Type 1 Gaucher Disease

Significant Disease Manifestations in "Asymptomatic" Homozygotes

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Background: Type 1 Gaucher disease (GD), an autosomal recessive lysosomal storage disease, is most prevalent in the Ashkenazi Jewish (AJ) population. Experts have suggested that up to two-thirds of AJ homozygotes for the common mutation (N370S) are asymptomatic throughout life and never come to medical attention. However, there are no systematic studies of N370S homozygotes to support this presumption.

Methods: Prenatal carrier screening of 8069 AJ adults for 6 common GD mutations was performed. Gaucher disease manifestations in 37 previously unrecognized homozygotes were assessed by clinical, laboratory, and imaging studies.

Results: Among the 8069 AJ screenees, 524 GD carriers (1:15) and 9 previously unrecognized GD homozygotes (1:897) were identified, consistent with the rate expected (1:949; $P > .99$). Six of these homozygotes and 31 AJ GD homozygotes identified by other prenatal carrier screening programs in the New York City metropolitan area were evaluated (age range of the homozygotes, 17-40 years). Of these, 84% were N370S homozygotes, others being heteroallelic for N370S and V394L, L444P, or R496H mutations. Notably, 65% reported no GD medical complaints. However, 49% had anemia and/or thrombocytopenia. Among the 29 who had imaging studies, 97% had mild to moderate splenomegaly and 55% had hepatomegaly; skeletal imaging revealed marrow infiltration (100%), Erlenmeyer flask deformities (43%), lucencies (22%), and bone infarcts (14%). Dual energy X-ray absorptiometry studies of 25 homozygotes found 60% with osteopenia or osteoporosis.

Conclusion: Contrary to previous discussions, almost all asymptomatic GD homozygotes serendipitously diagnosed by prenatal carrier screening had disease manifestations and should be followed for disease progression and institution of appropriate medical treatment.

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Type 1 Gaucher disease (GD), is the most common lysosomal storage disease and is particularly prevalent in the Ashkenazi Jewish (AJ) population, with an estimated frequency of approximately 1 in 1000.[1] This autosomal recessive inborn error of metabolism results from the deficient activity of the degradative enzyme, acid β-glucosidase (β-Glu), and the lysosomal accumulation of its glycosphingolipid substrate, glucosylceramide (GL-1), primarily in the monocyte-macrophage cells of the liver, spleen, and bone marrow.[1] Clinical manifestations include hepatosplenomegaly, anemia, thrombocytopenia, and clinically significant bone disease.[1] Enzyme replacement therapy (ERT) with a macrophage-targeted recombinant β-Glu has proven to be safe and effective in ameliorating, and even preventing, disease manifestations.[2-5]

The carrier frequency of GD in the AJ population has been estimated to be 1 in 14 to 18.[6-8] Four acid β-glucosidase (*GBA*) gene mutations (N370S, 84GG, L444P, and IVS2^{+1}) account for approximately 95% of the disease-causing lesions in AJ patients.[6,9] The most common mutation, N370S, a missense mutation that retains about 14% of wild-type expressed activity in vitro,[10,11] is present in over 70% of the AJ type 1 GD patients[12,13] who are either homoallelic or heteroallelic with another GD mutation.[12,13] Based on 2009 data from the Gaucher Registry (Genzyme Corp, Cambridge, Massachusetts; available from the authors on request), it is estimated that about 56% of AJ type 1 GD patients are N370S homozygotes. The clinical spectrum of N370S homozygotes in the AJ population is highly variable, ranging from severely affected children with hepatosplenomegaly, pancytopenia, and bone disease to adults who are asymptomatic un-

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til the eighth decade of life.[14-16] Previous studies have characterized the age at diagnosis and severity of manifestations in diagnosed N370S homozygotes.[12,15,16] Although some N370S homozygotes have early-onset disease and are treated by ERT in childhood or adolescence, most are diagnosed later.[16] About 32% of N370S homozygotes in the Gaucher Registry were diagnosed by age 20 years.[16] However, the median age at diagnosis of over 1100 N370S homozygotes in the registry was 29 years (data from the Gaucher Registry), consistent with the slowly progressive course of the disease. In contrast, the median age at diagnosis for over 550 patients with GD having the next most frequent N370S/L444P genotype was 16 years (data from the Gaucher Registry).

