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GNE Myopathy- A Rare Distal Myopathy with Rimmed Vacuoles: A Case Report

Case Report

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Abstract

GNE myopathy is a rare distal myopathy also known as hereditary inclusion body myopathy (HIBM) or Nonaka disease or Distal Myopathy with Rimmed Vacuoles (DMRV) or IBM2. It's an autosomal recessive disease that can present in homozygous or compound heterozygous forms, with predominantly compound heterozygous mutations found in Indian subcontinent. Clinically most striking feature is distal leg weakness sparing quadriceps, distinguishing it with other common myopathies. GNE myopathy most commonly presents in the third decade of life as foot drop because of predominant Tibialis Anterior muscle involvement. Later it progresses to other muscles of lower and upper limbs; however Quadriceps usually remain spared even in advanced stages. Muscle biopsy typically shows rimmed vacuoles with atrophied fibres and congophilic depositions. Distal muscle weakness with sparing of quadriceps and rimmed vacuoles in muscle biopsy make this rare myopathy a unique one. Here we are presenting a typical case of GNE myopathy with founder mutation (p.Val727Met) which is common in Indian population.

Keywords: GNE myopathy, Nonaka, Distal myopathy, Rimmed vacuoles

Introduction

GNE myopathy, also known as HIBM, Nonaka myopathy, IBM2 and distal myopathy with rimmed vacuoles, is a genetic disorder that affects primarily the skeletal muscles. First signs of the disease appear between 20 and 40 years of age and affect males and females at the same rate. This condition is characterized by progressive muscle weakness which typically worsens over time, decreased grip strength and frequent loss of balance [1,2].

GNE myopathy is caused by mutations in the GNE gene, which encodes for an enzyme known as glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase. Mutations in the GNE gene have been reported worldwide in approximately 4,000 patients although the incidence of the disease has been estimated to be 1-9/100,000 individuals.

GNE myopathy is a unique myopathy with distinct clinical and pathological features so awareness of this myopathy may help in identifying more cases in the future and thus increasing the understanding about this myopathy. We believe that this a rare case and that it can contribute to our knowledge about such kind of rare diseases.

Case Report

Here we present a case of young man, 25 years born out of a non-consanguineous marriage and second child in the family. He presented to us with progressive difficulty in walking for duration of one year. Initially it started with the left leg and over few months it progressed to right leg also. He was not having any family member suffering from similar complaints. On examination there was atrophy in the anterior compartment of both the legs with bilateral foot drop.

Other muscles in lower limb were normal including quadriceps. There was mild weakness of bilateral hand grip which went unnoticed by the patient. He had normal cognitive functions, cranial nerves and sensory examination but diminished reflexes.

His blood chemistry was normal except high CPK levels (approximately 5 times of the higher normal range). Electromyography showed small, polyphasic motor unit potentials with early and complete recruitment, most prominent in tibialis anterior muscles bilaterally. Cardiac evaluation including ECG and 2-D echo was within normal limits. Muscle biopsy from tibialis anterior showed myofibers of variable sizes, endomysial fibrosis with fatty infiltration and few fibres showed vacuoles with basophilic, granular material within rimmed vacuoles (Figures 1 and 2) suggestive of rimmed vacuolar myopathy.

Whole genome analysis showed a heterozygous (amino acid change: p.(Val727Met) Missense mutation) likely pathogenic variant in GNE gene which is consistent with most commonly found mutation in Indian subcontinent, in autosomal recessive GNE myopathy. The GNE variant c.2179G>A p.(Val727Met) causes an amino acid change from Val to Met at position 727.

Discussion

GNE myopathy was first described by Ikuya Nonaka in 1981 as a distal myopathy with Rimmed vacuoles and lamellar (myeloid) body depositions [3], hence it was called as Nonaka myopathy initially. Later it was described as "quadriceps sparing myopathy" by Argov Zohar in 1984 [4].

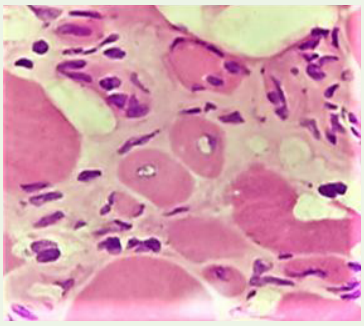

Figure 1: Hematoxylin and eosin stain showing two fibers with rimmed vacuoles with adjacent variable sized muscle fibers.

