Gaucher Disease in Arab Patients at an Israeli Referral Clinic

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Abstract

Background: With regard to ethnic predilections for Gaucher disease, the most common storage disorder, Ashkenazi Jews* are at risk for the non-neuronopathic form (type I), Norbottnian Swedes are at risk for the subacute neuronopathic form (type III), and perhaps Arabs are at risk for the very rare cardiac variant of the subacute neuronopathic form (type IIIc) for which there is a relatively tight genotype-phenotype correlation. Type II, the acute infantile form, being the rarest form, has not been associated with any ethnic predilection.

Objectives: To examine whether Arab ethnicity influences the Gaucher phenotype.

Methods: We reviewed the records of all Arab patients in a referral clinic of 586 patients in Israel.

Results: There were 46 patients (7.8%) of Arab ethnicity: 23 (50%) had type I disease, 16 (34.8%) had type IIIc disease, 4 (8.7%) had type IIIb disease, and 3 (6.5%) had type II disease. Type IIIc disease was characterized by genotype-phenotype correlation with homozygosity for the D409H (1342C) mutation. All five Bedouin patients (10.9%) had the R48W (C259T) mutation on at least one allele.

Conclusions: For all genotypes, disease severity among Arab patients was relatively similar to that reported among other Caucasian patients. Apparently Arab ethnicity does not impact phenotypic expression in Gaucher disease in a unique manner. The predilection for type IIIc may be a result of consanguinity.

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Gaucher disease, the most prevalent lysosomal storage disorder, is a panethnic disorder [1]. Classically, three clinical forms have been delineated, based on the absence (type I) or presence (types II and III) of neurological signs [2]. Type I ("adult"), the non-neuronopathic form, is the most common, with an ethnic predilection among Ashkenazi Jews. The presence of the single most common mutation, N370S (1226G), on one allele appears to be protective of development of a classic neuronopathic form, and indeed the genotype N370S/N370S is the most common among type I patients and especially among Ashkenazi Jewish patients in whom disease manifestations are consequently milder [3]. Type II ("infantile") disease is panethnic; presentation is more acute and typically more uniform, with onset of both visceral signs and neurological involvement, including hypertonic posturing, strabismus, trismus and retroflexion of the head, during the first 6 months of life [4]. Most patients die before the age of 2 years. Type III ("juvenile") disease is also panethnic and includes all patients who present some features in childhood and who evince at least one neurological sign [5]. Early cases were recognized in Norbottnia, Sweden. Symptoms include severe visceral enlargement including lung involvement and bone disease as well as central nervous system findings of spasticity, seizures and horizontal supranuclear gaze palsy. Homozygosity for the L444P (1448) mutation is the most prevalent genotype for this type.

The current classification designates patients with more than one neurological sign and mild organ involvement as type IIIa; whereas patients with only supranuclear horizontal gaze palsy but aggressive visceral involvement are designated type IIIb [6]. Although cardiac involvement was considered a rare manifestation in Gaucher disease, a unique variant of the neuronopathic forms, now known as type IIIc, has been described in Arab, Japanese and Spanish patients homozygous for the D409H (1342) genotype. These patients generally present with very mild visceral signs, with only supranuclear horizontal gaze palsy as a sign of neurological involvement, but have progressive calcification of the aortic and/or mitral heart valves that has proven to be fatal during the teenage years [7]. Valve replacements do not dramatically improve quality of life nor appreciably lengthen it.

With regard to ethnic predilections for Gaucher disease, there are apparently no at-risk groups other than those mentioned above. It may be posited that founder effects exist [8] among non-Jewish populations and/or that consanguinity impacts predicted incidence particularly when intermarriage is sanctioned over many generations [9]. In general, the Arab population is considered to be diverse but because of consanguinity, frequency of recessive disorders is increased [10].

Since it is conceivable that ethnicity modifies phenotypic expression and because descriptions in the literature of Arab patients with Gaucher disease have been limited to case reports and speculation about private mutations [11], the following study was undertaken to describe the phenotype-genotype correlation among Arab patients with Gaucher disease seen in a large referral clinic in Israel.

