on electromyography (EMG) in many cases. Genetic testing is the key to confirming the diagnosis after EMG. However, it may be appropriate to refer the patient directly for genetic testing when there is a strong family history of confirmed CMT, especially when a relative has a known mutation [1].

Furthermore, neuromuscular disorders that are presented in the neonatal period with hypotonia and weakness can be caused by a variety of conditions that affect the central nervous system (brain or spinal cord), peripheral nervous system, or skeletal muscle. Spinal muscular atrophy (SMA) is characterized by degeneration of anterior horn cells in the spinal cord and motor nuclei in the lower part of the brainstem, which results in progressive muscle weakness and atrophy [13].

In this sense, we report a case of a young patient diagnosed with a hereditary peripheral neuropathy associated with a neuromuscular disorder.

**CASE REPORT**

We report the case of a 40-year-old woman who reported that since childhood she had, according to the parents’ speech, delayed motor development and muscle flaccidity. She had never been a child who crawled “normally” when compared to another child of the same age. She narrated that when looking for toys, the biomechanics of the movements seemed disordered. Eventually she became exhausted and unproductive as she failed to achieve some goals. She never roamed, becoming wheelchair bound at the age of four years. As a child and later as a teenager, she acquired postural patterns and, obviously, inadequate movement synergies, which allowed her to perform some basic and instrumental activities of daily living. Problems in gripping objects, pain in the spine, and difficulties in stabilizing the feet were considered important during her life trajectory. She, seeking diagnostic elucidation and treatment, sought medical help.

Expert opinions with laboratory, electrophysiological, imaging, and biopsy screening were inconclusive. She had received varied diagnoses, but as the disease progressed, they were discarded. Early, after further investigation, she had been diagnosed with type VI spinal muscular atrophy, even with a report of the disease in the first months of life. At the age of 40, she attended a consultation with a neurologist, questioning this possibility. She had been questioned about her vaccination history, specifically for poliomyelitis, childhood infections, hospital admissions, illnesses in close and distant relatives, alterations in other systems (cardiovascular, locomotor, gastrointestinal, and urinary).

Mucosal evaluation, capillary filling time, lymph nodes, hydration did not present noteworthy (normal) data. Accelerated pulse, “short” breathing pattern and increased respiratory incursions, characterizing increased ventilatory work, but with normal cardiac and pulmonary auscultation. It is noteworthy the fact that it always tells the evaluators that the disease never stops in its evolution. On the contrary, evolution and limitations added up over the years, in a slow and progressive way. Upon inspection, she presented symmetrical limb atrophy, more evident in the brachial distal third (Figure 1A) and crural, despite the global character. Scoliosis (Figure 1B) associated with lumbar hyperlordosis (Figure 1C), in addition to hypotonia, difficulty in maintaining an erect neck and bell-shaped chest also drew the examiner’s attention.

Myofasciculations were seen in all four limbs, with the exception of the tongue, normal speech and swallowing, oriented in time and space, superficial and deep hypoesthesia in the distal third of the limbs were found, and deep reflexes abolished. Grade 1-2 paresis in practically all muscles evaluated in the upper and lower limbs. We highlight paresis of the neck extendors and of the intercostal and diaphragmatic muscles. Normal cranial nerve nuclei, except XI. After a thorough neurological evaluation, two lines of clinical and, obviously, topographic reasoning generated two hypotheses for the diagnosis: motor neuron disease and/or sensory-motor polyneuropathy.

Electroneuromyography: severe axonal sensory-motor polyneuropathy. Exome sequencing: Four potentially relevant variants were identified in heterozygosity in the

![Figure 1: Physical examination findings: Symmetrical limb atrophy featuring a cadaveric hand (A), scoliosis (B), and lumbar hyperlordosis (C).](image-url)
IGHMBP2 gene, being marked and compatible with the picture, a variant that affects both copies (in homozygous or compound heterozygosis) of the IGHMBP2 gene. It is commonly associated with two conditions of autosomal recessive inheritance: 2S axonal Charcot-Marie-Tooth disease (clinically characterized by sensorimotor involvement beginning in the first decade of life and slow progression) and type VI distal motor neuropathy (also referred to as spinal muscle atrophy with respiratory distress type 1), clinically characterized by predominantly motor involvement, onset up to the third month of life and rapid progression.