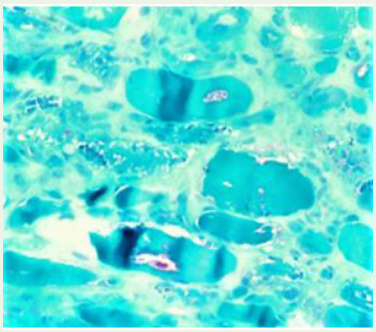

Figure 2: Modified Gomori Trichrome stain showing two fibers with rimmed vacuoles with adjacent variable sized muscle fibers.

Clinically GNE myopathy most commonly presents in the third decade of life as distal weakness in both legs because of predominant Tibialis Anterior involvement. Later it progresses to proximal muscles of lower limbs and the upper limbs with remarkable sparing of quadriceps even in late stages. Bilateral foot drop and other muscle involvements of lower limbs with relative sparing of quadriceps is a good clinical sign to have a suspicion of GNE myopathy [5]. The reported patient had progressive difficulty in walking and on examination; there was atrophy in the anterior compartment of both the legs with bilateral foot drop. Other muscles in lower limbs and quadriceps were normal but bilateral handgrip was weak. In approximately 5% of patients quadriceps may be involved in early stage making the diagnosis difficult [6]. Usually it takes 10 years for the patient to become wheelchair bound but some patients may be ambulatory even after 15-20 years of disease onset [7]. Disease may have a more benign course in patients having homozygous kinase mutation.

Cardiac involvement is not common in GNE myopathy, however few patients are being reported to have cardiac involvement [8]. These patients typically have mild to moderately elevated CPK levels with mild elevation of ALT sometimes [9]. In the reported patient, cardiac evaluation was within normal limits. MRI of skeleton muscles can help to diagnose the disease at early stage. Selective quadriceps sparing especially vastus lateralis even in advanced stages of disease may also be useful in diagnosis [10]. Needle Electromyography shows myopathic pattern while spontaneous activity is not a classical feature of GNE myopathy. Our patient Electromyography showed small, polyphasic motor unit potentials, most prominently in tibialis anterior muscles bilaterally.

Muscle biopsy is characterised by rimmed vacuoles, atrophied fibres and deposition of congophilic material in vacuolated or non-vacuolated muscle fibres. Inflammatory markers may be found in early stage of disease and can't help excluding hereditary inclusion body myopathy [11]. Being a distal myopathy, biopsy is usually taken from distal muscles including Gastrocnemius and Tibialis anterior. Figures 1 and 2 depict muscle biopsy from tibialis anterior which showed myofibers of variable sizes, endomysial fibrosis with fatty infiltration and few fibres showed vacuoles with basophilic, granular material within rimmed vacuoles suggestive of rimmed vacuolar myopathy.

GNE myopathy is an autosomal recessive disorder that can present in homozygous or compound heterozygous forms. Homozygous forms are common worldwide while heterozygosity is dominant feature in Indian subcontinent. The reported patient's Whole genome analysis showed a heterozygous variant (amino acid change: p.(Val727Met) Missense mutation). Bhattacharya et al analysed 67 GNE myopathy patients from Indian subcontinent, of whom 21% were homozygous for GNE variants, while the rest were found to be compound heterozygous [12]. They found 35 different mutations in the GNE gene, out of which p.Val727Met (65%) was the most common mutation found mainly in heterozygous form. Large case series with patients from all over India have been described by Nalini A. et al [13,14]. p.Val727 Met variant is found at high frequency in normal Indian population (1%-2%) and very high frequency (14%) in

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the normal Gujarati population. It is strongly believed that impaired sialylation is the main cause of disease pathology [15]. The GNE gene encodes the bifunctional enzyme, UDP- N- acetylglucosamine 2- epimerase/ N- acetylmannosamine- kinase (GNE/MNK) that catalyses the rate- limiting step of the 5- N- acetylneuraminic acid (sialic acid) biosynthesis [16]. Sialic acid (SA) is a modified sugar that helps in formation of large variety of glycoproteins and glycolipids.

