SEPN1-Related Myopathy: The Importance of Diagnosis and Challenges to Management of CMD in Resource Poor Settings

SEPN1-related myopathies (SEPN1 RM) (OMIM#602771) are due to mutations in SEPN1 gene and have a spectrum of manifestations including rigid spine muscular dystrophy1 (RSMD1). Here we present two siblings with a novel mutation in the SEPN1 gene causing RSMD1 phenotype. To the best of our knowledge, this is the first sibling pair being reported with SEPN1 RM with this mutation.

A 3-year-old girl, born to non-consanguineous parents hailing from a migrant working family, presented with failure to thrive and hyperlordosis [Figure 1a and b]. She presented with proximal muscle weakness since 11 months of age with no history of recurrent chest infections or sleep apnea. Her 18 months old brother had similar features, with onset of symptoms at 14 months [Figure 1c]. On examination she had short stature, hypotonia, muscle wasting, rigid spine, torticollis, plagiocephaly, an inverted V-shaped upper lip, nasal speech, a protruding chest and proximal weakness with multiple joint contractures, preserved deep tendon reflexes, and a normal intellect [Figure 1a and b]. She had a power of MRC 4/5 in upper limbs and 3/5 in lower limbs and was ambulant. Investigations showed a normal skeletal survey, creatine phosphokinase and echocardiography. Nerve conduction study showed bilateral common peroneal nerve motor-axonal neuropathy. Hence a congenital muscular dystrophy (CMD) was suspected and next generation sequencing was done to obtain a genetic diagnosis. This detected a homozygous missense variation in exon11 of SEPN1 gene (chr1:g.26140381G > A) that resulted in an amino-acid substitution of Glutamine for Arginine at codon 466 (pArg466Gln). This variation has previously been reported in the compound heterozygous state in patients affected with CMD with spinal rigidity. Sanger sequencing was done using primers covering the mutated exons, which confirmed heterozygous mutation in parents and homozygous mutation in the younger sibling [Figure 2]. Muscle biopsy, pulmonary function tests, physiotherapy, occupational therapy, and non-invasive positive pressure ventilation were planned for the siblings. However, they were lost to follow-up.

SEPN1 RM are a spectrum of disorders that includes RSMD, congenital fiber type disproportion (CFTD) myopathy, desmin-related myopathy with Mallory body like inclusions and classic multi minicore myopathy which are caused by homozygous or compound heterozygous variations in the SEPN1 gene located on chromosome 1p36. Distinct features of SEPN1-RM are early onset spinal rigidity, hypotonia, slowly progressive respiratory insufficiency often despite being ambulant, progressive scoliosis, joint contractures, and an absence of significant cardiac involvement with normal or mildly elevated creatine phosphokinase with non-specific muscle biopsy changes being the norm.[1]

The SEPN1 gene encodes Selenoprotein N, a glycoprotein found within the endoplasmic reticulum which is highly expressed in skeletal muscles and lung parenchyma. SEPN1 is involved in the contractile physiology of skeletal muscles, such as the diaphragm, by maintaining the redox environment. This explains the disproportionate respiratory involvement in affected children both from direct diaphragmatic muscle involvement and from lung parenchymal involvement.[2]

Occasionally SEPN1 RM may present in the neonatal period with rigidity of spine and thoracic cage, facial and neck weakness, and hypotonia of axial musculature, secondary to contractures of the spinal extensors, with thoracolumbar scoliosis and diaphragmatic weakness. This is accompanied by failure to thrive and muscle wasting. Even in these CMD, despite delay in gross motor milestones, ambulation is achieved.
and preserved in most patients. Most have nasal speech due to palatal weakness. But unlike other CMDs they do not exhibit cognitive abnormalities and have normal neuroimaging.\(^3\) Skeletal muscle biopsy often shows nonspecific myopathic changes such as prevalence of type 1 fibers, fiber diameter variability, and atrophy of nuclei.\(^4\)

Here we report a child who was cachexic, with generalized muscular atrophy and rigid spine. Her peculiar feature was torticollis, which was reported rarely in only 1 in 15 cases with congenital presentation of SEPN1 RM.\(^3\) She had no feeding difficulties but had failure to thrive and she was ambulant despite her joint contractures. Her younger brother had rigid spine and torticollis as well. Sleep disordered breathing (SDB) was suspected in view of failure to thrive and body habitus, though there were no overt clinical signs of SDB. Hence, non-invasive ventilation (NIV) was arranged through institutional funding, as were all the previous investigations including genetics. They were counseled about risk of morbidity, complications, and need for prenatal diagnosis for subsequent pregnancies. But the family being migrant workers had different priorities and were lost to further follow up.

CMD is often difficult to identify based on clinical features alone. Genetics aid in phenotype genotypic correlation, which in turn helps in counseling, prenatal diagnosis, and planning further management. The failure to thrive despite no overt feeding difficulties could have been indicative of SDB, which is well described in SEPN1 RM and which is often ably managed with NIV. This report highlights the challenges faced in clinical diagnoses while dealing with CMD and the contribution of molecular genetics in helping solve such clinical dilemmas. In view of the rarity of this condition, the information could contribute to existing literature.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for 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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