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A Rare case of RYR1 Minicore Myopathy with Marfanoid Habitus- A Case Report

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Abstract

Minicore myopathy (MM) is an autosomal recessive disorder characterized by clinical features of skeletal muscle weakness with other skeletal deformities. These are one of the primary inherited muscle disorders which are present at birth but may manifest in infancy or early childhood age. Exact prevalence is not known. Due to its genetic heterogenicity there are different phenotypes of MM. We here in report a case of 15 years old male, presenting with childhood onset quadriparesis associated with marfanoid features. Muscle weakness was initially progressive then remained static. Skeletal deformities (joint contractures, pes-cavus), and other features of marfanoid habitus like high arched palate, height arm span ratio, arachnodactyly were present. The diagnosis was based upon the clinical features, Muscle Magnetic Resonance Imaging (MRI) of thigh, leg and shoulder and genetic testing. Genetic mutation analysis of ryanodine receptor 1 (RYR1) and selenoprotein N (SEPN1) gene lead to the confirmation of the disease.

Keywords: Congenital Myopathy, Minicore Myopathy, Multi minicore disease, Ryanodine Receptor 1 (RYR1), Selenoprotein N (SEPN1), Marfanoid Habitus, Clinical exome Sequencing

Introduction

MM also known as Multi Minicore disease is a form of congenital myopathy with autosomal recessive inheritance, characterized by infancy or childhood onset proximal muscle weakness with myopathic facial features. Congenital myopathies carry an estimated incidence at around 0.06/1000 live birth [1]. MM is characterized by the presence of muscle fibers with irregular small areas with loss of oxidative enzyme activity (multi-minicores) on muscle biopsy [1]. Based upon the clinical phenotype, there are four forms of Minicore disease: 1) Classic form, 2) Moderate form with hand involvement, 3) Antenatal form with arthrogryposis multiplex congenita, 4) Ophthalmoplegic form [2]. Classic form (most common) accounts 75% of cases [2]. Based upon the genetic, MM subtypes are, a) SEPN1 genetic mutation and b) RYR1 genetic mutation. SEPN1 is associated with an early childhood onset myopathy with axial and proximal muscle weakness, spinal rigidity and respiratory failure [3]. RYR1 is associated with proximal weakness with occasional extraocular muscle involvement and relative sparing of the respiratory muscles [4].

Case report-

A 15 years old male with no positive family history of muscle disease or any general anesthesia associated complication, presented with complaints of lower limb weakness, in form of unable to run or walk fast since age of three. Initially patient used to walk on toes (due to Achilles tendon contractures) for which he was operated at age of five years and was able to walk on whole foot after that. Weakness was

initially progressive for two years, in the form of unable to get up from sitting position and requiring support, unable to run or walk fast later followed by weakness in upper limbs, mainly in the shoulder girdle muscles. The patient was unable to lift heavy things overhead. Following the onset after next two years, the patient had a static course of disease till now. His handgrip was well preserved. There was no history of muscle pain, rash, visual or sensory symptoms.

On general physical examination, the patient had Marfanoid habitus features of high arched palate, pes-cavus and his height arm span ratio was 1.07 (Figure 1 A.) and arachnodactyly (Figure 1 B.) On neurological examination, cranial nerves from I to XII were intact. Patient had hypotonia in all four limbs. The distribution of weakness was predominantly in proximal musculature with involvement of neck flexors and paraspinal muscles. Deep tendon reflexes were 2+ in all limbs. There was no sensory loss. Plantar were flexor bilaterally.

