Case Report

Spinal muscular atrophy with respiratory distress syndrome (SMARD1): Case report and review of literature

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Abstract

Spinal muscular atrophy with respiratory distress syndrome (SMARD1) is a rare cause of early infantile respiratory failure and death. No cases have been currently described from India. Two low-birth-weight infants presented prior to 6 months of age with recurrent apnea and respiratory distress. Both required prolonged ventilation, and had distal arthrogryposis and diaphragmatic eventration. Nerve conduction study revealed motor sensory axonopathy. Genetic testing confirmed mutations in immunoglobulin mu binding protein (IGHMBP2). These two cases establish presence of SMARD1 in our population. Both infants died on discontinuation of ventilation. Antenatal diagnoses done in one pregnancy. Though rare, high index of suspicion is essential in view of poor outcome and aid antenatal counseling.

Key Words

Atrophy, autosomal recessive, diaphragmatic spinal muscular atrophy, distal spinal muscular atrophy, muscular atrophy, neuronopathy, neuronopathy severe infantile axonal with respiratory failure, SMARD1, Spinal, Type VI

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Introduction

The etiological factors for an infant presenting with arthrogryposis multiplex and respiratory weakness are varied. The localization can be at various sites along the neuromuscular axis. Congenital myasthenic syndromes, congenital muscular dystrophies, congenital myotonic dystrophy, and congenital myopathies can present with early onset lower motor neuron weakness and respiratory insufficiency in the severe cases. The diversity of etiological factors makes it prudent to have a high index of suspicion for evaluation of appropriate etiology as discussed in this case series. Early identification will avoid prolonged ventilation and allows appropriate counseling.

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Case Reports

Case 1

A 6-month-old boy, first born child, birth weight of 1.8 kg without significant antenatal history, presented with frequent episodes of apnea since 2 months of age. At 6 months, he had acute onset respiratory distress and cyanosis requiring intubation and ventilation. He had microcephaly (head circumference-39 cm, <3rd centile), micrognathia, and contractures at Achilles and hamstrings. The extraocular movements were normal without evidence of ptosis, facial weakness, or tongue fasciculations.

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Wasting of distal more than proximal muscles and prominent lower limb involvement was noted. He had partial neck control, with antigravity movement of upper limbs, and minimal along gravity movement at hips and absent movements at the ankle. Chest X-ray showed eventration of right dome of diaphragm. He failed repeated attempts at extubation. On extensive evaluation, positive investigation was axonal motor sensory neuropathy. After 2 months of ventilation, parents decided to discontinue treatment, once the genetic diagnoses was made. Child died within few hours.

Report from Guy's & St Thomas Lab, London demonstrated homozygous mutation on c.958C > T (pArg 320X) on chromosome 11q13 confirming diagnosis of Spinal muscular atrophy with respiratory distress syndrome (SMARD1).

Case 2

Three months infant born small for gestational age, at birth had primary apnea requiring ventilation. He presented at 3 months with respiratory distress, apnea & cyanosis. He had microcephaly (head circumference- 36.5 cm, <3rd centile), retrognathia, and arthrogryposis. The clinical examination revealed evidence of distal muscle atrophy with foot drop. Minimal movement along with the gravity at the hips and weak antigravity movements at the shoulders was observed with no evidence of cranial nerve involvement. The summary of cases are mentioned in Table 1.

He required ventilator support. Chest X-ray showed eventration of right dome of diaphragm [Figure 1]. Repeated attempts at extubation over 2 weeks failed. Parents decided to discontinue ventilation once possibility of SMARD1 was discussed and genetic analysis sent. Child died in few hours. Genetic analysis done at Sandor proteomics, Hyderabad, India revealed homozygous nonsense mutation c.958 > T (p. R320*) in exon 7 confirming diagnosis of SMARD1. Both parents were tested positive for heterozygous mutation in IGHMBP2 gene (supplementary material). Fetus was tested during next pregnancy and was found to carry heterozygous mutation similar to that in one parent, hence pregnancy was continued.

Discussion

These cases exemplify the characteristic presentation of SMARD1 and need for high index of suspicion and appropriate genetic testing. The presence of arthrogryposis with early respiratory failure with or without eventration of diaphragm strongly points to neuromuscular pathology. Among early onset congenital myopathies, X-linked myotubular myopathy can have severe phenotype with bulbar dysfunction and respiratory weakness with affected other family members indicating typical inheritance pattern. Congenital myotonic dystrophy can have typical facial features, congenital cataract, and mother may show myotonia.

In the index infants, there was evidence of axonal sensory and motor abnormality. Infants with spinal muscular atrophy

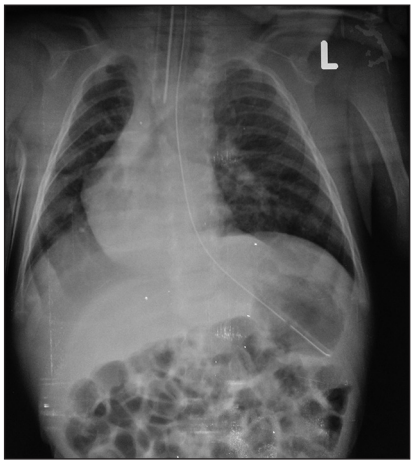

Figure 1: X ray Chest of Case 2 demonstrates eventration of right diaphragm

Table 1: Comparison of clinical and investigational profile of both the patients

Clinical features & investigations	Patient 1	Patient 2
Age at presentation	6 months	3 months
Apnea / cyanosis	3 months	3 months
Microcephaly	+	+
Retrognathia	+	+
Arthrogryposis	+	+
Distal muscle atrophy	+	+ (foot drop)
Eventration of diaphragm	+	+
Other anomalies	COBBs type urethral valve, Grade III GERD	Large PDA
CPK (IU/dl)	48	154
Nerve conduction	Motor sensory axonopathy	Motor sensory axonopathy
Muscle biopsy	Normal	Not done
Nerve biopsy	Dropout of axons	Not done
SMN gene	Negative	Negative
SMARD gene	Homozygous non-sense mutation c.958C>T (pArg 320*) in exon 7	Homozygous non-sense mutation c.958C>T (p.R320*) in exon 7
Laboratory	Guy's & St Thomas Lab London, UK	Sandor proteomics, Hyderabad, India

