

Early Infantile Onset Non-5q Spinal Muscular Atrophies: A Diagnostic Odyssey

Sir,

Spinal muscular atrophy (SMA) is the most common autosomal recessive neuromuscular disorder of infantile age, associated with progressive degeneration of alpha-motor neurons in the spinal cord and brain stem.^[1] About 95% of children with SMA have homozygous deletion of exon 7 or 8 of SMN1 gene on chromosome 5q, and about 2.5% have additional point mutations or other variations.^[2] However, patients with clinical features suggestive of lower motor neuron disease with negative SMN1 gene analysis are clubbed as non-5q SMA. Non-5q SMA are indeed rare and heterogenous group of disorders with diverse clinical phenotype, age of presentation, mode of inheritance and prognosis.^[3-5] Spinal muscular atrophy and respiratory distress (SMARD) is the most frequent non-5q SMA in infants.^[6-8] We report two cases of non-5q SMA, where clinical diagnosis of an anterior horn cell disease was made.

A 6-month-old boy presented with history of fever, cough, and rapid breathing for 7 days duration. For respiratory failure he required intubation and mechanical ventilation in emergency room. He was second born to third-degree consanguineous parents, with an uneventful antenatal period. He was born at term with birth weight of 1.2 kg (SGA) and noted to have bilateral ankle contractures. Motor milestones were delayed, but cognitive, social, and language milestones were age appropriate. On examination (intubated, on ventilation) baby was alert, had microcephaly, wasting, stunting, hypotonia, areflexia, paralytic weakness, and ankle contractures. He didn't have tongue fasciculations, muscle atrophy, hypertrophy or joint hyperlaxity. Mother's examination was negative for grip myotonia and her deep tendon reflexes were elicitable. His total creatinine phospho kinase levels (CK-NAC) was normal. Nerve conduction study revealed non-excitable motor and sensory nerves and electromyography (EMG) at quadriceps femoris showed normal motor unit action potentials (MUAPs) and fibrillation potentials. MRI brain was normal. Multiplex ligation probe analysis (MLAP) for SMN1 gene was negative. Electrocardiograph (ECG) was normal, and echocardiography showed normal heart size and function. Muscle biopsy from quadriceps femoris showed transverse section of skeletal muscle with multiple foci of group atrophy [Figure 1]. Next-generation sequencing revealed a biallelic indel variation in the Exon 3 (c.292_303del, p.Gly98MetfsTer7) of the IGHMBP2 gene (NM_002180.3), classified as pathogenic variant and suggestive of spinal muscular atrophy with respiratory distress type 1 (SMARD1). He remained ventilator dependent and succumbed to infections.

A 4.5-month-old girl presented with motor delay, feeding difficulty, and progressive weakness. She was born to a non-consanguineous couple with out significant family history. Antenatal period was uneventful. She was born at term

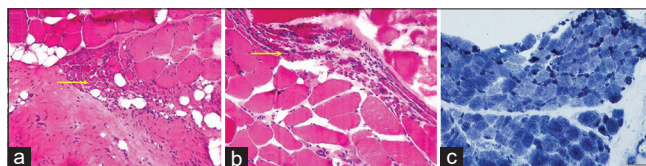


Figure 1: (a and b) Quadriceps muscle biopsy showing multiple foci of atrophic fibers (yellow arrow), along with remaining hypertrophic fibers (hematoxylin and eosin, $\times 100$). (c) NADH staining showing atrophic fibers are predominantly type 1 fibers ($\times 100$)

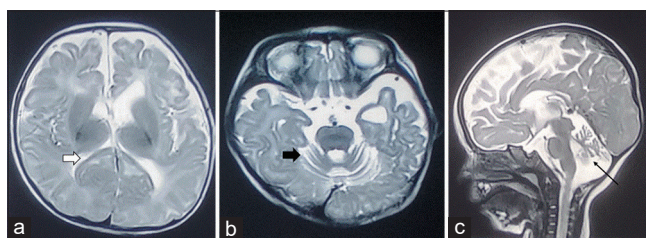


Figure 2: MRI brain (Case 2): T2 axial sections at the level of foramen of mono (a) showing thin corpus callosum (white arrow), cerebral atrophy and (b) marked cerebellar atrophy (black arrow). T2 Sagittal section (c) showing markedly atrophic cerebellar vermis and gracile corpus callosum