Conclusion

GNE myopathy is a differential diagnosis of other distal myopathies or CMT. Currently, there is no cure for the disease and treatment is focused on managing the symptoms. However, preclinical and clinical studies of several potential therapies are underway, including substrate replacement and gene therapy-based strategies.

References

1. Carrillo N, Malicdan MC, Huizing M (2018) GNE Myopathy: Etiology, Diagnosis, and Therapeutic Challenges. Neurotherapeutics 15: 900-914.
2. Huizing M, Malicdan MC, Krasnewich DM, Manoli I, Carrillo-Carrasco N (2014) GNE Myopathy. OMMBID - The Online Metabolic and Molecular Bases of Inherited Diseases. McGraw-Hill, New York.
3. Nonaka I, Sunohara N, Ishiura S, Satoyoshi E (1981) Familial distal myopathy with rimmed vacuole and lamellar (myeloid) body formation. J Neurol Sci 51: 141-155.
4. Argov Z, Yarom R (1984) "rimmed vacuole myopathy" sparing the quadriceps. A unique disorder in Iranian Jews. J Neurol Sci 64: 33-43.
5. Argov Z (2014) GNE myopathy: a personal trip from bedside observation to therapeutic trials. Acta myol 33: 107-110.
6. Argov Z, Eisenberg I, Grabov-Nardini G, Sadeh M, Wirguin I, et al. (2003) Hereditary inclusion body myopathy: the Middle Eastern genetic cluster. Neurology 60: 1519-1523.
7. Mori-Yoshimura M, Monma K, Suzuki N, Aoki M, Kumamoto T, et al. (2012) Heterozygous UDP- GlcNAc 2-epimerase and Nacetylmannosamine kinase domain mutations in the GNE gene result in a less severe GNE myopathy phenotype compared to homozygous N-acetylmannosamine kinase domain mutations. J Neurol Sci 318: 100-105.
8. Chai Y, Bertorini TE, McGrew FA (2011) Hereditary inclusion-body myopathy associated with cardiomyopathy: report of two siblings. Muscle Nerve 43:133-136.
9. Chaouch A, Brennan KM, Hudson J, Longman C, McConville J, et al. (2014) Two recurrent mutations are associated with GNE myopathy in the north of Britain. J Neurol Neurosurg Psychiatry 85: 1359-1365.
10. Tasca G, Ricci E, Monforte M, Laschena F, Ottaviani P, et al. (2012) Muscle imaging findings in GNE myopathy. J Neurol 259: 1358 -1365.
11. Krause S, Schlotter-Weigel B, Walter MC, Najmabadi H, Wiendl H, et al. (2016) A novel homozygous missense mutation in the GNE gene of a patient with quadriceps-sparing hereditary inclusion body myopathy associated with muscle inflammation. Neuromuscul Disord 13: 830-834.
12. Bhattacharya S, Khadilkar SV, NaliniA, GanapathyA, MannanAU, et al. (2018) Mutation spectrum of GNE myopathy in the Indian sub- continent. J Neuromuscul Dis 5: 85- 92.
13. Nalini A, Gayathri N, Dawn R (2010) Distal myopathy with rimmed vacuoles: Report on clinical characteristics in 23 cases. Neurol India 58: 235- 41.
14. Nalini A, Gayathri N, Nishino I, Hayashi YK. (2013) GNE myopathy in India. Neurol India 61: 371-374.
15. Gagiannis D, Orthmann A, Danssmann I, Schwarzkopf M, Weidemann W, et al. (2007) Reduced sialylation status in UD P- N- acetylglucosamine- 2-epimerase/N- acetylmannosamine kinase (GNE)- deficient mice. Glycoconj J 24: 125-130.
16. Nishino I, Noguchi S, Murayama K, Driss A, Sugie K, et al. (2002) Distal myopathy with rimmed vacuoles is allelic to hereditary inclusion body myopathy. Neurology 59: 1689-1693.

Citation: Agrawal V, Chavali P, Lagishetty V, Kachu R, Gongati NC. GNE Myopathy- A Rare Distal Myopathy with Rimmed Vacuoles: A Case Report. Indian J Neurol. 2022;3(1): 112.