A review of the frequency of the D409H mutation in the acid β-glucosidase gene among Gaucher disease patients from the Gulf region

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ABSTRACT

Gaucher disease (GD) is an inherited autosomal recessive lysosomal storage disease resulting from biallelic mutations in the Glucocerebrosidase gene located on chromosome 1q21. The sub-acute neuronopathic form, Gaucher disease type 3c, is commonly identified in the Arab population and associated with cardiac manifestations. It is uniquely linked to homozygosity for the D409H gene mutation in all identified mutated alleles. Despite being a commonly identified Gaucher genotype in the region, few reports of D409H mutation have been reported in the Middle East. Nevertheless, the increased rate of consanguinity among Arabs, ranging from 10% to 70%, contributes to a high rate of genetic diseases, including GD. However, with its associated gene mutation, GD, D409H, remains an area for further exploration in the Gulf area.

Keywords: Gaucher disease, D409H, acid β-glucosidase gene, gene mutation, Gulf region.

Definition

Gaucher disease (GD) is the most prevalent autosomal recessive lysosomal storage disorder [1,2]. It is caused by abnormal acid β-glucosidase function due to an inherited deficiency of the acid β-glucosidase enzyme (GCase), encoded by the Glucocerebrosidase GBA1 gene located on chromosome 1 in region 21 [3]. The reduced GCase activity leads to its substrate’s (glucocerebroside) accumulation within the lysosomes of cells. GD has diverse clinical presentations, including bone infarcts and malformations, hepatomegaly, splenomegaly, abdominal discomfort, anemia, neutropenia, thrombocytopenia, and neurological dysfunctions [4,5]. GD is a multi-systemic condition that can occur in all age groups depending on the GD phenotype. The most common presentations of GD in its three phenotypes are splenomegaly (85%) and thrombocytopenia (68%) [6].

Epidemiology

GD incidence is approximately between 1/40,000 and 1/60,000 births [7,8]. Based on the Human Gene Mutation Database, more than 400 different GBA gene mutations are detected in GD patients. Therefore, GD is classified into three basic subtypes. Type 1 (GD1) is a non-neuronopathic form. Gaucher disease types 2 (GD2) and 3 (GD3) both have an early manifestation of the central nervous system, but they exhibit different neurological progression rates. The subtypes can be distinguished by the presence and rate of neurological involvement deterioration [9-12]. Studies completed to date, which have been mostly conducted in North America and Western Europe, have reported that Gaucher disease type 1 is the most frequent subtype of GD, accounting for 94% of Gaucher cases. It is accompanied by clinical manifestations, mainly hematological, visceral, and skeletal. In severe cases, the lungs and kidneys are also affected [12-14]. Patients with Gaucher disease type 2, the acute aggressive neuronopathic form, present with symptoms that occur either prenatally or during infancy. The estimated incidence of Gaucher disease type 2 is 1 in 150,000 and occurs in all ethnic types. It is commonly lethal within the early 2 years of life [15]. Although Gaucher disease type 3 is a chronic and gradual progressive

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neuronopathic form and has an improved survival than Gaucher disease type 2, it causes death in children or young adults [16]. It has an estimate of 1 in 50,000 [10]. Gaucher disease type 3 appears to be common in Northern Europe, East Asia, and Arab countries [17]. Moreover, Gaucher disease type 3 is subdivided into three subtypes (3a, 3b, and 3c). The cardiovascular subtype form (3c) is usually found in populations originating from Spain, Jordan, Greek, Japan, England, Germany, or the Middle East [18-21]. Two gene mutations, N370S and 84GG, account for 80%-90% of the GD cases amongst the Ashkenazi-Jewish patients. In the non-Ashkenazi-Jewish population, the two most frequent gene mutations are N370S and L444P, which account for 50%-70% of GD cases [14,22]. In general, Gaucher disease type 3c is associated with the D409H gene mutation [23,24].

Treatment strategies for GD

Patients with GD will need lifelong treatment. Currently, two treatment strategies are used for these patients. The first one is enzyme replacement therapy, which involves providing patients with intravenous, recombinant acid β-glucosidase to correct the enzyme deficiency [7]. The second treatment strategy is substrate reduction therapy, which reduces the excessive production of glucosylceramide through a glucosylceramide synthase inhibitor, which is orally administered [7,25].

D409H GBA1 mutation and cardiovascular involvement

D409H is a significant Gaucher gene mutation. Since the seventies, abnormal cardiac involvement in Gaucher patients was reported, including calcification in aorta, mitral and aortic valves [26-32]. Later, unique manifestations, including cardiovascular and ocular motor involvement and hydrocephalus manifestation but lesser visceromagely, were detected in GD patients bearing the D409H/D409H genotype [18,20-22,29,33]. Homozygous and heterozygous D409H genotypes have been previously described in multiple ethnic groups including Japanese [21,29,34], Spanish [20,35], British/German [24], Greek [19], Balkan [36,37], Canadian [38], Indian [39], Turkish [40], and Arab [18] populations. A cohort study including 131 GD patients with neurological manifestations from 17 countries revealed that L444P/D409H and D409H/D409H were among the most prevalent genotypes detected in 8% and 7% of the patients, respectively. Included patients were Egypt, the United Kingdom, the United States, Poland, Sweden, Albania, Belgium, Brazil, Bulgaria, Colombia, Czech Republic, Denmark, Germany, Israel, Italy, Malaysia, and the Netherlands. Thirty-six percent of the total studied patients were Arab. Other ethnic groups included Jewish, non-Jewish, Caucasian, Hispanic, Asian, African American/Caribbean, and multi-ethnic patients. The most prevalent genotypes had [17].