Based on heterozygote frequencies of 1 in 15 to 18 for GD reported by prenatal carrier screening programs for Jewish genetic diseases,[7,17,18] it is estimated that 1 in 900 to 1300 AJ individuals is homozygous for GD. It has been suggested that only one-third of N370S homozygotes come to medical attention and that about two-thirds remain asymptomatic throughout life.[6,19,20] That type 1 GD is a "low penetrant" disorder, similar to hemochromatosis,[21,22] has led to discussions on the value of including GD in the disease panel for prenatal carrier screening in the AJ population.[23-25]

Is homozygosity for the N370S genotype truly "low penetrant,"[23] with most patients remaining asymptomatic throughout life, or will these individuals eventually become symptomatic and require therapeutic intervention after clinically significant, and possibly irreversible, disease has occurred? Early recognition and characterization of the natural history of N370S homozygotes would provide data for improved genetic counseling and informed medical care, including the rationale for early therapeutic intervention. To our knowledge, there have been no systematic studies to determine the frequency of AJ N370S homozygotes or to evaluate their clinical manifestations and progression, particularly in those who report no symptoms.

Because prenatal carrier screening programs for diseases prevalent in the AJ population serendipitously detect previously undiagnosed GD homozygotes, we analyzed our experience in screening over 8000 individuals who reported that both parents and all grandparents were of AJ descent.

METHODS

PARTICIPANTS

The study population included 8069 unrelated AJ individuals who requested prenatal carrier testing for AJ genetic diseases at our center from 1996 to 2008. All screenees reported that both their parents and grandparents were of AJ descent. Heterozygotes and homozygotes for GD were identified by molecular studies (see the following subsection) and were informed of their genetic status by a geneticist and/or genetic counselor. Homozygous individuals were offered a GD-focused clinical, imaging, and laboratory evaluation at our center. Six of these homozygotes and 31 AJ GD homozygotes identified by other prenatal carrier screening programs in the New York metropolitan area were evaluated. Women who were pregnant at initial assessment had radiologic studies after delivery. Informed consent was obtained from all screenees, and subsequently identified GD homozygotes gave informed consent for evaluation by a GD physician expert (including M.B. and R.J.D.) following a protocol approved by the Mount Sinai School of Medicine institutional review board.

GENOTYPE STUDIES

Initially, screening was performed for the 4 most common AJ mutations causing GD, N370S, 84GG, L444P, and IVS2^{+1}, and after 2005, V394L and R496H were added to the screening panel. We performed DNA extraction, polymerase chain reaction amplification, and mutation detection by multiplex allele-specific primer extension using the Tag-It AJ panel kit (Luminex Molecular Diagnostics, Toronto, Ontario, Canada).

CLINICAL, IMAGING, AND LABORATORY STUDIES

Family and medical histories, review of systems, and physical examinations were performed for all 37 homozygotes by a GD expert physician (including M.B. and R.J.D.). Routine laboratory studies of all 37 homozygotes included complete blood cell counts, liver function tests, electrolyte levels, and iron studies. Chitotriosidase enzyme activities and chitotriosidase (*CHIT 1*) genotypes were performed as previously described.[26] Hepatic and splenic volumes were measured using magnetic resonance imaging (MRI) or computed tomography (CT) and converted to multiples of normal based on body weight. Bone marrow infiltration was assessed by MRI or bone marrow scans, and bone infarctions were assessed by MRI. Erlenmeyer flask deformity, lucencies, and osteopenia were detected on radiographic examination. Bone mineral density (BMD) was measured using dual energy x-ray absorptiometry (DEXA).

