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COMPREHENSIVE CLINICAL AND GENETIC ANALYSIS OF MYOTONIA CONGENITA: CASE SERIES AND GENETIC INSIGHTS FROM NORTH INDIA

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ABSTRACT Myotonia congenita (MC) is a rare genetic disorder that affects the skeletal muscles, causing difficulty in relaxing muscles after they contract. This condition, classified as a neuromuscular channelopathy, typically presents in early childhood. MC significantly impacts patients and their families, leading to difficulties with movement, swallowing issues, gastrointestinal problems, and respiratory complications. It is caused by mutations in the CLCN1 gene, which encodes a chloride channel predominantly expressed in striated muscle. Most cases have been reported in the European population, and only mexiletine has demonstrated effectiveness in randomized, placebo-controlled, double-blind studies. We present a series of two cases: a 30-year-old male who experiences frequent falls and transient muscle stiffness after voluntary activity, and a family comprising a 26-year-old father with difficulty releasing held objects and fatigue, and his 5-year-old daughter with delayed motor milestones. Both cases demonstrate muscle hypertrophy and myotonia, and EMG findings are indicative of myotonic myopathy. Exome sequencing results suggest autosomal recessive myotonia congenita (Becker's type) in the former case and autosomal dominant myotonia congenita (Thomsen type) in the latter. To the best of our knowledge, this is the first reported case of congenital myotonia from North India.

KEYWORDS : Myotonia congenital, Becker's type, Thomsen type

INTRODUCTION

Congenital myotonia is an uncommon hereditary disease of skeletal muscles that begins early in life and is characterized by myotonia and muscular hypertrophy. The condition can appear in autosomal dominant or recessive forms. The dominant form includes Thomsen's disease and myotonia levior, while the milder recessive form is known as Becker's disease.[1] Both forms are classified as channelopathies, characterized by faulty chloride ion transport. The condition can occur in autosomal dominant or recessive forms. The dominant type is subdivided into Thomsen's disease and myotonia levior, with the latter being milder in manifestation and known as Becker's disease. Both forms are classified as channelopathies due to faulty chloride ion transport. Clinically, the disease is characterized by muscle stiffness and the inability to relax after voluntary contraction. Both variants have a similar clinical profile, but Thomsen's variant is typically associated with an early age of onset and a milder disease course. In contrast, Becker's variant is associated with a progressive disease course that can sometimes result in generalized weakness and bulbar involvement. The CLCN1 gene is located on chromosome 7q34 and encodes the skeletal muscle chloride channel-1 (ClC-1), which is primarily expressed in striated muscle.[2] This channel plays a crucial role in the repolarization of the plasma membrane.[3] In myotonia congenita, reduced chloride ion influx into the cell results in hyperexcitation of the cell membrane and prolonged action potential in striated muscle cells. This prolonged action potential generates sustained muscle contraction with an inability to relax. Other symptoms that may be present include transient weakness, generalized muscular hypertrophy, and depressed deep tendon reflexes. The reported incidence of myotonia congenita disorders ranges from 0.3 to 0.6 per 100,000 individuals in the general population. The majority of cases of myotonia congenita are documented in the European population, with a higher prevalence observed in Nordic countries.[4,5] Several cases have been reported from India, mainly from southern states and predominantly in pediatric population with significant response to phenytoin and carbamazepine. [6,7] We report a 30-year-old male laborer who was ultimately diagnosed with Becker's type myotonia congenita, as well as a 26-year-old male and his 5-year-old daughter, who were both ultimately diagnosed with Thomsen's type myotonia congenita.

Case -1

A 30-year-old male, born to non-consanguineous parents and originally from Bihar but currently working as a laborer in Shimla, presented to our outpatient department with a six-year history of frequent falls, more weakness in the proximal muscles than the distal ones, transient muscle stiffness, and symptoms suggestive of grip myotonia. He reported difficulty walking with leg stiffness whenever he started walking after prolonged sitting, which improves after a few steps. He also noted difficulty releasing objects after firmly grasping them, with the palm remaining partially open. No other significant medical history was noted."

Physical examination: The physical examination revealed muscle hypertrophy in the muscles of the upper limbs, lower limbs, and trunk (see figures 1, 2, 3, and 4). Muscle strength was 4/5 in proximal muscles and 5/5 in distal muscles. The rest of the central nervous system examination was normal. There were no clinical stigmata of myotonic dystrophy, paramyotonia congenita, or chondrodystrophic myotonia.

