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Case report

Dropped head syndrome as a manifestation of Charcot–Marie–Tooth disease type 4C

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Abstract

Charcot Marie Tooth disease type 4C (CMT4C) is considered the most frequent autosomal recessive form of CMT worldwide, being described as an early-onset disorder with marked clinical heterogeneity. We report a CMT4C case associated with dropped head syndrome and predominant involvement of proximal muscles. An 11-year-old boy born to consanguineous parents presented with predominantly proximal muscle weakness with facial involvement, associated with dropped head and severe scoliosis. Symptoms started at the age of 3 years-old with frequent falls. Nerve conduction studies showed a sensorimotor demyelinating polyneuropathy. A comprehensive multigene next-generation sequencing panel for CMT revealed the homozygous pathogenic missense variant c.1969G > A (p.E657K) in *SH3TC2* gene, confirming CMT4C diagnosis. The present report broadens the phenotype associated with CMT4C and raises the importance of considering early-onset inherited polyneuropathies in the differential diagnosis of patients with proximal muscle wasting associated with dropped head syndrome.

Keywords: Charcot–Marie–Tooth disease type 4C; Dropped head syndrome; CMT; Proximal muscle weakness; CMT4C.

1. Introduction

Charcot–Marie–Tooth disease (CMT) refers to a heterogenous group of inherited sensorimotor polyneuropathies, ranging from severe congenital to mild adult-onset phenotypes [1]. The main clinical features of CMT are of a length-dependent weakness and sensory loss that begins in the feet and gradually ascends to the knees and hands, generally associated with feet deformities [2,3].

Classically, CMT is classified according to electrophysiological findings, mainly based on median motor nerve conduction velocity (MNCV): demyelinating forms (CMT1) with MNCV below 38 m/s, axonal forms (CMT2) with MNCV above 38 m/s, and intermediate CMT with MNCV between 30 and 40 m/s. In each of these categories, hereditary transmission may be autosomal dominant, autosomal recessive and X-linked [1].

CMT1, the most common subgroup, includes autosomal dominant demyelinating forms; CMT2 is the group of axonal polyneuropathies, with both autosomal dominant and recessive inheritances; CMTX is composed by polyneuropathies inherited in an X-linked manner. Finally, CMT4 is a group of autosomal recessive demyelinating polyneuropathies caused by mutations in at least 11 known genes, one of which is responsible for CMT4C phenotype: *SH3TC2* [1].

CMT4C was first described in 1996 in Algerian families [4], and recent evidence points to this form as the most common autosomal recessive CMT in different populations [5,6,7,8]. CMT4C is caused by biallelic mutation in *SH3TC2* gene, mapped to chromosome 5q23-q33 [4]. *SH3TC2* is specifically expressed in Schwann cells and its loss of

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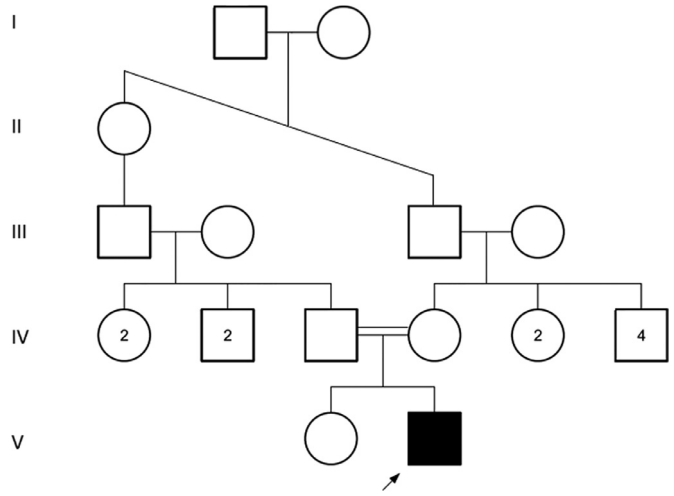

Fig. 1. Family pedigree. Black-filled shape represents individual affected by polyneuropathy. Numbers inside shapes indicate the number of sibships with a given sex.

function lead to dysregulation of endocytic recycling pathways and to an altered proliferation and migration of Schwann cells, resulting in abnormal myelination of peripheral nerve axons [9,10,11,12]. Regarding the clinical picture, it is classically described as an early-onset disorder with distal muscle weakness, foot deformities, severe scoliosis and cranial nerve involvement as prominent features, although with significant clinical variability [4,5,13,14].

