Clinical Vignette

Spinal Muscular Atrophy Beyond the SMN gene: New Learnings for Common Phenotypes

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Abstract

The most common cause of spinal muscular atrophy (SMA) is biallelic deletion of exon 7/8 of the *SMN1* gene. However, SMA can also be caused by variants in genes other than *SMN1* (non 5q-SMA). We describe a child with motor delay since infancy and progressive muscle weakness of the lower extremity due to non 5q-related spinal muscular atrophy.

Keywords: Non 5q-spinal muscular atrophy, *DYNC1H1*

Introduction

Spinal muscular atrophy (SMA) is a rare genetic disorder characterized by progressive degeneration of the anterior horn cells of the spinal cord leading to muscle weakness and atrophy. The commonest cause of SMA is biallelic deletion of exon 7/8 of *SMN1* gene located on 5q13. However, SMA can also be caused by pathogenic variants in genes other than *SMN1* (non 5q-SMA). We describe a 10-year-old girl with motor delay since infancy and progressive muscle weakness of the lower extremity due to non 5q-related spinal muscular atrophy.

Patient details

A 10-year-old girl, first child of a non-consanguineous marriage, was evaluated in the genetic clinic for infantile-onset progressive lower extremity weakness. Antenatal and perinatal history was unremarkable. Bilateral clubfoot was noted at birth. She came to medical attention in early childhood for delayed motor milestones (sitting at 1 year, standing with support at around 2 years, and walking at 2.5 years). The other developmental domains were age-appropriate. She also had high myopia with strabismus noted at 3 years. She had frequent falls and was unable to climb stairs, run, jump, or kick. On examination, the child was obese [body mass index (BMI) – 30.4 (+2.4 Z)] There was no facial dysmorphism. Her higher mental functions were normal. She had a waddling gait. The muscle bulk and tone in all four limbs were normal. There was symmetric weakness of hip flexion, extension, abduction, adduction, and knee flexion with relative sparing of knee extension and ankle flexion/extension. Gowers sign was positive and power in the upper extremities was normal. There was also truncal weakness with lumbar lordosis. Deep tendon reflexes were normal except for a depressed patellar reflex. Bilateral ankle contractures were present. There was laxity in bilateral wrist joints. Examination of other systems revealed no abnormality. A clinical diagnosis of limb girdle muscular dystrophy (LGMD) was considered in view of the progressive lower extremity and truncal weakness along with preserved reflexes.

Serum creatine phosphokinase (CPK) was 235 IU/L. Nerve conduction studies were normal. Electromyography revealed large-amplitude motor units in the tibialis anterior and quadriceps along with multiple myopathic motor units in the gastrocnemius, gluteal muscles, and upper limb muscles (deltoid and extensor digitorum communis). No fibrillations or positive sharp waves in any muscle groups were seen. Differential diagnosis included muscular dystrophies, congenital myopathies and myasthenic syndromes.

To address the genotypic heterogeneity for the provisional diagnosis of LGMD, whole exome sequencing was performed which identified a heterozygous missense variant NM_001376.5:

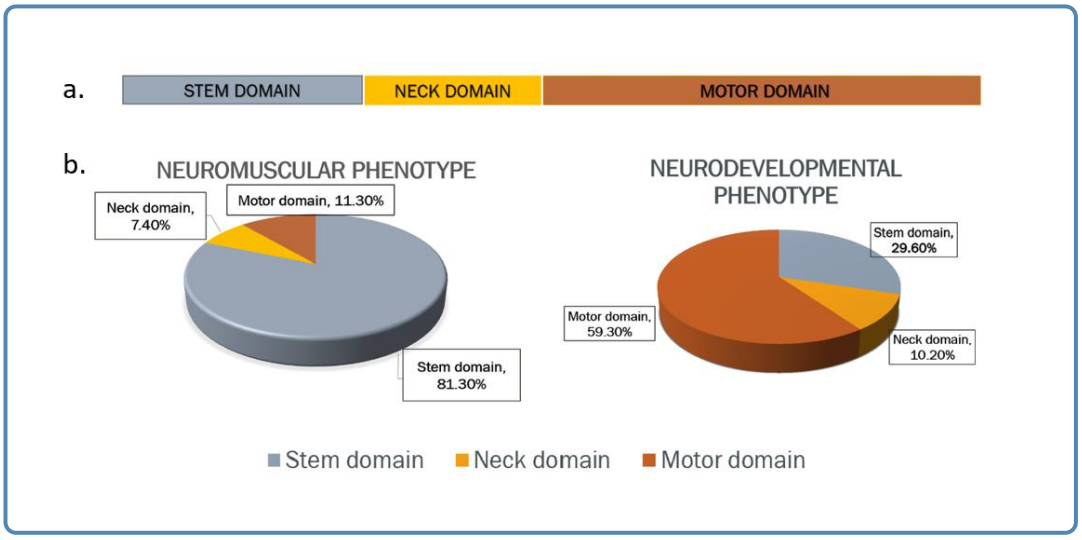

Figure 1 a. DYNC1H1 protein domains and associated *DYNC1H1*-related phenotypes. b. Pie-charts depicting the spectrum of *DYNC1H1*-related disorders. A predominant neuromuscular phenotype [spinal muscular atrophy (SMA)/Charcot-Marie-Tooth disease (CMT)/myopathy with or without central nervous system (CNS) features] is more commonly seen in mutations in the stem domain whereas predominant neurodevelopmental phenotype (intellectual disability (ID)/ autism spectrum disorder (ASD) with or without neuromuscular involvement) is seen in mutations in the motor domain. (Adapted from Amabile et al., 2020) .

c.752G>A (p.Arg251His) in exon 4 of *DYNC1H1*gene. The variant was validated with Sanger sequencing and parental studies showed the variant to be *de novo*. This variant has been previously reported in a patient with peripheral neuropathy (Antoniadi et al., 2015) as well as in patients with spinal muscular atrophy, lower extremity predominant-1 (SMA-LED1) but with a different amino acid substitution (p.Arg251Cys) (Chan et al., 2018) and not been reported in population databases. The in-silico prediction tools show that the variant is deleterious and is in the mutational hotspot. Hence, as per American College of Medical Genetics and Genomics/ Association for Molecular Pathology (ACMG/AMP) criteria, it is classified as 'likely pathogenic'. Based on the phenotype and molecular studies, the child was diagnosed to have spinal muscular atrophy, lower extremity predominant-1 (SMA-LED1).

Discussion

Chronic progressive lower limb muscle weakness is a common presenting feature in a variety of genetic disorders. Common differentials include muscular dystrophies, congenital myopathy, neuropathies, hereditary spastic paraplegia and spinal muscular atrophy. Some non-genetic causes of such presentations can be inflammatory myopathies, hypothyroidism, drugs and vitamin D deficiency which should always be ruled out prior to genetic testing.

SMA-LED1 is a rare motor neuron disease characterised by early-onset symmetric proximal lower limb weakness. Patients have a characteristic broad-based waddling-type gait, lumbar lordosis, feet deformities and joint contractures. Reflexes are normal except for a depressed patellar reflex in a few that differentiates it from 5q-linked SMA. The upper limbs are initially spared but might get involved later. Our patient also presented with this typical clinical profile. Muscle MRI shows atrophy and fat infiltration of the quadriceps femoris with hypertrophy of the semitendinosus and adductor magnus.

SMA-LED1 is caused by variants in the *DYNC1H1* gene (14q32.31) which codes for the cytoplasmic dynein complex heavy chain protein. This protein is involved in the intracellular transport of various proteins, organelles as well as organisation of the spindle pole. Disorders associated with *DYNC1H1* are all autosomal dominantly inherited and include Charcot-Marie-Tooth disease type 2O, Mental retardation-13, and SMA-LED1.

All the three *DYNC1H1*-related disorders show overlapping features in the form of sensorimotor neuropathy, lower limb weakness and central nervous system (CNS) involvement. A recent paper (Amabile et al., 2020) has suggested a novel classification system for the *DYNC1H1*-related disorders with those having predominant neuromuscular disorder (*DYNC1H1*-related NMD) as our patient, those having a combined NMD-CNS phenotype and those with a predominant neurodevelopmental disorder (*DYNC1H1*-related NDD). Patients with the neurodevelopmental phenotype may present with varying degrees of intellectual disability, learning disability, speech delay or global developmental delay. Neuroimaging can reveal brain abnormalities like ventriculomegaly, pachygyria, hypoplasia of the corpus callosum, pons or cerebellum. A few may develop epilepsy responsive to medications. Nerve conduction studies might sometimes indicate axonal impairment of the sensory or motor nerves. Extra-CNS manifestations like strabismus, amblyopia, congenital cataract, bicuspid aortic valve etc. have also been reported in them. A genotype-phenotype correlation has also been proposed with variants in the stem domain of the protein more likely resulting in a neuromuscular presentation and those in the motor domain more likely leading to a neurodevelopmental phenotype (Figure 1) (Amabile et al., 2020) Our patient has the variant in the stem domain consistent with an isolated neuromuscular presentation.

Conclusion

SMA-LED1 is an uncommon differential for spinal muscular atrophy with early onset, lower extremity predominant, progressive muscle weakness and preserved reflexes. A high index of suspicion is essential to consider this diagnosis.

References

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