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Case Report

Expanding the phenotype of *DYNC1H1*-associated diseases with a rare variant resulting in spinal muscular atrophy with lower extremity predominance (SMA-LED) and upper motor neuron signs

Jessica Lee[1], Philip Millington[1], Kavinda Dayasiri[2], Sithara Ramdas[1], Sandeep Jayawant[1], Geetha Anand[1]

[1]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [2]Faculty of Medicine, University of Kelaniya, Sri Lanka, and, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.

ABSTRACT

Background. Spinal muscular atrophy with lower extremity predominance (SMA-LED) is an autosomal dominant disorder. Since SMA-LED affects lower motor neurons, the disease is characterized by weakness and atrophy of lower limb muscles. We present a familial case series of SMA-LED with upper motor neuron signs associated with a rare variant in *DYNC1H1*.

Case. The index case was referred to Pediatric Neurology at the age of two and half years, due to delayed mobility. The child was diagnosed with congenital vertical talus at birth, which was managed with serial bilateral casting and surgery. The delayed mobility was initially attributed to lower limb weakness secondary to prolonged periods of immobilization from casting of his lower limbs. He had a striking waddling gait and proximal muscle weakness on neurological assessment. He had lower motor neuron signs predominantly in his lower limbs that were in keeping with SMA-LED. Surprisingly, he also demonstrated a brisk crossed adductor response that was not in keeping with an isolated primary neuro-muscular disorder and suggested a mixed upper and lower motor neuron pathology. The inherited neuropathy gene panel revealed a heterozygous sequence change in the *DYNC1H1* gene which was present in all affected family members.

Conclusions. We present the first report of a familial case series of SMA-LED with upper motor neuron signs associated with an extremely rare variant in *DYNC1H1*: c.1808A>T (p.Glu603Val). As per the American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification, we would recommend that this variant be reclassified as "Likely Pathogenic" due to matching 1 moderate (PM1–PM6) and ≥4 supporting (PP1–PP5) criteria in the reported case series.

Key words: spinal muscular atrophy with lower extremity predominance, upper motor neuron signs.

Spinal muscular atrophy with lower extremity predominance is a small group of autosomal dominant neurological disorders. SMA-LED affects lower motor neurons and is thus characterized by wasting and weakness of the lower limb muscles. Two genetic variants have been associated with SMA-LED: *BICD2* and *DYNC1H1*. The *DYNC1H1* gene encodes cytoplasmic dynein 1 heavy chain 1, a protein of the dynein family.[1] Variants in the *DYNC1H1* gene have previously been associated with SMA-LED, with Charcot-Marie-Tooth disease, and separately with hereditary spastic paraplegia (HSP).[1-3] *BICD2* encodes a golgin (a component of dynein-based transport). Pathogenic variants of *BICD2* have been reported with SMA-LED, with SMA-LED with upper motor neuron signs, and separately with the HSP phenotype.[4-6] We present a familial case series of SMA-LED with

✉ Kavinda Dayasiri
kavindadayasiri@gmail.com

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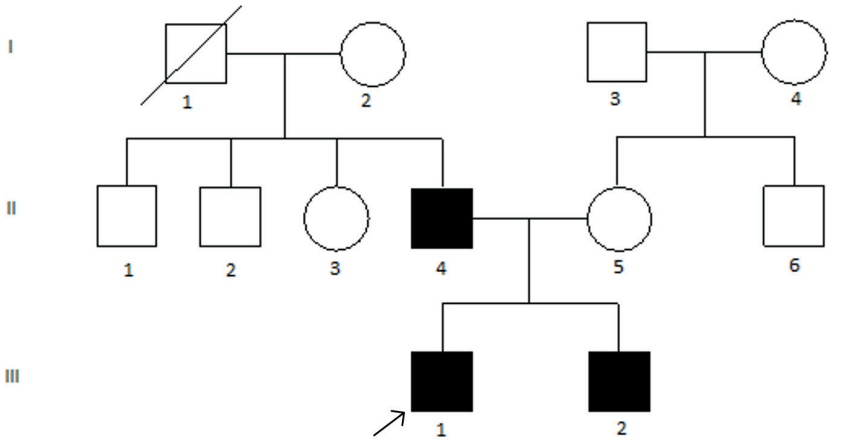

Fig. 1. Family Tree - Index case identified by arrow. Three affected family members as shown by filled squares.

upper motor neuron signs associated with a rare variant in *DYNC1H1*. We describe the clinical phenotypes of three family members across two generations - a father and two sons (Fig. 1).

Case Report

The index case is a five-year-old male child born at term after an uneventful pregnancy and a forceps delivery. He was noted to have congenital vertical talus, which was managed with serial bilateral casting and surgery. His walking was delayed but the rest of his developmental milestones were within normal range. This delay in ambulation was initially attributed to lower limb weakness secondary to prolonged periods of immobilization from casting of his lower limbs. However, at two and a half years he was still able to mobilize only when in bilateral ankle-foot orthoses and with the assistance of a walking frame, and so was referred to Pediatric Neurology by his Orthopedics team. He was unable to take more than a couple of steps unsupported, falling primarily due to proximal weakness. On examination, the most striking abnormality was a waddling gait. He walked with externally rotated lower limbs and his hip mobility demonstrated excessive external rotation and limited internal rotation bilaterally. He had almost lichenified prepatellar skin thickening, as a result of ambulating on his knees. The proximal and distal muscles of his lower limbs were markedly wasted. Tone was generally decreased in both lower limbs but with tightness noted bilaterally in his iliotibial bands, hamstrings, and Achilles tendons. Power in all muscle groups of his lower limbs was diminished. Deep tendon reflexes in his lower limbs were difficult to elicit given the ankle deformity and lichenification of the skin overlying the patella. However, a crossed adductor response was present. Tone, power, and deep tendon reflexes were normal in his upper limbs, with no evidence of muscle wasting. Sensation was normal in both his upper and lower limbs. Cranial nerve and cerebellar examinations were normal, as was cognition. He was attending a mainstream school without any special educational needs.