Blood Investigations including serum electrolytes and other metabolic parameters were normal but Serum Creatinine Phosphokinase (CPK) total was 378.6 U/L. Electrophysiological studies were done for localizing the pathology of which Nerve conduction studies of all 4 limbs was suggestive normal nerve conduction studies in all nerves. Electromyographic Study (Table 1) was suggestive of myopathic pattern in Deltoid, Brachioradialis, Vastus lateralis and Gluteus maximus bilaterally. The findings were confirmed radiologically by Magnetic Resonance Imaging (MRI). MRI of both shoulders was suggestive of Fatty infiltration and mild atrophy of supraspinatus, infraspinatus subscapularis and teres major muscle. MRI of pelvic muscles was suggestive of fatty infiltration of gluteus maximus, gluteus medius, bilateral psoas and iliac muscles. MRI bilateral thigh muscles was suggestive of fatty infiltration of all anterior compartment muscles except Rectus femoris and adductor longus, fatty infiltration of posterior compartment muscles except semitendinosus and gracilis. A coincidental finding of fibrous dysplasia of shaft of left femur bone was detected. MRI bilateral leg muscles was suggestive of involvement of soleus muscle and lateral gastrocnemius muscle with relative sparing of the medial part. To ascertain the diagnosis, Clinical Exome Gene Sequencing was done which was suggestive of heterozygous missense variant in exon 95 of RYR1 gene suggestive of MM. Patient's parents were advised for genetic testing but permission was not obtained. Patient was mainly given supportive therapy.

Table 1- Electromyographic values in selected muscles of our patient

Muscles	Spontaneous activity	Muscle Action Potentials	Interference Pattern
Left Deltoid	Nil	Low Amplitude with polyphasia	Early complete
Right Brachioradialis	Nil	Low Amplitude with polyphasia	Early complete
Right vastus lateralis	Nil	Low Amplitude with polyphasia	Early complete
Left Gluteus Maximus	Nil	Low Amplitude with polyphasia	Early complete

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Figure 1. A) Arm Span to Height Ratio-1.07 (Height- 184cm, Arm span-198cm) B) Arachnodactyly

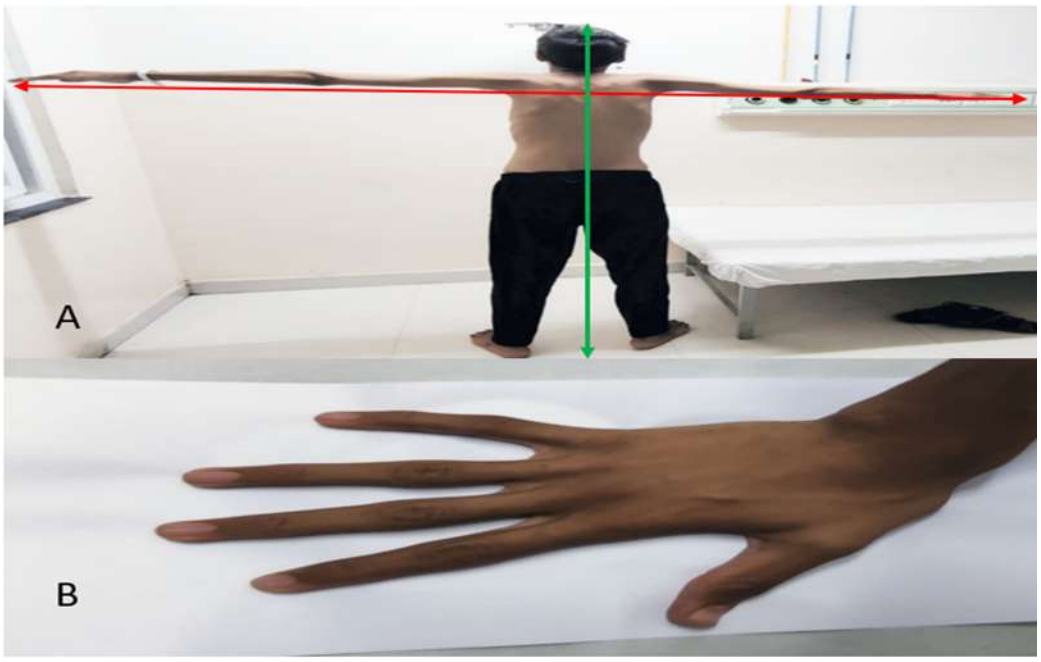

Figure 2. A & B depicting Axial STIR and T1 weighted image of thigh muscles, arrow (white) showing sparing of Rectus Femoris and Gracilis muscle. C and D depicting Axial STIR and T1 image of leg muscles, arrow showing relative sparing of Medial gastrocnemius muscle in comparison to Lateral part.