Subjects and Methods

Patient records from a large referral clinic for Gaucher disease were reviewed. All patients with Arab ethnicity regardless of birth place were included in this retrospective study going back 15 years. Demographic and clinical data were gleaned from patient records.

* Of East European origin

Results

Of a patient population of 586 adults and children, 46 Arabs (7.8% of the clinic population) including 5 Bedouin were identified (10.9% of all Arab patients). The demographic characteristics of this population are shown in Table 1. Except for two patients who were diagnosed at ages 23 and 37 years, respectively, all the patients are currently less than 33 years old and all were diagnosed before age 23.

Most of the Arab patients with type IIIc disease live in the Jenin area (Palestinian Authority), but other than siblings, few patients live in the same city/village as other patients. There were eight patients who traveled to Israel from neighboring countries.

The genotypes for this population are shown in Table 2. The most common mutation was D409H (1342C) that was seen in homozygosity in 16 patients (34.8%); all of the patients homozygous for D409H had the type IIIc variant. Of these, six died because of complications secondary to heart valve calcifications: these were the oldest patients and all died between the ages of 17 and 23. Four of the above six patients had undergone valve replacement surgery, one of whom died after surgery (see below).

All the Bedouin patients had at least one allele with the R48W (259T) mutation [12], and all had mild to moderate type I disease (possibly disease severity is determined by the non-R48W allele), only two of whom had massive hepatosplenomegaly with growth retardation in one patient and destructive bone disease (post-splenectomy) in another. All of these patients complained of bone pain and suffer from osteopenia. All the children had failure to thrive and/or were below the10th percentile for height and weight in childhood.

Four patients had type IIIb disease and all were homozygous for L444P (1448C) mutation. Each patient presented with massive hepatosplenomegaly between the ages of 1 and 4 years. Two of these children developed a gibbus, one of whom has undergone corrective spinal surgery. This child had presented with massive hepatosplenomegaly and lung involvement at age 2 years, but the pulmonary component had not appreciably improved despite more than a decade of enzyme therapy. None has had pathological fractures or avascular necrosis of any joint. All of these children had failure to thrive and/or were below the 10th percentile for height and weight in childhood. There was no patient with type IIIa disease.

Altogether, 23 patients had putatively type I disease, including two siblings with RecNci1/R48W genotype. Ten patients had the N370S/N370S genotype: 7 of the patients belong to a single kinship and live in the same village. Most of the patients with type I disease presented with mild hepatosplenomegaly. Only two patients had undergone splenectomy, both of whom are now 25 years old: one patient suffered avascular necrosis of both hips subsequent to splenectomy [13] and the other complains of exertional dyspnea and fatigue; both receive enzyme therapy. Two sisters with N370S/N370S are married and have two and three children respectively. None of the other female patients have children.

There were three children with putatively type II disease (genotyping was not performed), all of whom died before 12 months of age with multiple system failure including a range of neurological signs and symptoms. Two of these were first-degree cousins. Consanguinity is noted in the histories of all these patients, often both horizontally and longitudinally.

In all, 19 patients (41.3%) have been receiving enzyme replacement therapy for 1–12 years, none of whom is currently older than 32 years.

Table 1. Clinical characteristics of 46 Arab patients

	No. of patients	Age (yrs) at presentation	Enzyme therapy	Follow-up (yrs)
Type I	23 (50.0%)	5–37	13	0.5–12
Type II	3 (6.5%)	< 1	0	< 1
Type IIIb	4 (8.7%)	2–4	4	5–13
Type IIIc	16 (34.8%)	2–18	2	2–13

