Letter to the Editor

Hereditary inclusion body myopathy in Persian Jews: a case report from Iran

To the Editor:

Hereditary inclusion body myopathy (HIBM; OMIM#600737) and the allelic distal myopathy with rimmed vacuoles (DMRV; OMIM#605820) are rare autosomal recessive myopathies caused by mutations in the bifunctional 722 amino acid enzyme UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) (1, 2). Recently HIBM/DMRV has been renamed to GNE myopathy. These myopathies are characterized by both proximal and distal progressive muscle weakness as well as the presence of rimmed (autophagic) vacuoles, abnormal small grouped fibers, and occasional amyloid deposition in muscle biopsies (3, 4). The most distinct feature of GNE myopathy, the quadriceps sparing, was first recognized in Jews of Iranian, and later of other Middle Eastern descents (1, 3). GNE myopathy-related muscle weakness typically starts in the second or third decades of life leading to waddling gait, foot drop, and upper extremity weakness. Diagnosis is based on clinicopathological findings as well as genetic analysis of the GNE gene, which is located on chromosome 9p12-13 (1–3).

So far, more than 300 cases of GNE related myopathy have been reported worldwide, including two Japanese and the Persian-Jewish isolates (1, 2). Almost all Persian-Jewish GNE myopathy cases are homozygous for the founder missense mutation p.M712T in the GNE protein, and the disease prevalence is estimated to be 1:1500 in the Persian Jewish population (3).

In this article, we present two unrelated Iranian families with GNE myopathy. After obtaining approval from the Medical Ethics Committee of Tehran University of Medical Sciences, peripheral blood samples from six patients and two obligatory carriers were collected from two unrelated Persian-Jewish families from the Iranian provinces of Tehran and Isfahan. Preliminary diagnosis

Fig. 1. Characteristics of UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) myopathy patients. (a) Pedigree of the two index families. (b) GNE sequence analysis of normal control (above), patient (middle) and a carrier (below) show a c.2135T>C mutation. (c) Numerous rimmed vacuoles (arrows) in tibialis anterior muscle fibers of patient A4 (H&E staining ×400).
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Table 1. Clinical data of patients

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age of onset (years)</th>
<th>Age at study (years)</th>
<th>Hip abductor force*</th>
<th>Hip adductor force*</th>
<th>Quadriceps force*</th>
<th>Gait</th>
<th>Ck level (Normal range: 20–200 IU L⁻¹)</th>
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<tr>
<td>A1</td>
<td>43</td>
<td>68</td>
<td>3/5</td>
<td>3/5</td>
<td>5/5</td>
<td>Waddling</td>
<td>140</td>
</tr>
<tr>
<td>A2</td>
<td>37</td>
<td>58</td>
<td>4/5</td>
<td>4/5</td>
<td>5/5</td>
<td>Steppage</td>
<td>79</td>
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<tr>
<td>A3</td>
<td>37</td>
<td>55</td>
<td>3/5</td>
<td>1/5</td>
<td>4/5</td>
<td>Waddling</td>
<td>270</td>
</tr>
<tr>
<td>A4</td>
<td>32</td>
<td>44</td>
<td>1/5</td>
<td>3/5</td>
<td>5/5</td>
<td>Bedridden</td>
<td>130</td>
</tr>
<tr>
<td>B1</td>
<td>16</td>
<td>43</td>
<td>2/5</td>
<td>1/5</td>
<td>4/5</td>
<td>Bedridden</td>
<td>75</td>
</tr>
<tr>
<td>B2</td>
<td>22</td>
<td>37</td>
<td>2/5</td>
<td>2/5</td>
<td>5/5</td>
<td>Waddling</td>
<td>85</td>
</tr>
</tbody>
</table>

*Muscle force was rated on a scale of 0/5 (no contraction) to 5/5 (normal strength).

of GNE myopathy in affected family members was based on ethnicity and clinicopathological criteria (1–3). Hematoxylin and eosin (H&E) and modified Gomori trichrome staining were performed on samples from a muscle biopsy of the tibialis anterior muscles of patients. Genomic DNA extracted from peripheral blood was amplified using GNE gene primers amplifying exons 2–12 and their boundaries as described (1) and polymerase chain reaction products were analyzed by direct sequencing.

Family A had four and family B had two affected members (Fig. 1a). The average age at onset of symptoms was 37.2 in family A, and 19 years in family B. The initial presentation in all patients was proximal muscle weakness, foot drop, or both with relative sparing of the quadriceps (Table 1). Fiber size variation, endomysial fibrosis, and rimmed vacuoles were present on histology sides from tibialis anterior muscle biopsies (Fig. 1c). In both families, patients were homozygous for the c.2135 T>C (p.M712T) mutation in exon 12 of GNE (Accession number NM_005476) (Fig. 1b). Carriers were heterozygous for this mutation.

Our locally ascertained study of Persian patients with GNE myopathy demonstrates again the variability of the phenotype and suggests that in myopathic patients of Persian Jewish descent, direct sequencing of GNE for presence of the p.M712T mutation, should be considered as an initial diagnostic approach. When p.M712T appears absent upon sequencing, analyzing the entire GNE gene in Persian patients is justified.

Also, the p.M712T GNE mutation is not limited to Jews, nor to people of Iranian descent, since the mutation has been also been found in Egyptian-Muslim, Tunisian, Italian, and Asian patients (4). A recent study from the Iranian province of Semnan showed that the prevalence of the p.M712T GNE mutation is higher in the city of Sangesar compared with the general world population (5).

Although GNE myopathy typically presents in the second or third decades of life, with wheelchair confinement around 20 years after onset of symptoms, there are cases described with atypical of age of onset and disease progression. Our study shows the large spectrum of age of onset and disease progression, even in patients with the same mutations and ethnic background. Family A presented with an early onset of disease (as early as age 16) and a rapid progression of symptoms (bedridden around age 40), while family B presented a late onset (as late as 43 years) and relatively slow progression (waddling gait at age 68 years). It is suggested that modifier gene(s) or environmental factors may result in phenotypic variability (4–6).

GNE catalyzes the first two steps in the biosynthesis of N-acetyleneuraminic acid (sialic acid) (1, 2). The sialic acid modifications of cell surface glycoproteins are crucial for cell adhesion and signal transduction and may result in muscle fiber degeneration. There is hope that supplementation with sialic acid increasing compounds, including sialic acid and N-acetylmannosamine could be useful in the treatment of GNE myopathy (www.clinicaltrials.gov).

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