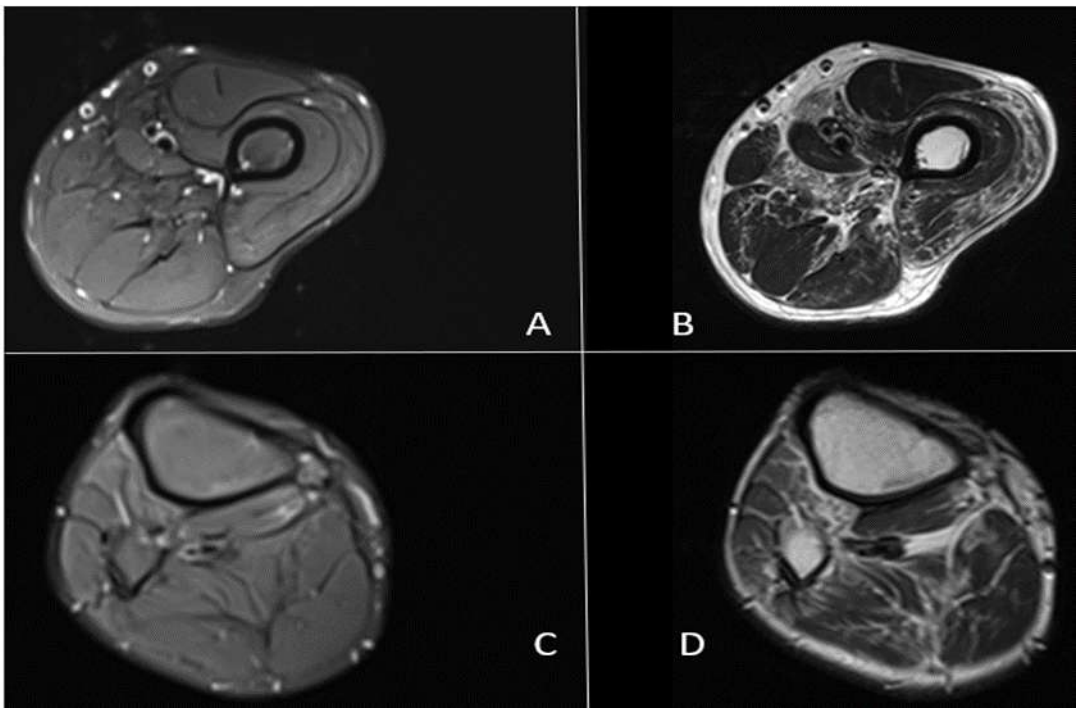

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Figure 3- MRI Thigh muscles STIR image suggestive of Fibrous Dysplasia of left Femur bone