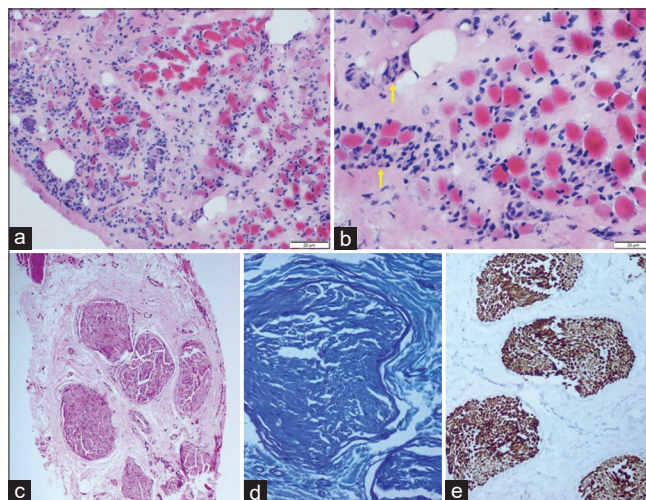


Figure 3: (a) Muscle biopsy shows large areas of group atrophy with few preserved fibers (hematoxylin and eosin, $\times 40$), (b) The group of atrophic fibers show angulation (yellow arrow, hematoxylin and eosin, $\times 100$). (c) Nerve biopsy shows normal nerve fascicles (hematoxylin and eosin, $\times 40$), with (d) preserved myelin (luxol fast blue, $\times 200$) and (e) preserved axons (neurofilament protein immunohistochemistry, $\times 100$)

with lower segment cesarean section, required mechanical ventilation and treatment for sepsis, encephalopathy and jaundice. She was discharged at 3rd week of life but had persistent feeding difficulty. She could coo, had social smile

and partial neck holding. At 3rd month of life, parents noticed progressive looseness of body, reduced spontaneous antigravity movements, feeding difficulties, and lethargy. She suffered an episode of hypoxic cardiac arrest during hospital visit, resuscitated and subsequently remained ventilator dependent.

On examination, she had normal head size (OFC-40 cm) and weighed 4.3 kg (-3.5 Z score). She was encephalopathic, had persistent up-gaze, tongue fasciculation, hypotonia, severe paralytic weakness, and areflexia. There was no organomegaly or cardiac involvement. Serum biochemistry, ammonia, lactate, CPK levels, tandem mass spectrometry and urine gas chromatography and mass spectrometry were normal. MRI brain showed very thin corpus callosum and cerebellar vermis atrophy [Figure 2]. Nerve conduction study showed features of neuropathy. SMN1 gene analysis and CTG repeats for congenital myotonic dystrophy were negative. The muscle and nerve biopsy findings were suggestive of spinal muscular atrophy [Figure 3]. For suspected non-5q SMA, whole exome sequencing showed a biallelic stop gain variation in the exon 20 of AGTPBP1 gene (p. Gln997). Heterozygous carrier state of the known variant in both the parents was confirmed with Sanger sequencing. She remained ventilator dependent for 2.5 months and succumbed to an episode of ventilator associated pneumonia at 6 months of age.

Neuromuscular disorders presenting with respiratory failure in the neonatal or early infantile age are congenital myopathy, congenital myotonic dystrophy, SMA type 0 and 1, SMA variants, and congenital myasthenic syndrome. Differentiation among these disorders is clinical, and maternal examination can give important clue.^[1] Among the non-5q SMA, SMARD1, SMARD2, pontocerebellar hypoplasia (PCH) with SMA, SMA plus syndrome with skeleton involvement and contractures present in neonatal or early infantile age.^[4]

SMARD1 is an autosomal recessive disorder with early onset respiratory failure in first 6 weeks to 6 months of life, diaphragmatic weakness, distal muscle atrophy, and central apnea. SMARD1 is caused by mutations in the gene encoding immunoglobulin mu binding protein 2 (IGHMBP2) on chromosome 11q13, also known as distal SMA type 1 or distal hereditary neuropathy type 6 (HMN 6). Grohmann *et al.*^[9] tested 65 infants with neuropathy of unclear etiology with respiratory failure for IGHMBP2 gene. Among these 65 infants, 29 (44%) showed mutations in IGHMBP2 gene. Infant with SMARD1 have initially distal lower limb weakness manifesting at contractures and foot deformity.^[10] Acute respiratory failure mimicking a respiratory infection or sudden infant death is also known in SMARD1.^[11] Deep tendon reflexes may be preserved in first year of life. Children with SMARD1 require early respiratory support and develop ventilator dependency.^[12] Neuropathology shows degeneration of motor neurons in spinal cord, sensory axonal loss, and muscle fibers atrophy and size variability.^[12]

In the case 2, clinical features, MRI brain and neuropathology findings were consistent with diagnosis of CONDCA

syndrome (childhood-onset neurodegeneration with cerebellar atrophy, OMIM 618176). Shashi *et al.* reported 13 infants with CONDCA. All these children presented within first 6 months of life with failure to thrive, microcephaly, feeding difficulties, hypotonia, abnormal eye movements, global developmental delay, hypotonia, and marked motor weakness.^[13] Neuroimaging showed cerebellar atrophy and dysplastic corpus callosum in all. EMG showed features of anterior horn cell degeneration.^[13] Karakaya *et al.* described 2 children with CONDCA presenting with cognitive regression, motor delay, weakness, swallowing difficulties, and respiratory weakness.^[14] The clinical and neuropathology of CONDCA syndrome are similar non-5q SMA with PCH1, hence AGTPBP1 gene should be added to the non-5q SMA group.^[15]

To conclude non-5q SMA's are diverse, heterogenous disorders with rapidly expanding genetic etiologies. Diagnosis of non-5q SMA should be suspected in infants and children with features of anterior horn cell involvement and negative SMN1 gene analysis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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