The severity of GD manifestations was assessed using the International Collaborative Gaucher Group guidelines.[27,28] Anemia was defined as a hemoglobin value lower than 12.0 g/dL for adult men and <11.0 g/dL for adult women (to convert hemoglobin to grams per liter, multiply by 10.0). Thrombocytopenia was classified as mild, moderate, or severe when the platelet counts were 120 to 150×10^3/μL, 60 to 119×10^3/μL, and less than 60×10^3/μL, respectively (to convert platelet counts to $\times 10^9$/L, multiply by 1.0). Splenomegaly was classified as mild (<5 × normal), moderate (5-15 × normal), or severe (>15 × normal volume). Hepatomegaly was classified as mild (<1.25 × normal volume for weight), moderate (1.25-2.5 × normal volume), or severe (>2.5 × normal volume).

RESULTS

IDENTIFICATION OF GD HETEROZYGOTES AND HOMOZYGOTES

Prenatal carrier screening of 8069 consecutive AJ individuals (60% of whom were female) identified 524 carriers of the 6 type 1 GD mutations, an overall heterozygote frequency of 1 in 15 (**Table 1**), thus predicting the frequency of homozygotes to be about 1 in 950, and the frequency of AJ couples with a 1 in 4 risk for an affected pregnancy to be about 1 in 240. The frequency of heterozygotes for the common N370S mutation was 1 in 17, predicting approximately 1 in 1130 for N370S homozygotes, or 7 N370S homozygotes among the screenees. In this cohort, 9 homozygotes (66% of whom were female)

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for the GD mutations were identified, including 8 who were homozygous for the N370S mutation, and 1 who was heteroallelic for N370S and V394L.

CLINICAL, IMAGING, AND LABORATORY STUDIES OF GD HOMOZYGOTES IDENTIFIED BY PRENATAL CARRIER SCREENING PROGRAMS

A total of 37 previously undiagnosed type 1 GD homozygotes were evaluated, including 30 women (mean age, 31 years [range, 17-40 years]) and 7 men (mean age, 29 years [range, 21-36 years]), reflecting the fact that in most centers women are screened first, and if heterozygous, their partners are then screened. Of these, 31 of 37 (84%) were homozygous for the N370S mutation, while 6 (16%) were heteroallelic for N370S and either R496H (3), L444P (2), or V394L (1). Their baseline demographics, GD genotypes, clinical manifestations, and imaging and laboratory findings are summarized in **Table 2**.

On review of systems, 24 patients (65%; mean age, 31 years [range, 17-40 years]) reported no GD-related symptoms, while 13 patients (35%; mean age, 29 years [range, 21-37 years]) reported symptoms compatible with type 1 GD. The most common symptom was easy bruisability (12 of 37 [32%]); others included bone pain (3 of 37 [8%]) and/or fatigue (2 of 37 [5%]).

Of the 37 homozygotes, 4 (11%; 3 women and 1 man; mean age, 31 years [range, 21-36 years]) were anemic on evaluation, including 2 women whose anemia was presumably due to their concurrent pregnancies. Sixteen homozygotes (43%) were thrombocytopenic, of whom 6 (2 men and 4 women; mean age, 29 years [range, 21-35 years]) had moderate thrombocytopenia (platelet count, $60\text{-}119 \times 10^3/\mu L$) and one 30-year-old woman had severe thrombocytopenia (platelet count, $<60 \times 10^3/\mu L$).

Of the 37 homozygotes, 29 (78%) had an MRI or CT scan of the abdomen; of these, 28 of 29 (96%) had splenomegaly, and of these, 25 of the 29 (86%) had mild splenomegaly (>1 to 5 × normal for body weight), 3 of the 29 (10%) had moderate splenomegaly (>5 to 15 × normal for body weight), and 16 of the 29 (55%; 4 men and 12 women; mean age, 30 years [range, 21-40 years]) had hepatomegaly, including 7 (5 women and 2 men; mean age, 30 years [range, 21-35 years) who had moderately increased liver volumes (1.25-2.5 × normal for body weight).