Table 2. Genotypes among 46 Arab patients

Comments	No. (%)	Type	Genotype
4 unrelated families: one kinship of 11 with 3, 4, and 4 siblings whose parents are siblings or cousins; 2 sets of 2 siblings; and a single patient	16 (34.8%)	IIIc	D409H/D409H
5 unrelated families: 1 kinship of 4 siblings and 2 first cousins; and a single patient	10 (21.7%)	I	N370S/N370S
	1 (2.2%)	I	N370S/IVS2+1
	1 (2.2%)	I	N370S/RecTL
	1 (2.2%)	I	N370S/L444P
Unrelated	4 (8.7%)	III	L444P/L444P
Unrelated	2 (4.3%)	I	R48W/R48W
3 unrelated families: 2 sets of siblings, and a single patient	5 (10.9%)	I	R48W/ RecNciI
	1 (2.2%)	I	W393R/W393R
Unrelated	2 (4.3%)	I	No genotype
Unrelated	3 (6.5%)	II	No genotype

Discussion

Interestingly, other than one Bedouin man who was diagnosed at age 37 but is asymptomatic, and one young woman who was symptomatic but who was not diagnosed until age 23 (see above), all the Arab patients in this cohort were identified in childhood, invariably because of organomegaly in those patients who did not have the cardiac variant. This implies a reasonable index of suspicion in the medical community for the possibility of Gaucher disease in Arabs.

In terms of the diversity of genotypes, the cardiac variant in this cohort is prominent with a further large group having non-cardiac but neuronopathic disease; thus, half the cohort presented with neurological involvement. This observation is similar to the larger number of patients with type III among the Egyptian patients with Gaucher disease [14]. Some of the remaining patients, other than those with one N370S mutation, have moderate disease expression. These results confirm that patients who do not have at least one N370S mutation are more likely to have combinations of "severe" and null mutations [15] and therefore exhibit more severe expression of Gaucher disease.

In Tunisia where 98% of the population is Arab, a series of 27 patients was reported during an 18 year period: 20 patients with type I disease, 3 patients each with type II and type III disease, and 1 patient whose genotype was not known [16]. The authors concluded that "Gaucher's disease is not exceptional in Tunisia," reflecting their finding of the natural course of Gaucher disease that was clinically comparable to that described in other non-Arab patients.

In the cohort described in the current study, there is considerable diversity in terms of phenotypic severity that can essentially be ascribed to the genotypes, but as suggested by the Tunisian retrospective, it does not appear that ethnicity per se is a factor in ascribing severity of Gaucher disease among Arabs. It may therefore be posited that as Caucasians, but unlike Asian or black populations, Arab patients do not suffer more severe phenotypic expression than other Caucasian patients. Japanese patients with Gaucher disease, on the other hand, have a different phenotypic expression than Caucasians with the same genotype [17].

Enzyme therapy was required by many of the patients and this may be reflective of more severe disease expression. Early signs and symptoms of the disease were indications for enzyme treatment in all cases except for those with type II disease. We continue to believe that enzyme therapy may be ethically problematic in type II disease [18]. All the children with type IIIb disease received enzyme therapy from about the age of 2–4 years; the oldest is 16 years old today. Parents have mentioned a slow but progressive cognitive decline despite good quality of life.

Among patients with type IIIc disease, progressive heart valve calcification, regardless of surgical replacement, has resulted in death by early adulthood. The longest-lived patient is today 24 years old with very poor quality of life: she has a gibbus formation and suffers from severe congestive heart failure. To date, only four children, two brother-sister sibling pairs, with type IIIc Gaucher disease have been treated with enzyme therapy. Despite treatment for nearly 10 years, the oldest of these patients died while undergoing heroic heart valve and aortic arch replacement surgery. This young man had evidence of a porcelain aorta with calcifications into the abdominal aorta at age 17 years, markedly worse than what had been seen in other patients with type IIIc who had not been treated. His younger sister, who had also received enzyme therapy for the same period and is today 16 years old, no longer wants medical follow-up and is poorly compliant with therapy.

In conclusion, it is our impression that Arab ethnicity does not impact phenotypic expression in Gaucher disease differently to other Caucasians. The putative predilection for type IIIc among Arabs in the circumscribed area around the city of Jenin may be the result of a founder effect and consanguinity.

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