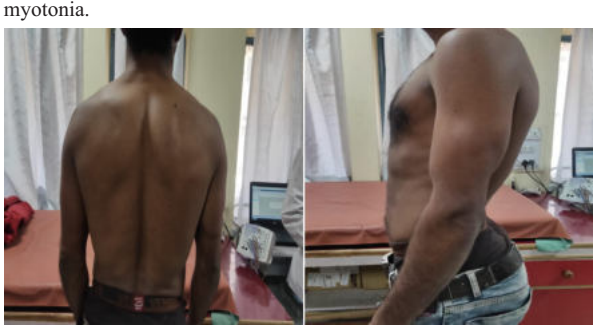

Figure: 1
Figure: 2

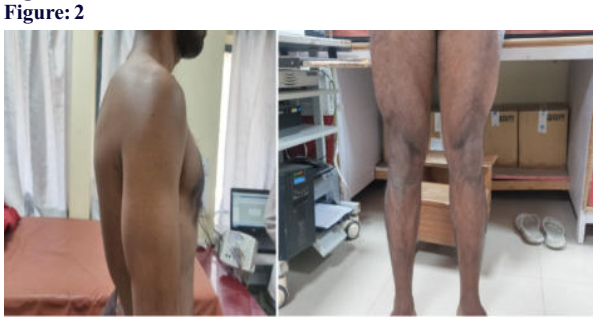

Figure: 3
Figure: 4

Case 2

A 26-year-old male, born to non-consanguineous parents, presented to our OPD with a five-year history of difficulty in releasing held objects and fatigue, which improved with repeated activity. His 5-year-old daughter also had a history of delayed motor milestones. No other significant history was noted.

Physical Examination: The physical examination was normal except for muscle hypertrophy (see figures 5) and hand and foot myotonias observed in both the father and daughter.

Figure-5

Investigations: Laboratory values were within normal limits. EMG showed evidence of myotonic myopathy. Genomic analysis revealed a c.869T>C mutation in exon 8 of the CLCN1 gene on chromosome 7, indicating autosomal dominant inheritance and diagnosing Thomsen's type myotonia congenita.

Treatment: Both patients were started on oral carbamazepine, which led to symptomatic improvement.

DISCUSSION

These two cases presenting with frequent falls, grip myotonias, proximal weakness (case 1) and grip myotonias and positive family history (case2) along with muscle hypertrophy and emg showing myotonic myopathy, after genomic analysis were diagnosed as myotonia congenita.

The brunt of myotonia congenita falls on the lower limbs, probably as a result of work hypertrophy. The cranial musculature is also frequently involved, where classically there is visible myotonia of the eyelids after the patients is asked to open the eyes following forceful closure. Serum CK is elevated two to three times and serum potassium is normal during and between attacks. Both the dominant and the recessive forms of myotonia congenita are linked to CLCN-1 gene on chromosome 7q35 encoding the skeletal muscle chloride channel and the differences between the two types of myotonia are probably caused by different mutations of the same gene suggesting that the diseases are allelic.[8] Attempts to identify trinucleotide repeat expansion in both the varieties of myotonia congenita have turned negative. Sunohara et al in their work on a sporadic case of myotonia congenita could not find any abnormal expansion of CTG repeat within the myotonic dystrophy gene.[9] Wadia et al described a case of generalized recessive myotonia and Prabhakar et al reported an identical case. Sheela et al described a family where five subjects suffered from myotonia and that conformed to the autosomal dominant variety of the disease.[10,11,12]

CONCLUSION

To conclude, this is the first case series of myotonia congenita reported from Northern India to the best of our knowledge. Increasing awareness among healthcare providers about this type of disease in India and specifically in north India could lead to the identification of undiagnosed patients. We propose that the members of the family of every child presenting with myotonia should undergo detailed screening clinically and be tested for trinucleotide repeats, since congenital myotonia, in comparison to myotonic dystrophy or congenital myotonic dystrophy carries better prognosis and the subjects may have normal life expectancy.

Therefore, further research is needed to understand the specific genetic mechanisms underlying the different forms of myotonia congenita and to develop targeted therapies for this rare condition.

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