D409H GBA1 mutation in Gulf Area:

In Arab countries, there are few case reports and case series of GD, especially type 3c form, with the D409H gene mutation. In 2010, Abrahamov et al. [18] found a new clinical syndrome in Arabic GD patients with cardiac affliction. Eleven out of twelve patients had homozygous D409H mutation. Like the last report, homozygous D409H gene mutation associated with cardiac manifestation was also confirmed in twelve Arab-origin patients [23]. In one case study, a Palestinian man with GD was also reported to have a homozygous D409H genotype [22]. Furthermore, in another study characterizing the genotype-phenotype correlations of patients in the International Collaborative Gaucher Group Gaucher Registry database, most of the Gaucher disease type 3 patients were Egyptian (31%), and a sizeable proportion was homozygous or heterozygous for the D409H mutant allele [41]. In an investigation of the impact of Arab ethnicity on the phenotypic expression in GD, more than one-third of the Arab patients were found to have Gaucher disease type 3c, and this disease type was correlated with homozygosity for the D409H mutation. The authors related the increased prevalence of type 3c to the consanguinity among the Arab population [42].

A few reports on the prevalence of the D409H mutation in the greater Gulf region (Saudi Arabia, Kuwait, Qatar, Bahrain, Oman, and United Arab Emirates) are discussed in Table 1. In a study identifying gene mutations in GD in Saudi Arabia in 2008, 1 patient out of 12 had a D409H gene mutation [43]. In 2018, another case study identified the homozygous D409H genotype in a Saudi girl with Gaucher disease type 3 who developed valvular and aortic calcifications. An older sibling, who also had Gaucher disease type 3 disease, had died at age 12 [44]. Four siblings presented with Gaucher disease type 3c manifestations of ocular motor deficit and heavily calcified aortic and mitral valves from consanguineous Saudi Arabian parents. Two siblings were tested where genotyping showed homozygosity for D409H mutation [45].

Prevalence and relationship between consanguineous marriage and GDGD in the Gulf region

Consanguineous marriage exists in all countries of the Middle East and North Africa region, including the Gulf area; nonetheless, the prevalence varies substantially (10.6%-67.7%) [46,47]. In Saudi Arabia, consanguinity accounts for 60%-70% of all marriages [48]. In Qatar, consanguineous marriage accounted for 54% [49]. In Oman, the rate of consanguinity is estimated to be 49% [50]. Most autosomal recessive disorders, including GD, are more common in the Middle East. This increased prevalence is attributed to the high consanguineous marriage rate, especially first cousin marriage [48,51-
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[57x795]A review of the frequency of the D409H mutation in the Acid β-glucosidase gene among Gaucher disease patients

[288x46]1341

In a study examining the acid β-glucosidase gene mutation in Egyptian patients with GD, homozygous mutations were detected in 87.5% of the patients, which was correlated with a very high rate of consanguineous marriage (70.8%) [59]. In other reports from India and Saudi Arabia in patients with Gaucher disease type 3c and homozygous for the D409H mutation were born of consanguineous marriage [39,44,45].

Gaps in the literature

This paper identified some gaps in the literature that would guide future research on GD in the greater Gulf region. Up until now, the prevalence of GD in the greater Gulf area is not well established. Most probably, the majority is underestimated due to the small sample size of conducted studies and the misdiagnosis of the disease. Further studies on GD in the greater Gulf region are expected to reveal higher prevalence due to the high consanguinity rate in the area.

List of Abbreviations

GBA1 Glucocerebrosidase
GD Gaucher disease

Conflict of interest

Authors are employees of Sanofi-Genzyme, Gulf region and may hold shares and/or stock options in the company.

Table 1. Prevalence of D409H gene mutation in the Gulf area.

<table>
<thead>
<tr>
<th>Comments</th>
<th>Outcome</th>
<th>Age at diagnosis (years)</th>
<th>Presentation</th>
<th>GBA mutation(-cases)</th>
<th>GD.type</th>
<th>Consanguineous parents</th>
<th>Ethnicity</th>
<th>Gender</th>
<th>No of cases</th>
<th>Study Design</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy was mentioned</td>
<td>-One underwent aortic valve and ascending aorta replacement. -Three died at age 16 and 17</td>
<td>1</td>
<td>3-5</td>
<td>-Ocular-motor reflex -Aortic and mitral valves Calcification</td>
<td>Homozygous for D409H (4)</td>
<td>GD3c</td>
<td>Yes</td>
<td>Saudi</td>
<td>Male</td>
<td>Letter</td>
<td>Bohlega et al. [45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2</td>
<td>-6</td>
<td>-Hepatomegaly. Sclerotic changes, mild brain changes -NA. -NA. -NA.</td>
<td>-L444P/ F397S (1)</td>
<td>GD1</td>
<td>NA</td>
<td>-Saudi</td>
<td>Male</td>
<td>Four siblings</td>
<td>Casereports</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>-Deceased older brother at age 12 with GD3</td>
<td>-Died before surgery as a result of cardio-vascular complications</td>
<td>-4</td>
<td>-11</td>
<td>-Hepatomegaly. Pancreatic apraxia, valvular and aortic calcifications</td>
<td>Homozygous for D409H</td>
<td>GD3</td>
<td>Yes</td>
<td>Saudi</td>
<td>Female</td>
<td>A case report</td>
</tr>
</tbody>
</table>

58]. In a study examining the acid β-glucosidase gene mutation in Egyptian patients with GD, homozygous mutations were detected in 87.5% of the patients, which was correlated with a very high rate of consanguineous marriage (70.8%) [59]. In other reports from India and Saudi Arabia in patients with Gaucher disease type 3c and homozygous for the D409H mutation were born of consanguineous marriage [39,44,45].
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