Nonaka Myopathy: First Report of a Rare Mutation from India (c.1571C>T)

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DOI: https://doi.org/10.62830/mmj3-01-22

Abstract:

A young male presented with long-standing foot drop with no significant personal or family history. On detailed clinical examination, the patient exhibited quadriparesis, distal more than proximal, predominantly affecting the lower limbs. Initial evaluation at another centre revealed no significant abnormalities. Examination demonstrated significant distal motor weakness, while sensory examination was unremarkable. Nerve conduction studies and creatine phosphokinase (CPK) levels were normal. The patient refused a muscle biopsy. A possibility of distal myopathy, with a differential diagnosis of Charcot–Marie–Tooth disease, was considered. Whole-exome sequencing was done, which identified c.1571C>T mutation suggestive of Nonaka myopathy. This represents the first report of this rare mutation from India. The prognosis of the disease remains poor, with a possibility of the patient becoming wheelchair bound by 10–15 years of diagnosis. However, the life expectancy remains normal as cardiovascular muscles are not affected. This case emphasises the need for a detailed genetic evaluation for patients diagnosed with rare neurological disorders.

Key words: Nonaka Myopathy, Inclusion Body, Foot Drop.

Introduction

Glucosamine N-acetylmannosamine kinase (GNE) myopathy, also known as Nonaka myopathy or hereditary inclusion body myopathy (HIBM), is a rare and progressive autosomal recessive disorder caused by mutations in the GNE gene.[1] In 1981, Ikuya Nonaka and colleagues described a rare distal myopathy with rimmed vacuoles and lamellar body depositions called distal myopathy with rimmed vacuoles (DMRV) or Nonaka myopathy.[2] In 2001, the Mitrani-Rosenbaum group identified mutations in the GNE gene, which encodes N-acetylglucosamine epimerase/GNE.[3]

Case Report

A 22-year-old male presented with progressive quadriparesis for 7 years. He was born of a non-consanguineous marriage and had an uneventful perinatal and neonatal period. He remained healthy until the age of 15, when he began to lag behind his cousins while walking. He subsequently developed difficulty in clearing the ground while walking, frequent tripping, and an inability to retain his footwear. Over the next 2 years, he developed difficulty in gripping objects with his hands. There was no history suggestive of proximal upper limb weakness, voice change, dysarthria, dysphagia, visual complaints, or facial weakness.

On examination, the patient was moderately built. Higher mental functions were intact. Neck weakness was present. Shoulder strength was normal, while weakness was observed across all the muscles at the elbow and small muscles of the upper limbs symmetrically. Wasting of the small muscles of the hand was noted. The lower limbs had significant weakness at the hip and ankle. The patient was noted to have bilateral foot drop.

A workup revealed normal haemogram, liver and kidney function tests. Creatine phosphokinase (CPK) levels were within normal limits. Electromyography (EMG) was suggestive of a myopathic pattern in both proximal and distal muscles of the upper and lower limbs. Protein electrophoresis and vasculitic profile were unremarkable. A muscle biopsy could not be performed. After obtaining a written consent, the genetic analysis was sent to MedGenome Laboratories. Whole-exome sequencing (WES) showed a heterozygous missence mutation on Exon 9 of the GNE gene on chromosome 9 (c.1571C>T), classified as pathogenic. This resulted in an amino acid substitution of valine for alanine at codon 524 (p.Ala524Val).

Discussion

The observed variation lies within the regulator of optimum kinases (ROK) family domain of the GNE protein. Early-onset cases of GNE myopathy are rare,[1] generally manifesting in the third decade of life. However, early-onset cases before the age of 10 and late-onset cases in the fifth decade of life have also been reported.[4] The primary presentation of the disease is foot drop. Progressively, the patient develops weakness in the hamstrings and hips. However, characteristic sparing of the quadriceps is noted. Investigations may reveal a normal or mildly increased creatine kinase (CK) level. The clinical and biochemical findings of the present case were comparable to those of previously reported cases. Magnetic resonance imaging (MRI) may show short tau inversion recovery (STIR) hyperintensity with fatty infiltration in the affected muscles. Muscle biopsy may show rimmed vacuoles, fibre size variation, amyloid deposition, endomysial fibrosis, and 14–18 nm filamentous inclusions, without inflammatory infiltrates. The patient declined muscle biopsy due to personal reasons.

More than 1,000 individuals with GNE myopathy and about 255 GNE variants have been reported worldwide. Most of the pathogenic variants are missense mutations. Other less common mutations include insertions, deletions, large deletions, intronic mutations, and splice-site mutations. Diagnosis of GNE myopathy is confirmed by homozygous or compound heterozygous GNE gene mutations.[1]

Thirty-one patients with undiagnosed genetic myopathies in the Indian subcontinent were found to harbour a pathogenic GNE mutation. In a review of 207 genetic myopathies from the Indian subcontinent, GNE mutations contributed to 28% of cases.[5] The c.2179G>A (p.Val727Met) variant is a common mutation in India, identified in approximately 75% of GNE-myopathy patients in a reported Indian cohort. It also accounts for 32.7% of all GNE mutations reported in Indian studies, supporting p.Val727Met as a likely founder mutation in the Indian subcontinent.

Khadilkar *et al.* have recently documented an interesting occurrence of homozygous mutation c.1853T>C (p.I618T) (24.5%) in the Rajasthani Jain and Maheshwari communities, a founder mutation encountered exclusively in European Roma Gypsies.[6,7] The present mutation was previously reported in a single patient from mainland China.[8]

Declarations

Informed consent: Written informed consent was taken from the patient.

Conflict of interest: Nil.

Conclusion

GNE mutation is a rare genetic myopathy caused by a missense mutation in the GNE gene. This case represents the first report of the c.1571C>T mutation from India.

Abhishek Wankar. Nonaka Myopathy: First Report of a Rare Mutation from India (c.1571C>T). MMJ. 2026, March. Vol 3 (1).

DOI: https://doi.org/10.62830/mmj3-01-22

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