Our aim was to describe the case of a patient with molecularly confirmed diagnosis of CMT4C that broadens the disease-related phenotype to also include predominantly proximal muscle wasting and dropped head syndrome.

2. Case report

An 11-year-old male patient started with recurrent falls and abnormal feet positioning at the age of 3. Thoracic spine scoliosis was noted at the age of 4. Soon after, four-limb weakness was observed by his parents, with proximal predominance, associated with dropped head. At that time point, he also complained of fatigue after minimal efforts. Walking aids were required when he was 6 years old, and, by the age of 9, he became wheelchair-dependent. Recently, he started to have swallowing problems and urinary incontinence. There were no sensory or cognitive complaints.

He was born to consanguineous parents (first-degree cousins) and he has a healthy 15-year-old sister. There are no other similar reported cases in the family (Fig. 1).

His mother denied any complication within pregnancy or delivery: he was born at term by vaginal delivery. He acquired head control at 4 months of age, sat without support at 8 months and started walking and talking at 1 year and 2 months of age. When last assessed, he was in the fourth grade of elementary school, with good performance.

On the first neurological examination at our clinic he was 9 years old and presented with proximal limb, cervical and facial weakness, including dropped head (Fig. 2), global hypotonia and non-fixed plantar flexion and elbows contractures. He had *pes cavus* and hammer toes, although these findings were not prominent. He also presented significant cranial nerve involvement with bilateral ptosis, right internuclear ophthalmoparesis, bilateral facial weakness (VII cranial nerve), dysphagia, tongue weakness and fasciculation (XII cranial nerve), and diminished strength in sternocleidomastoid and trapezius muscles (XI cranial nerve). His strength, according to the MRC scale, was 3/5 points in the upper limbs (proximal and distal), and 4/5 distal and 3/5 proximal in the lower limbs. Deep tendon reflexes were globally absent and vibratory sense was diminished in the interphalangeal joint of the *hallux*, but with normal pain, touch, temperature and proprioceptive evaluations.

Fig. 2. Dropped head and severe scoliosis at the age of 11 years.

Neuropathy Impairment Score of the Lower Limb (NIS-LL) was performed retrospectively with data collected from his last outpatient visit record, when he was 11 years and 9 months, with a total score of 69.

Nerve conduction studies (NCS) were markedly abnormal in the upper and lower limbs. Median and ulnar motor studies presented prolonged distal latencies, with conduction velocities around 10 m/s with absent sensory potentials on upper limbs. There were absent motor and sensory potentials on the distal lower limbs, compatible with a sensorimotor demyelinating polyneuropathy. Blink reflex showed prolonged R1, R2 and R2' responses bilaterally, with latencies of 25 ms, 55 ms and 57 ms, respectively. NCS and electromyo-

graphy (EMG) were performed four times due to discrepancy with topographic diagnosis based on physical examination. All of them showed similar results, with neither signs of myopathic changes nor of neuromuscular junction abnormalities. Dorsal and lumbosacral magnetic resonance imaging showed paravertebral, psoas, gluteus e abdominal wall atrophy, besides scoliosis. Electrocardiogram and echocardiogram were normal. Spirometry was normal when he was 8 years old, with a forced vital capacity (FVC) of 1.57l (94% of predicted value); and a forced expiratory volume in 1 s (FEV1) of 1.35l (95% of predicted value). Normal blood levels of creatine kinase, lactate and very long chain fatty acids, and normal activities of β-galactosidase, galactocerebrosidase and arylsulfatase A on leukocytes were found. Urinary sulfatides and isoelectric focusing of serum transferrin were normal. Due to the hypothesis of an early-onset autosomal recessive demyelinating form of CMT with atypical features, a comprehensive 32 genes next-generation sequencing panel for inherited neuropathies was ordered (Invitae, USA), revealing the homozygous pathogenic missense variant c.1969G > A (p.E657K) in *SH3TC2* [5,11,15], confirming the diagnosis of Charcot–Marie–Tooth disease type 4C (CMT4C).

At the age of 12, he was admitted to an intensive care unit (ICU) of a countryside city in our state with respiratory failure due to bronchopneumonia. In the next couple of days, his symptoms markedly improved and he was weaned from ventilation and discharged from ICU. In the same night, his clinical picture suddenly deteriorated and he died due to acute respiratory failure. Autopsy was not performed.

