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Case Report

Nonaka myopathy: First report of a rare mutation (c.1702T>C) from India

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ABSTRACT

Nonaka myopathy is an autosomal recessive muscle disease which is slowly progressive. It typically presents between age 20 and 40 years with bilateral foot drop caused by tibialis anterior muscle weakness. Subsequently involvement of the posterior compartment of the leg, followed by involvement of hamstrings, then hip girdle muscles occur, with relative sparing of the quadriceps. About ten to 20 years after the onset, patient may become wheel chair bound. It is caused by mutation in GNE gene on chromosome 9. Here we describe a case of Nonaka myopathy caused by homozygous missense mutation in GNE gene at codon 1702T>C(p.Phe568Leu) which has not been reported from India so far.

1. Introduction

Glucosamine (uridine diphosphate-N-acetyl)-2-epimerase/ N-acetylmannosamine kinase (GNE) myopathy, also called Nonaka myopathy, hereditary inclusion body myopathy, distal myopathy with rimmed vacuoles (OMIM 605820) is a rare, progressive autosomal recessive disorder caused by mutations in the GNE gene.[1] Ikuya Nonaka and colleagues in 1981 described a rare distal myopathy with rimmed vacuoles and lamellar body depositions called Distal Myopathy with Rimmed Vacuoles (DMRV) or Nonaka myopathy.[2] In 1984, Argov Zohar described a unique muscle disorder, Rimmed Vacuole Myopathy or Quadriceps Sparing Myopathy (QSM) in 4 Iranian-Jewish families.[3] Later, due to the histological similarities to Inclusion Body Myositis (IBM), this disorder was also termed as Hereditary Inclusion Body Myopathy (HIBM) or hIBM. In 2001, the Mitrani-Rosenbaum group identified mutations in GNE gene, which encodes for the N-acetylglucosamine epimerase/ N-acetylmannosamine kinase (GNE).[4] Its later found out that all the above-mentioned myopathies in fact represent the same neuropathological condition. Since the identification of GNE as the disease causative gene, a consortium of researchers working on various aspects of this disease has decided in 2014 to unify the name and call it GNE myopathy.[5]

GNE gene encodes the rate-limiting enzyme of sialic acid biosynthesis. Hypo sialylation of muscle glycans is thought to play an essential role in pathophysiology of this disease. The typical presentation is bilateral foot drop in early adulthood caused by weakness of the tibialis anterior muscle. Over next few decades it slowly progresses to involve skeletal muscles throughout the body, with relative sparing of the quadriceps until late stages of the disease. Histopathologic findings on muscle biopsies include lack of inflammation, fibre size variability, atrophic fibres, and the characteristic rimmed vacuoles on modified Gomori trichome staining.[1]

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2. Case Report

A 59-year-old man born of a non-consanguineous marriage presented to outpatient department with weakness of right lower limb followed by weakness of left lower limb since last five years. He noticed weakness in the form of difficulty in lifting forefoot off the ground. For the last 1 year he has difficulty in getting up from chair. There was no history of any buckling or difficulty in walking on forefoot. There no h/o any truncal weakness, upper limb weakness or any cranial nerve symptoms. No history of any muscle pain, second wind phenomenon, out of wind phenomenon or cola coloured urine after exercise. There was no history of any sensory or bladder symptoms. He is a diabetic and hypertensives for the last one year. There was no history of thyroid disease. There is no history statin use. There was no family history of any similar illness in family. On examination he was moderately built and moderately nourished. His vitals were normal. Cranial nerve examination was normal. There was mild neck flexion weakness. His upper limbs were normal. There was no scapular winging. Lower limb examination showed grade 0/5 weakness of foot dorsiflexion bilaterally (Bilateral foot drop) Figure 1 Plantar flexion and inversion were normal. His hip flexion, adduction and hip extension and knee flexion were weak. Hip abduction and knee extension were normal. Beevor's sign was absent. His knee jerk and ankle jerks were absent. Blood investigations showed mild elevation of creatinine phosphokinase [Table 1]. Nerve conduction study showed sensory axonal neuropathy involving both lower limbs. EMG showed a myopathic pattern. [Table 2] We did not do MRI of the lower limbs or muscle biopsy.

Blood was sent to Medgenome Labs for clinical exome sequencing. Next generation sequencing (NGS) showed homozygous missense mutation in exon 9 of the GNE gene on Chromosome 9 (c.1702T>C), which is classified as likely pathogenic mutation. This resulted in amino acid substitution of Leucine for Phenylalanine at codon 568(p.Phe568Leu). The observed variation lies in the ROK family domain of the GNE protein. Nonaka myopathy is caused by homozygous or compound heterozygous mutations in the GNE gene.

