Myosin Myopathy Presenting as Chronic Progressive External Ophthalmoplegia

Respected Sir,

Progressive external ophthalmoplegia involves a combination of progressive ptosis with restricted extraocular movements without diplopia. Chronic progressive external ophthalmoplegia is seen in many neuromuscular disorders like mitochondrial myopathies, congenital myopathies, congenital myasthenic syndromes, and oculopharyngeal muscular dystrophy.[1] Congenital myopathies associated with mutation in skeletal muscle myosin heavy chain (MYHC) genes are a rare group of hereditary muscle diseases that have a variable age of onset and clinical features. MYHC genes have three major isoforms in adult limb muscle fibers: MYHC I, encoded by MYH7 gene and expressed in slow type I muscle fibers and in the heart; MYHC-IIa, encoded by MYH2 gene and expressed in fast type IIA muscle fibers; and MYHC-IIx expressed in fast type IIB muscle fibers.[2] Myosin heavy chain 2 (MYH2)-associated mutations are a very rare muscle disease that presents in autosomal dominant and recessive forms. Here, we report a rare case of autosomal recessive MYH2 myopathy presenting with chronic progressive external ophthalmoplegia and certain unique features that made the diagnosis challenging.

A 20-year-old male from the Buldhana district of Maharashtra, India, was born to a third-degree consanguinous marriage. His birth history was uneventful, and he had normal development of early motor milestones. He presented with childhood-onset proximal limb weakness causing difficulty to lift heavy weights, raise hands above his head, and get up from squatting position. His weakness was very mild and nonprogressive, not causing any limitations in daily activities. He had dysphagia with a weak cough. He complained of frequent redness and dryness of eyes with limited movements of his eyeballs, and he sleeps with eyes half open. His family has noticed these changes in him since childhood, and it is nonprogressive. He also complained of tremors in his hands. There is a history of early death of two siblings in his family. The cause of death could not be determined due to insufficient data. No other member is affected.

Examination revealed near complete ophthalmoplegia with bifacial weakness and nasal voice. He had diffuse muscle atrophy that was prominent over distal muscles –thenar and interossei, hyperextensibility of finger joints, and pes cavus without contractures. Muscle power assessment showed a symmetrical weakness with 4/5 strength over the deltoid, 4+/5 over the biceps, triceps, wrist flexors, extensors, and small muscles of hands. In lower limbs, iliopsoas strength was 4/5, and gluteus medius 4+/5. He had prominent neck flexor weakness. There were fine postural tremors in both hands. His gait, muscle tone, deep tendon reflexes, and sensory examination were normal.

Investigations revealed serum creatine phosphokinase (CPK) of 165 U/L, thyroid-stimulating hormone (TSH) 1.75 μIU/mL, normal serum lactate, pyruvate levels, and acetylcholine receptor antibodies were negative. The nerve conduction study was

normal. Electromyography revealed short amplitude and short duration motor unit action potentials in deltoid and facial muscles suggestive of muscle disease. Magnetic resonance imaging (MRI) brain and whole spine study was done using 1.5 Tesla MRI Scanner and reported normal. The genetic study was done using the whole exome sequencing method, which revealed: Homozygous mutation in the MYH2 gene on Exon 3, variant c.52C>T, with autosomal recessive inheritance, which was pathogenic for proximal myopathy and ophthalmoplegia. Mitochondrial exome testing was normal. His parents did not give consent for Sanger sequencing. Since whole exome sequencing revealed the diagnosis, muscle biopsy was deferred for the patient.

MYH2 gene-associated myosinopathies are a rare group of congenital myopathies with distinct pathologies and phenotypes.[1] To the best of our knowledge till now, very few cases have been reported in India. In this patient, the combination of early-onset nonfluctuating and nonprogressive limb weakness with chronic external ophthalmoplegia is characteristic of recessive MYH2 mutation. Autosomal dominant MYH2 myopathy presents as congenital joint contractures, adolescent onset external ophthalmoplegia, and progressive proximal weakness. Muscle biopsy reveals dystrophic changes, rimmed vacuoles, and intranuclear and cytoplasmic inclusions. So, it is called as hereditary inclusion body myopathy (HIBM).[3,4] The autosomal recessive form of MYH2 myopathy presents with progressive external ophthalmoplegia and early onset diffuse limb weakness that is usually nonprogressive.[5-8] A variable degree of skeletal muscle weakness is found in MYH2 myopathies. Muscle biopsy shows small or absent type 2A fibers without vacuoles or protein inclusions.[6-8] Andrew R. Findlay *et al*.[1] described a homozygous missense variant in the MYH2 gene in a patient with major clinicopathological characteristics seen in autosomal dominant mutations. Several patients with autosomal dominant MYH2 mutations have been reported with phenotypes and pathologic features more consistent with autosomal recessive forms.[9] This indicates frequent pathological and clinical overlap. However, external ophthalmoplegia is a constant clinical hallmark seen in both dominant and recessive forms of MYH2 myopathies. Hence, although rare, MYH2 mutation should be considered in a patient presenting with chronic progressive external ophthalmoplegia with or without limb weakness.

Our patient had certain unique features like distal upper limb weakness with wasting and tremors in the hands, which made the diagnosis difficult. Distal limb weakness is commonly not a feature of MYH2 myopathy and is reported in only a few studies.[9]

This case highlights that MYH2 gene-associated congenital myopathy is a rare neuromuscular disease having variations in clinical and pathological features. Chronic progressive external ophthalmoplegia is a common hallmark feature seen in all patients. So, MYH2 defect should be considered in congenital myopathy associated with extraocular muscular involvement. The patient reported here had certain unique features not commonly seen in MYH2-associated myosinopathies. These findings could expand the phenotypic spectrum of MYH2 mutations and should be confirmed in future studies.

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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