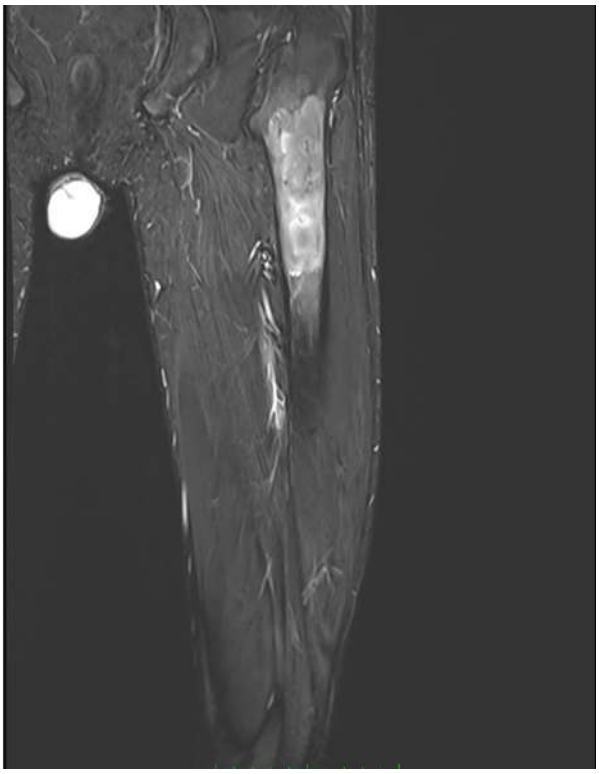

Figure 4 Clinical Exome sequencing report of the case

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
RYR1 **(+)** (ENST00000359596.8)	Exon 95	c.13892A>G **(p.Tyr4631Cys)**	Likely compound Heterozygous	Minicore myopathy with external ophthalmoplegia (OMIM#255320)	Autosomal recessive	Likely Pathogenic **(PS1,PM2,PP3)**
	Exon 106	c.15088C>T **(p.Arg5030Cys)**				Uncertain Significance **(PM2,PP3)**
SCN4A **(-)** (ENST00000435607.3)	Exon 13	c.2045C>G (p.Ser682Trp)	Heterozygous**	Congenital myasthenic syndrome, 16 (OMIM#614198); Paramyotonia congenita (OMIM#168300)	Autosomal recessive** Autosomal dominant	Uncertain Significance **(PM2)**

Discussion:

Patient presented with childhood onset proximal muscle weakness with skeletal deformities (Achilles tendon contractures, Marfanoid Habitus) unique in our case. No cases of MM with marfanoid habitus have been reported in literature so far. Though earlier studies showed association of external ophthalmoplegia with MM but in our case, it was not so. Myopathic pattern in electromyographic study further confirmed the diagnosis. The ancillary non-

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invasive modality such as MRI is useful for differential diagnosis, interpretation of novel genetic findings and scoring disease severity. MRI of both thigh muscles showed sparing of rectus femoris, adductor longus, gracilis (Figure 2A & B) which favors the diagnosis of RYR1 receptor associated myopathy [5]. Patient also had sparing of medial gastrocnemius muscle than lateral part (Figure 2C& D) and fibrous dysplasia of shaft of left femur bone (Figure 3). The ryanodine receptor is the principal sarcoplasmic reticulum calcium release channel. RYR1 mutations are associated with Congenital myopathies such as MM, Central Core Disease (CCD), and Congenital Fiber-Type Disproportion (CFTD) and Malignant Hyperthermia [6]. RYR1 has been involved in both dominant and recessive congenital myopathies. Most RYR1 mutations are linked to congenital Myopathies and Malignant hyperthermia are missense mutation and located at N-terminal (amino acid residues 2,163–2,458; exons 1-17), central (amino acid 35–614 2,163–2,458; exons 39-46), and C-terminal regions (amino acid residues 4,550–4,940; exons 90-104) in the amino acid sequence of RyR1 [7]. There has been novel heterozygous *RYR1* p.Ser2300Pro variant classified as PS3 which have been found associated with Malignant hyperthermia [8]. With the evolution of genetics, the diagnosis of Congenital myopathies can be made by Gene Exome sequencing noninvasively with accuracy. In our case, mutation p.Tyr4631Cys resides at Exon 95 lies in the ryanodine receptor TM 4-6 domain of RYR1 protein which was a missense mutation and of autosomal recessive inheritance (Figure 4). Muscular Dystrophies are important differential but muscle involvement (on MRI) and genetic testing may aid in differentiating it from Congenital myopathy. The treatment of congenital myopathy is supportive management and primarily emphasizing the importance of genetic counselling in the family members.

Conclusion: The importance of clinical history and detailed neurological evaluation is undeniable, especially in case of young patient presenting with myopathy, where proper analysis with aid of radiological and genetic modalities could lead to a definite diagnosis.

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