



Clinico-Radiological Diagnosis of Merosin Deficient Congenital Muscular Dystrophy- A Case Report

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Abstract

Merosin Deficient Congenital Muscular Dystrophy (MDCMD) is a rare disorder reported in Indian literature. The following case highlights the importance of combined clinical and radiological approach for diagnosis of this condition. We report this 1 year old male child, born of 3rd degree consanguineous marriage, noticed to have delayed attainment of predominantly motor milestones with normal intelligence. There was history of admission for respiratory illness 15 days back. On examination, child was hypotonic, with globally decreased power and absent Deep Tendon Reflexes with no sensory deficits. Investigations revealed elevated Serum CPK levels. EMG NCS showed myopathy pattern. Brain MRI showed evidence of dysmyelination involving periventricular and subcortical white matter along the bilateral fronto-parietal lobes. Genetic testing revealed pathogenic variation in LAMA2 gene confirming diagnosis of MDCMD. Child given supportive physiotherapy and parents offered Genetic counselling.

Keywords: Merosin; Dystrophy; Cpk; Motor.

Introduction

Congenital Muscular Dystrophy comprises of a heterogeneous group of disorders present at birth with muscle weakness, hypotonia and contractures. A particular subset of CMD is characterised by partial or complete absence of merosin, an extracellular matrix protein. It is caused due to defect in LAMA2 gene¹. Majority of merosin-deficient CMD variants often reveal diffuse white matter changes on MRI of the brain, which is referred to as dysmyelinating leukoencephalopathy. MR spectroscopy would also add a value in diagnosis². This case is being reported for its rarity and to highlight the

importance of brain imaging in the diagnosis of this subtype of congenital muscular dystrophy even in a child with no clinical features suggestive of CNS involvement.

Case Report

1 year old male child, born of third degree consanguineous marriage, presented to us with delayed attainment of motor milestones. Parents noticed the child to have persistent head lag even at 6 months of age and subsequent motor delay. He was able to sit only with support and was not able to stand or walk. His mentation and speech were normal. Vision and hearing were normal.

The child had no difficulty feeding; there was no history of seizures. No respiratory difficulty was noted at present but there was history of admission for pneumonia 15 days back. His birth and family history was unremarkable.

On examination, vitals were stable. He had inverted “u”-shaped upper lip with no other dysmorphic features and both testes were descended. Neurological examination revealed symmetrical decrease in bulk of muscles of upper and lower limbs. There were no contractures. There was no fasciculation or hypertrophy of any group of muscles. Muscle power was decreased globally (MRC grading 2/5) with hypotonia, absent deep tendon reflexes and bilateral flexor plantar response with no sensory deficits. Examination of other systems was normal. Investigations revealed normal blood counts, RFT, LFT and electrolytes with serum CPK level of 411 IU/L (elevated). Thyroid function test was normal. EMG-NCS was suggestive of myopathy pattern. Ophthalmological assessment was normal. We performed an MRI of the brain to look for features associated with congenital muscular dystrophy. The MRI showed T2-weighted and fluid-attenuated inversion recovery (FLAIR) hyperintensities involving periventricular and subcortical white matter along the bilateral frontoparietal lobes. Cerebellum, brain stem, Corpus Callosum and Internal capsule were normal for age. No diffusion restriction/blooming was noted. No post contrast enhancement was seen. MR Spectroscopy revealed elevated Choline to Creatine ratio (>1.5). This gave us a clue to suspect merosin-deficient variety of congenital muscular dystrophy. Clinical exome sequencing was done. A pathogenic Homozygous nonsense variation in exon 55 of LAMA2 gene was identified (c.7732C>T) that results in stop codon and premature truncation of protein at codon 2578 thus confirming the diagnosis. Parents were advised to undergo Gene Sequencing and Genetic counselling for future pregnancies but the patient was lost to follow-up.



Figure 1- Photograph of the case presented showing inverted U shaped upper lip, flaccid posture and ability to sit when supported.

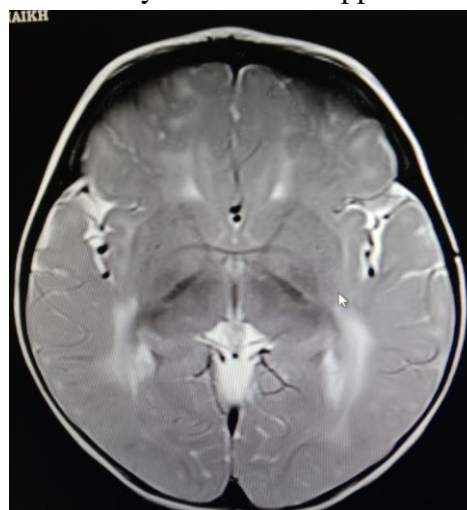


Figure 2- T2W MRI Brain white matter hyperintensities suggestive of dysmyelination.

Discussion

Muntoni and Voit classified CMD phenotypes into four categories, one of which is defect in extracellular matrix protein namely laminin $\alpha 2$, also called merosin, designated as merosin-deficient congenital muscular dystrophy³. It is the most common and most severe form, representing 40% of all CMDs. The estimated incidence is about 0.68 to 2.5 per 100,000. The disease affects both male and female equally and the disease often starts at 6-12 months of age. The mode of

inheritance is generally autosomal recessive for this condition. Children with complete deficiency of merosin, as occurs in majority, present in the neonatal period with profound muscular weakness. A minority can have a partial deficiency, as in our case, presenting in early infancy with delayed motor milestones and hypotonia⁴.

A dystrophic pattern is present on muscle biopsy specimens⁵. Merosin binds to dystroglycan and in turn is linked to the subsarcolemmal cytoskeleton. Deficiency of merosin can disrupt the link between the extracellular matrix and the subsarcolemmal cytoskeleton, and thus causing muscle degeneration. Elevation in CPK levels will correlate with disease severity. Other manifestations reported in these patients include extra-ocular muscle involvement and myocardial involvement, which were absent in our case⁶.

In the literature, CNS involvement is rarely clinically evident, but MR White matter abnormalities are always present⁷. MR imaging findings were strikingly similar in patients suffering from MDCMD. On T2-weighted images, diffuse and symmetrical increase in signal is seen in the white matter of the cerebral hemispheres and normal white matter signal in the cerebellum. These MRI changes are known to progress with age. Hence longitudinal imaging assessments are useful⁴. The exact pathogenesis of these white matter changes is not known. Hypothesis postulated by Villanova et al states that merosin forms an integral component of basement membrane of cerebral blood vessels, thus its deficiency may result in disruption of blood-brain barrier, leading to vascular hyper permeability. Thus, increased T2 prolongation time and hence the above mentioned changes. The metabolite (choline, creatine, N-acetyl aspartate) level reductions in MR Spectroscopy suggests increased free extracellular water concentrations in the affected white matter of patients with MDCMD⁸. However, further studies are needed to prove this hypothesis. Recently there have been reports of structural brain changes

occurring in merosin-deficient CMD, including but not limited to focal cortical dysplasia and focal agyria⁹.

There is no definitive management protocol for this condition. Supportive care is essential in the form of physiotherapy. Ventilator support and tracheotomy, when necessary, have contributed to a marked increase of the life expectancy for the most severely affected patients. Considerable importance regarding nutritional management is also required. Entire family of an index case needs to be genetically tested for the responsible mutation so that parents can be given the option of genetic counselling in all their future pregnancies.

Conclusion

Brain imaging studies are increasingly playing a crucial role in establishing diagnosis of all types of Congenital Muscular Dystrophy and differentiating among the different subtypes.

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