Case 1 had MRI brain and EEG both of which were normal

(SMA) lack sensory involvement as it is primary anterior horn cell pathology, this along with early contracture, respiratory failure due to early unilateral or bilateral diaphragmatic involvement, and negative SMN gene testing pointed towards alternative genetic etiology like SMARD1. In SMA type 1, infants become floppy due to weakness of the proximal limb muscles before progressing to respiratory failure secondary to paralysis of the intercostal muscles.

SMARD1 is rare, autosomal, recessive, motor neuron disorder affecting infants and characteristically have diaphragmatic weakness, distal muscle atrophy, motor sensory neuropathy, and autonomic dysfunction (apneic episodes); all of which were noted in this case series. It has fatal outcome and usual life expectancy without ventilation is up to 13 months. Mutations have been identified in gene encoding immunoglobulin mu binding protein 2 (IGHMBP2), located on chromosome 11q13.[1] SMARD1 has been variously termed as distal SMA, neuronopathy severe infantile axonal with respiratory failure, and diaphragmatic SMA.

In a series of 200 infants by Rudnik-Schöneborn *et al*., with SMA, 1% were negative for SMN gene and had phenotype of SMARD1, hence making it a rare entity.[2] Grohmann *et al*., described 29 infants with SMARD1 phenotype with mutations in IGHMBP2.[3]

The degeneration of α-motor neurons is caused by mutations in the IGHMBP2 gene producing defective protein. This protein has been implicated in deoxyribonucleic acid (DNA) replication, pre-messenger ribonucleic acid (mRNA) splicing, and transcription, but its precise function in all these processes has remained unknown. Data have revealed IGHMBP2 as an ATP-dependent 5′-3′ helicase, which unwinds RNA and DNA duplicates *in vitro*.[4]

The combination of respiratory failure between 6 weeks and 6 months, and presence of diaphragmatic eventration or preterm birth, predicted the presence of IGHMBP2 mutations with 98% sensitivity and 92% specificity[5] Both infants had diaphragmatic eventration and early respiratory failure. Wide interfamilial phenotypic heterogeneity is noted in SMARD1.[6]

The diagnosis of SMARD1 should be considered in infants with atypical SMA, respiratory distress of unclear cause. Consanguineous parents of a child with sudden infant death syndrome should be examined for IGHMBP2 mutation.[3]

Recent studies demonstrated heterogeneity in long-term outcome of SMARD1 with stabilization of the disease course after 2 years of age. All infants were ventilated by 9 months of age with only one child on part time ventilation by age of 4 years.[7] It is interesting to note both cases had similar mutation although they were from Gujarati and South Indian descent, respectively. An infant born to Indian origin parents in UK was diagnosed with symptom onset by 15 days of age and diagnosis was established after death of the infant.[8]

Both infants were discontinued from life support in view of life-limiting nature of disease and challenges in home ventilation in resource-restrained settings. Parents were informed about nature of disease and futility in continuing treatment. Discontinuation of treatment was done after adequate investigations and parents' understanding of disease and on their request.

Lack of data from Indian subcontinent points towards inadequate awareness and problems with bedside neurophysiological testing in sick infants. Currently, the scenario for genetic testing is much better and readily available across various centers in India, and they are efficacious tests to manage these life-limiting disorders.

Proposed algorithm

Step 1: Look for following features in child with early onset neuromuscular cause of respiratory distress (cardiac and respiratory causes to be ruled out)

1. Head and cervical cord compression circumference: Low in SMARD1, +/- congenital muscular dystrophy
2. Ptosis/facial weakness: Congenital myopathy (X-linked myotubular myopathy: Neonatal, nemaline rod myopathy, etc.) and congenital myasthenic syndromes
3. Early joint contractures/arthrogryposis: SMARD1, congenital muscular dystrophy, and congenital myotonic dystrophy (club foot)
4. Autonomic disturbances: SMARD1

Step 2: Nerve conduction study/creatinine phosphokinase (CPK)/chest X-ray

1. Seizures/microcephaly/early joint contracture/hypotonia/raised CPK/normal nerve conduction study (NCS): Congenital muscular dystrophy
2. Alert expressive child/severe hypotonia/intercostal weakness/motor axonopathic/neuronopathic pattern on NCS/normal or mild elevation of CPK: SMA
3. Facial weakness/ptosis/joint contractures/normal to mildly elevated CPK/normal NCS: Congenital myopathy/congenital myasthenia (repetitive nerve stimulation test (RNST) at different frequencies and neostigmine testing)
4. Distal > proximal weakness/diaphragmatic weakness/alert child on ventilator/normal CPK/joint contracture/motor sensory axonopathy eventration of diaphragm: SMARD1

Step 3: MRI brain

1. If suspected congenital muscular dystrophy (CMD) White matter changes and cerebellar cysts are obvious phenotype in CMD (merosin negative)

Step 4: Ophthalmology evaluation

1. Myopia, astigmatism, optic nerve pallor, and retinal greyish pigmentation in CMD
2. Myopia may be present in myotubular myopathy
3. Congenital cataract in myotonic dystrophy

Step 5: Genetic analysis depending on phenotype

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Conflicts of interest
There are no conflicts of interest.

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