The association of clinical, electrophysiological, and genetic panel findings leave no doubt about the genetic alteration IGHMBP2, causing, in some cases, impairment of the central and peripheral nervous system. As for the respiratory function, the patient has no changes in forced vital capacity (FVC) and expiratory volume in the first second (FEV1) and in the FEV1/FVC ratio, the total lung capacity (TLC) is also unchanged, as well as the residual volume (RV)/TLC ratio representing the absence of restrictive disease. However, the maximum inspiratory pressure (MIP) is reduced (85 cm H₂O vs. 61 cm H₂O) reaching 72% of predicted.

DISCUSSION

Charcot-Marie-Tooth disease (CMT) of the 2S subtype is caused by variants that affect both copies (homozygosity and complete heterozygosity) in the IGHMBP2 gene and are associated with two autosomal recessive inheritance conditions: CMT type 2S (clinically marked by involvement sensorimotor onset in the first decade of life and slow progression) and type IV spinal muscular atrophy (SMA), marked by respiratory impairment, motor predominance, onset until the third month of life and rapid progression. This disease presents an overlap of findings of suffering of the peripheral nerves and the second motor neuron [2, 3].

Charcot-Marie-Tooth disease is also characterized by slowly progressive weakness, muscle atrophy, and sensory loss without significant respiratory impairment. Mutations in IGHMBP2 are also a cause of spinal muscular atrophy with type 1 respiratory distress (SMARD1) [1]. In this sense, the patient has a hereditary peripheral neuropathy, confirmed through genetic tests associated with a neuromuscular disorder that is SMA. Spinal muscular atrophy disorders are characterized by degeneration of anterior horn cells in the spinal cord and motor nuclei in the lower part of the brainstem, which results in progressive muscle weakness and atrophy [14, 15]. Cognition is not affected, which is noticeable in the patient’s semiological assessment.

The impairment of the respiratory system is manifested at first through the reduction of strength and resistance of the respiratory muscles, especially those involved in inspiration (diaphragm and intercostal), resulting in a reduction in MIP, with the evolutionary process occurring reduction in volumes and capacities and, consequently, a restrictive condition arises that can lead to hypoventilation, affecting oxygen saturation, and causing dyspnea [16]. As it is an overlap of diseases, it becomes more complex to define when this will occur, for this reason the respiratory assessment must always be present and, if possible, the insertion of respiratory muscle training as soon as possible [17–19]. The patient presented by us is already suffering from a reduction in MIP.

The phenotypic manifestation of Charcot-Marie-Tooth disease, together with findings of injury to the anterior tip of the spinal cord, with rapid evolution of the condition, reveals a rare condition in which genetic mapping was essential for the investigation of the case. It is also known that patients with CMT can also manifest additional deficiencies with disorders that cause or exacerbate neuropathy, for example, presentation of diabetes mellitus, vitamin deficiencies, and immune-mediated neuropathies [2]. Genetic testing was extremely important in the present case, as it revealed two variants, expanding the phenotype of these conditions and warning about respiratory involvement.

CONCLUSION

The present case reported demonstrates the importance of knowing the variants of hereditary neuromuscular disorders. Therefore, patients should be screened periodically for these conditions and treated promptly if detected. In particular, patients with CMT who have abnormally rapid progression of symptoms should be evaluated for an overlapping immune-mediated or inflammatory neuropathy.

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Author Contributions

Marco Orsini – Conception of the work, Design of the work, Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antônio Marcos da Silva Catharino – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mauricio Sant’ Anna Junior – Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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