3. Discussion

Dropped head syndrome is a rare condition defined as a correctable kyphotic deformity of the cervicothoracic spine due to weakness of neck extensors or increased tone of neck flexors [16]. Differential diagnosis for this condition is extensive and comprises mainly muscular diseases, including hereditary myopathies and dystrophies as well as inflammatory myopathies, and neuromuscular junction disorders, such as congenital myasthenic syndromes, myasthenia gravis and Lambert-Eaton myasthenic syndrome. Other possible diagnosis rarely associated with this phenotype are Parkinson's disease, multiple system atrophy, dementia with Lewy bodies, amyotrophic lateral sclerosis, cervical dystonia, cervical myelopathy, post-polio syndrome and tardive dyskinesias [17].

Considering the clinical picture of the presented patient of early-onset proximal weakness with facial involvement and dropped head together with the history of parental consanguinity, the first diagnostic hypotheses were congenital myopathies or congenital myasthenic syndromes [17]. However, as nerve conduction studies consistently suggested a demyelinating polyneuropathy with cranial nerve involvement, an atypical form of Charcot Marie Tooth disease type 4 (CMT4) became the leading hypothesis in the differential diagnosis.

The missense variant found in homozygous state in our patient (p.E657X) is present in less than 0.01% of alleles in population databases (ExAC and gnomAD), and it has been previously described in two other families with CMT4C, one in homozygous [15] and the other in compound heterozygous states [5]. Moreover, experimental studies have shown that this change disrupts SH3TC2 cellular localization, protein-protein interaction and function [11,18]. Therefore this variant was classified as pathogenic according to the 2015 American College of Medical Genetics and Genomics criteria [19].

The comparison of our patient phenotype with the Turkish patient reported by Senderek et al. (homozygous for the p.E657X variant) and the patient reported by Houlden et al. illustrates well the heterogeneity of the condition. While the Turkish [15] and the compound heterozygous [5] patients presented with a CMT phenotype with predominant distal weakness, our patient, unexpectedly for a CMT, showed prominent proximal weakness, besides the dropped head syndrome presentation. Nevertheless, there were some similarities between the three cases, such as early-onset, scoliosis, arreflexia and diminished vibration sense, which seem to be common characteristics to most CMT4C cases, regardless of the genotype. When we consider the most common pathogenic variant in some case series (p.R954X) there is also considerable inter- and intrafamilial variability [5,20]. Therefore, CMT4C seems to be a clinically heterogeneous disorder without a clear genotype-phenotype correlation.

With the advent of massive and parallel sequencing technologies, several distinct phenotypes are being gathered around mutations in single genes and *SH3TC2* is exemplary for this phenomena. For instance, Jerath et al. recently described five cases of CMT4C, one resembling a facioscapulohumeral muscular dystrophy phenotype, with scapular winging, a second one with gait ataxia and a third one with retinitis pigmentosa [14]. Our description broadens even more the phenotypic presentation of CMT4C, including proximal weakness and dropped head as part of the disease phenotype, although one should bear in mind that this patient also presented some well-described CMT4C characteristics such as severe scoliosis, third and seventh cranial nerves impairment and diminished vibration sense.

To our best knowledge, the association of CMT4C with dropped head syndrome has not been reported before, even when we consider the atypical cases reported in the literature [14]. We were able to find only a single case report that causally associated a polyneuropathy, chronic inflammatory polyneuropathy, with dropped head syndrome [21] and, therefore, CMT as whole has not been previously related to this phenotype. Nerve conduction studies and EMG in such scenario will be paramount to guide the correct topographical diagnosis and etiological hypothesis and to guide the decision for molecular analysis.

Respiratory dysfunction was described in the disease [5] and screening tests are important to the early detection of these abnormalities. Our patient had previously normal spirometry parameters when he was 8 years old; however, three years he died due to bronchopneumonia after a very short period on ICU with fast mechanical ventilation weaning. Therefore, we consider that future studies should target

and detail respiratory function in CMT4C, but in the meanwhile continuous special respiratory attention should be given for all patients with this disease.

In summary, the present report adds dropped head as a CMT4C disease feature and raises the importance of considering early-onset inherited polyneuropathies in the differential diagnosis of patients with proximal muscle wasting associated with dropped head syndrome. Furthermore, it highlights the possibility of acute respiratory failure in these patients even with normal respiratory function tests.

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