The father of the index case was not able to recollect his age of independent ambulation. He recalled requiring a wheelchair during his childhood. He reported gradual improvement in his strength during his youth and that he was eventually able to walk unsupported on flat surfaces. Nonetheless, he still requires the support of a banister when ascending stairs, while able to descend stairs unsupported. When examined he also exhibited bilateral lower limb proximal weakness with a waddling gait, proximal and distal lower limb muscle atrophy, and brisk crossed adductor responses.

Additionally, his youngest son, the index case's infant brother, demonstrated a similar phenotype, including the crossed adductor response (Fig. 2). Despite the proximal and distal lower limb wasting and weakness, the presence of a brisk crossed adductor response was not in keeping with an isolated primary neuromuscular disorder and suggested a mixed upper and lower motor neuron pathology.

Following the initial consultation, an inherited neuropathy gene panel was sent. Electromyography, nerve conduction tests and genetic tests looking at dynein heavy chain variants were performed. Imaging was requested, including magnetic resonance imaging (MRI) of his spine as well as anteroposterior and lateral X-ray views of his thoracolumbar spine and pelvis.

Thoracolumbar and pelvic X-rays did not show any evidence of spondyloepiphyseal dysplasia. The spine MRI was normal. Given the normal cognition in the father, lack of cognitive concerns in the index case, and clinical features pointing to a likely primary lower motor neuron pathology, brain MRI was felt not to be clinically indicated. Neurophysiological testing showed moderate to severe chronic denervation of the lower limb muscles with normal sensory responses. Creatine kinase was 210 IU/L (normal range: 30-200). The inherited neuropathy gene panel revealed a heterozygous sequence change in the *DYNC1H1* gene: c.1808A>T p.(Glu603Val), a single nucleotide missense variant, which was present in all affected family members.

Since diagnosis, the index case and his sibling have been followed up by the Pediatric Neuromuscular team. Further care has also been provided by Neuromuscular Physiotherapy, Community Pediatrics, and Orthopedics. Clinical progress is slow, with both brothers stable and ambulant with support.

Fig. 2. Findings of bilateral vertical talus, lower limb muscle atrophy, and thickened skin overlying patella shown in the index case (right), with similar features demonstrated in his father (left) and younger brother (center).

Discussion

We present a familial case series of SMA-LED with upper motor neuron signs associated with a rare variant in *DYNC1H1*. This was the first observation of the c.1808A>T (p.Glu603Val) variant at the reference laboratory and has not previously been listed in the Genome Aggregation Database (gnomAD), suggesting an extremely rare variant. Due to the segregation of the variant within the family, this was presumed to be a *de novo* variant in our patient's father. Searching the ClinVar database revealed one reported case with the same variant, in a patient with SMA-LED.[1] This case demonstrated similar findings to our index case, presenting with congenital talipes, lower limb muscle atrophy and weakness, and a requirement for ankle-foot orthoses for independent walking. A sibling without diagnostic genetic confirmation was noted to have similar features and an autosomal dominant mode of inheritance was postulated. However, in contrast to our index case, there were no associated upper motor neuron signs. Previous work has expanded the clinical phenotype of *DYNC1H1* to include upper motor neuron disease, describing a family with hereditary spastic paraplegia, complicated by intellectual disability, epilepsy, cataracts, and a thin corpus callosum.[2,3] Additionally, the clinical phenotype of SMA-LED with upper motor neuron signs has also been previously demonstrated with mutations in *BICD2*.[6]

According to ClinVar, the *DYNC1H1* gene c.1808A>T (p.Glu603Val) variant was hitherto classified as being a variant of uncertain significance. As per the American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification, we would recommend that this variant be reclassified as "Likely Pathogenic" due to matching 1 moderate (PM1–PM6) and ≥4 supporting (PP1–PP5) criteria[7]; the variant has not been detected in population controls and is thus not listed in the gnomAD database (PM2). Other missense variants in the *DYNC1H1* gene are known to cause similar neurological disease[1] and we have shown this variant has been demonstrated to co-segregate with disease in members of one family (PP1, PP2). The family's phenotype and presentation are highly specific for a disease with a single genetic etiology (PP4) and *in silico* analysis performed in the laboratory predicts a deleterious effect of this variant on the gene product (PP3).

We have submitted this variant to the ClinVar database, accession number: SCV001793786.1 https://www.ncbi.nlm.nih.gov/clinvar/variation/637517/

Ethical approval

Written informed consent for patient information and images to be published was provided by parents of reported children.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SJ, GA; data collection: JL, PM, KD; analysis and interpretation of results: SR, SJ, GA; draft manuscript preparation: KD, JL, PM. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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