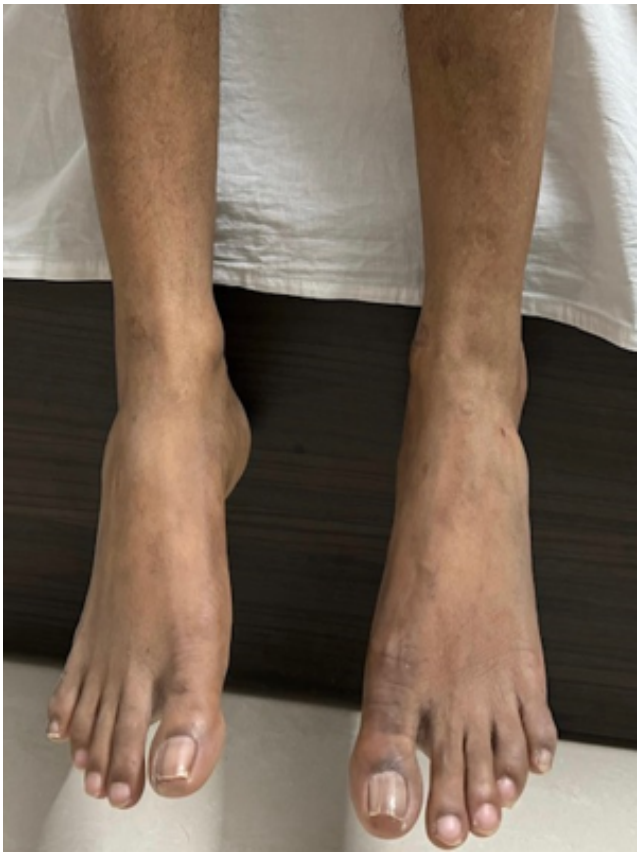

Figure 1: Leg showing bilateral foot drop

3. Discussion

Worldwide prevalence of GNE myopathy is around 1in 1,000,000. First symptoms usually occur in the third decade of life. Few early onset cases (at 10 years of age) and late onset in the 5th decade have been reported. They usually present with bilateral foot drop. There is subsequent sequential involvement of posterior compartment of the leg, followed by hamstrings and hip girdle muscles, with relative sparing of the quadriceps. The upper extremities can be affected later in the course of illness and do not follow a distal-to-proximal progression. Strong quadriceps in spite of major involvement in other leg muscles is a strong pointer to the diagnosis of GNE myopathy as it is rarely found in other neuromuscular disorders.[6,7] The cause of the quadriceps sparing remains an enigma in this disease. Beevor's sign is a common feature in Indian patients with GNE myopathy. Simultaneous involvement of semimembranosus, semitendinosus and tibialis anterior is a diagnostic pointer for GNE myopathy. Investigations may reveal normal or mildly increased creatine kinase (CK) level. MRI may show STIR hyperintense muscles with fatty infiltration. Muscle biopsy may show rimmed vacuoles, fibre size variation, amyloid deposition, Endomysial fibrosis and 14–18 nm filamentous inclusions, without inflammatory infiltration.

The GNE gene is located on chromosome 9 and consists of 13 exons. More than 1,000 individuals with GNE myopathy and about 255 GNE variants have been reported so far worldwide. Most of the pathogenic variants are missense mutations. Other less common mutations are insertions, deletions, large deletions, intronic mutations, and splice site mutations. Mutation can occur in kinase domain (KD) or epimerase domain (ED). The mutations occur in both homozygous (ED/ED, KD/KD) and compound

Table 1: Blood Investigations

Fasting Blood Glucose	134 mg%	70-110 mg%
Creatinine	0.68 mg%	0.7-1.4 mg%
Potassium	4.1mEq/L	3.5-5 mEq/L
Calcium	9.5mg%	8.8-10.5 mg%
ESR	10 mm/hour	<30 mm/Hr
TSH	2.5 U/L	0.35-4.5 U/L
CPK	373 U/L	24-195 U/L

Table 2: Electromyography findings

Muscle	Spontaneous activity	MUAP	Interference pattern
Tibialis anterior	Nil	Small amplitude, polyphasic	Early recruitment
Gastrocnemius	Nil	Small amplitude, polyphasic	Early recruitment
Quadriceps	Nil	Normal	Normal
Flexor carpi radialis	Nil	Normal	Normal
Biceps	Nil	Normal	Normal
Deltoid	Nil	Normal	Normal

heterozygous (ED/KD) combinations. The latter is more commonly seen.[8]

Diagnosis of GNE myopathy is confirmed by homozygous or compound heterozygous GNE gene mutation. Thirty-one percentage of patients with undiagnosed genetic myopathies in the Indian subcontinent were found to have pathogenic GNE mutations.[9] Different ethnic backgrounds have different mutations. p.Val572 Leu mutation is common in Japanese and Korean patients and p.Met712Thr is common in the Jewish population. p.Val696Met (pVal727Met new nomenclature) is the most common mutation in both India and Thailand.[10] There are ethnic GNE founder mutations found in Middle Eastern (Met743Thr), Japanese (Cys44Ser, Asp207Val, and Val603Leu), Roma Bulgarian (Ile618Thr) and Indian/Asian (Val727Met) populations.

There are few studies of GNE myopathy patients is available from India. c.2179G>A (p.V727M) is a common mutation (75%)[10] and (32.7%)[11] in India. p.Val727Met is likely to be a founder mutation of Indian subcontinent.[12] Khadilkar et al. have recently documented an interesting occurrence of homozygous mutation c.1853T>C (p.I618T) (24.5%) in Rajasthani Jain and Maheshwari communities: a founder mutation encountered exclusively in European Roma Gypsies.[11]

4. Conclusion

GNE myopathy is a very rare distal onset myopathy with characteristic quadriceps sparing. Here we describe a case of GNE myopathy with onset in sixth decade. Genetic analysis showed a very rare homozygous missense mutation in GNE gene (c.1702T>C) (p.Phe568Leu) which has not been reported so far from Indian subcontinent.

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6. Conflict of Interest

None.

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