Spinal Muscular Atrophy Lower Extremity Predominant (SMA-LED)

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Objective

To describe the rare non 5q SMA -Spinal muscular atrophy lower extremity predominant (SMA-LED).

Methods

A case series of two cases of SMA-LED who presented to pediatric neurology OPD of a tertiary care centre

Results Case-1

A 5month old boy, born of non consanguineous marriage, with paucity of lower limb movements since birth. The upper limb movements and cognitive development were age appropriate

He had mild respiratory distress at birth but no significant antenatal issues.

On examination, he had bilateral hamstrings and ankle contractures ,had lower limb weakness, proximal > distal, arefelexia in lower limbs. The spine and upper limbs were normal. Cranial nerves were normal. No tongue fasciculations.

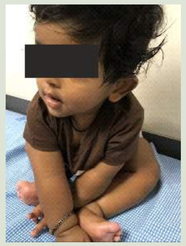

Fig 1A: At 8 months, sitting with support when made to

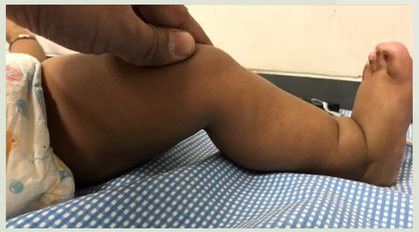

Fig 1B: ankle and hamstring contracture causing restriction of knee extension

NCS revealed motor sensory axonal neuropathy pattern in lower limbs.

Fig 1C: Follow-up of case 1 showing improvement in motor functions, with standing with support and taking steps

Clinical exome showed mutation in DYNC1H1 gene, de novo heterozygous, AD- likely pathogenic for lower extremity predominant spinal muscular atrophy-1 .

He was started on physiotherapy and orthotics support as required, underwent 2 plaster cast sessions.

Last follow up at 3yr 8mth: he was able to walk with both hands support with braces, pulls to sit sideways. His language and cognitive development was good- he was speaking in short sentences and could tell alphabets.

Case-2

A 3 month old boy, born to non consanguineous marriage, with paucity of all limb movements. He had social smile and cooing, fixing and tracking well.

There was history of reduced antenatal movements but no respiratory distress at birth.

On examination: he had contractures of both elbows (R>L) and ankles (L>R). He had weakness in lower limbs -proximal= distal, left > right. He had anti-gravity movements in upper limbs. Arefelxia

NCS: Lower limb motor axonal neuropathy. CPK was normal

MLPA for SMN gene mutation was negative. MRI LS spine was normal

Whole exome sequencing showed mutation in BICD2 gene- AD, de novo heterozygous, likely pathogenic for Prenatal onset lower extremity predominant spinal muscular atrophy- 2B

He was started on physiotherapy and orthotic support.

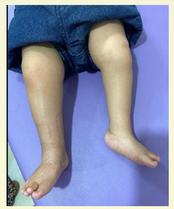

Figure 2: Contractures of hand muscles, elbows and ankles, rocker bottom feet and distal atrophy of legs and hands

Last follow up : at 1.5 yr, he had motor> cognitive delay. He could sit with support when made to, has monosyllable speech and recognises gestural commands.

The lower limb weakness with proximal > distal gradient persisted, whereas upper movements have improved range of motions, reaching out for objects antigravity. Sensory examination and cranial serves were normal.

Discussion

Spinal muscular atrophies (SMAs) are hereditary disorders characterized by degeneration of spinal cord motor neurons

Mostly AR due to homozygous deletion or mutation of the SMN1 gene on 5q

Non-5q SMAs are rare, clinically diverse, and genetically heterogeneous

Commonly classified by inheritance pattern and whether weakness involves predominantly distal or proximal musculature.

SMA-LED phenotype is unusual, distinguished from most other reported cases of autosomal dominant proximal SMA24 by the absence of clinically apparent upper extremity involvement

12 mutations identified to cause autosomal dominant form of SMA, including these two genes- DYNC1H1 and BICD2

- the proteins are part of dynein-dynactin microtubule transport in the Golgi network is crucial for the functional integrity of lower motor neurons.

Both the genes have wide range of phenotypic variations and SMA-LED is one of them

Pathophysiology

DYNC1H1 and BICD2 - encode the proteins which are part of dynein-dynactin microtubule transport in the Golgi network

SMN interacts with alpha-coatomer, which mediates vesicle trafficking between the Golgi compartments and regulates SMN granule secretion from the Golgi apparatus

Animal studies showed disruption of Golgi-mediated granule secretion led to reduced SMN levels in neuritis

Thus, these genes are crucial for the functional integrity of lower motor neurons and mutations lead to neuronal disruption.

Clinical Features

Features can be noted in utero, at birth, or in early childhood, and consisted of lower limb-predominant non-length dependent weakness, wasting and contractures of variable severity, reduced or absent lower limb deep tendon reflexes (i.e. a 'typical' spinal muscular atrophy, lower extremity predominant phenotype)

Non length-dependant weakness and no sensory abnormalities differentiate it from neuropathy and favour motor neuron pathology

Malformations of cortical development and epilepsy may present with DYNC1H1 mutations, not a feature of BICD2

References

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