Beevor's sign in a novel glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE) myopathy

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Dear Editor,

Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE) myopathy (Nonaka myopathy or hereditary inclusion-body myopathy) is an autosomal recessive myopathy characterized by symmetrical weakness of the distal muscles in the lower limbs with preferential involvement of the tibialis anterior with sparing of quadriceps muscles. GNE myopathy is caused by mutations in the gene encoding UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE). This gene encodes a bifunctional protein with two enzymatic activities: UDP-GlcNac2-epimerase and ManNac kinase. Beevor's sign is a common finding in Indian patients with p.Val727Met mutation. Here, we report Beevor's sign in a case of late-onset GNE myopathy with a novel mutation in GNE gene p.Phe568Leu.

A 64-year-old man born of a non-consanguineous marriage presented to the outpatient department with insidious onset and slowly progressive bilateral foot drop for the last 10 years. For the last 6 years, he had difficulty getting up from the chair. There was no history of truncal weakness, upper limb weakness, or any cranial nerve symptoms. There was no history of sensory or bladder symptoms. He is a diabetic and hypertensive for the last 6 years. There was no history of any similar illness in the family.

His blood pressure was 140/80 mm of Hg and pulse rate was 68/min and was regular. The cranial nerve examination was normal. His upper limbs were normal. There was no scapular winging. Lower limb examination showed grade 0/5 weakness of foot dorsiflexion bilaterally. 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 present (Fig. 1). His knee jerks and ankle jerks were absent.

Blood investigations showed mild elevation of creatinine phosphokinase. The nerve conduction study showed sensory axonal neuropathy involving both lower limbs. Electromyography showed a myopathic pattern. Next-generation sequencing 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 the amino acid substitution of leucine for phenylalanine at codon 568 (p.Phe568Leu) (hGNE2 nomenclature). The observed variation lies in the ManNac kinase domain of the GNE protein.

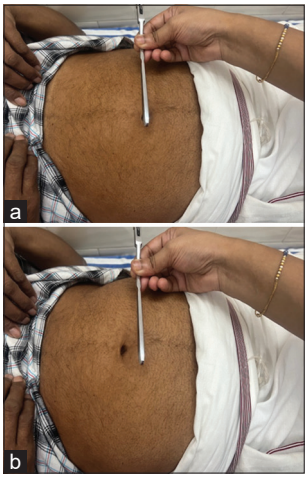

Figure 1: (a) Position of umbilicus in supine resting position; (b) upward movement of umbilicus on neck flexion (positive Beevor's sign)

GNE myopathy is a rare slowly progressive adult-onset distal myopathy with autosomal recessive inheritance. It has distinctive features of quadriceps sparing with preferential anterior tibial involvement. GNE myopathy is caused by mutations in the UDP-N-acetylglucosamine 2-epimerase/N-acetyl mannosamine kinase (GNE) gene. GNE myopathy is due to biallelic mutations in the GNE gene residing in chromosome 9p13.3 with 13 exons. GNE protein with 753 amino acids has bifunctional enzymatic activity involved in the biosynthetic pathway of sialic acid, 5-N-acetylneuraminic acid (Neu5Ac). Neu5Ac is involved in sialylation of glycolipids and glycoproteins of mammalian cells, reduced sialylation has been attributed to clinical features of myopathy. With more than 200 mutations in the GNE gene reported worldwide, many ethnic founder mutations have been described including Middle East (p.Met743Thr), Japanese

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(p.Asp207Val, p.Val603Leu), Roma Bulgarian (p.Ile618Thr) and Indian (p.Val727Met). In the Indian subcontinent, p.Val727Met variant in the compound heterozygous state is noted in majority (82.2%) of the cases. The most common mutation in the Indian series was compound heterozygous followed by homozygous mutation. The next common mutation was p.I618T, mainly in patients from the state of Rajasthan [1].

Beevor's sign, an upward deflection of the umbilicus on flexion of the neck, is the result of paralysis of the inferior portion of the rectus abdominis muscle so that the upper fibers pull the umbilicus upwards. Charles Edward Beevor first described Beevor's sign in spinal cord lesions at T10 level. Other than spinal cord lesions, this neurological sign is classically seen in facioscapulohumeral muscular dystrophy. Positive Beevor's sign has been described as a sign of more than 90% sensitivity and specificity with regard to the diagnosis of facioscapulohumeral muscular dystrophy [2]. Beevor's sign is less frequent in patients with atypical phenotype [3]. It has also been reported in Pompe's disease, tubular aggregate myopathy, myotonic dystrophy, sporadic inclusion body myositis, and dysferlinopathy, although rarely [4]. This sign was demonstrable in 88.2% of a small case series of GNE myopathy [5] and in 59.2% of cases in a large case series [1]. In the Indian series, the predominant mutation associated with GNE myopathy and Beevor's sign is p.Val727Met and is not reported in other GNE gene mutations. Our case is the first reported mutation in this locus (p.Phe568Leu) [6] and is associated with the later development of Beevor's sign and supports the notion that phenotypic heterogenicity exists in GNE myopathy.

Beevor's sign in neuromuscular disorders is a rare clinical sign with very few differential diagnoses. Even though it is a common sign in GNE myopathy with p.Val727Met mutation, it has not been reported so far in GNE myopathy with p.Phe568Leu mutation.

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