Twenty-nine homozygotes (78%; 22 women and 7 men; mean age, 30 years [range, 17-40 years]) had imaging studies to assess the skeletal involvement due to GD (28 had MRIs of the femur, and 1 had a bone marrow scan). Of these, all had marrow infiltration of the spine and/or femur. Four homozygotes (4 of 29 [14%]) had a bone infarction detected on MRI. Skeletal radiographs performed in 23 homozygotes revealed the Erlenmeyer flask deformity, due to failure of bone remodeling, in 10 of 23 (43%) of homozygotes, lucencies in 5 of 23 (22%), and osteopenia in 13 of 23 (57%). Baseline BMD evaluated in 25 homozygotes by DEXA (Table 2) showed low BMD at the hip, spine, and/or forearm in 60% (15 of 25; 11 women and 4 men; mean age, 30 years [range, 21-40 years]); osteopenia in 52%; and osteoporosis in 8%. More patients (52%; 9 women and 4 men) had low BMD at the lumbosacral spine compared with the hip (20%; 4 women and 1 man). Two women, a 31-year-old with the N370S/R496H genotype and a 37-year-old N370S homozygote, both had a clinically significant fracture history, including the 31-year-old who had experienced a nontraumatic fracture while pregnant. Subsequent evaluation of these 2 patients did not identify an endocrine cause for the bone disease. Of the 7 men in our cohort, 4 (57%), aged 21 to 32 years, had osteopenia, indicating that early-onset osteopenia also occurs in males with type 1 GD.

Table 1. Frequency of Gaucher Disease (GD) Heterozygotes and Homozygotes Among Prenatally Screened Ashkenazi Jewish (AJ)[a] Individuals

Screening Data	No.	Frequency
Total screenees	8069	
Female, No. (%)	4890 (61)	NA
Noncarriers	7536	NA
All GD carriers	524	1:15
N370S	480	1:17
84GG	30	1:269
L444P	7	1:1153
IVS2+1	5	1:1614
V394L[b]	0	NA
R496H[b]	2	1:295
GD homozygotes	9	1:897
N370S/N370S	8	1:1009
N370S/V394L	1	1:8069

Abbreviation: NA, not applicable.
[a] Carrier screening was performed for the 6 mutations frequent among AJ GD patients.
[b] V394L and R496H genotyping began after 2005.

PLASMA CHITOTRIOSIDASE ACTIVITY

This biomarker of macrophage activation[29] serves as an indicator of GD severity and response to treatment.[30] The plasma chitotriosidase enzymatic activity[30] (normal, <180 nmol/h/mL) and CHIT 1 genotype[31,32] were determined in these patients at initial evaluation, and the patients were classified by their number of functional wild-type *CHIT 1* genes because about 6% of white individuals are homozygous and 30% to 40% are heterozygous for a nonfunctional 24 base-pair duplication allele.[33,34] As expected, the 2 patients with the more severe N370S/L444P genotype had markedly elevated chitotriosidase activities (3390 and 3500 nmol/h/mL). The plasma chitotriosidase activities in the 31 N370S homozygotes ranged from 0 (2 null alleles) to 6400 nmol/h/mL (**Table 3** and **Table 4**). When stratified by the CHIT 1 genotype, 19 of the 20 N370S homozygotes with at least 1 wild-type allele had elevated plasma chitotriosidase activities (250-6400 nmol/h/mL). Of the 12 who had clinically significant disease manifestations and were recommended to receive ERT, the mean plasma chitotriosidase activities were 910 and 4081 nmol/h/mL for those with 1 or 2 wild-type *CHIT 1* alleles, respectively. In contrast, the mean plasma chitotriosidase activities for the 17 N370S homozygotes with milder manifestations were 599 and 1760 nmol/h/mL for those with 1 or 2 wild-type *CHIT 1* alleles, respectively. Thus, the mean baseline plasma chitotriosidase levels, clas-

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Table 2. Clinical Manifestations of Gaucher Disease Homozygotes at Baseline Evaluation[a]

Patient No./ Sex/Age, y	Genotype	RS	HF	VM	MI	Infarction	EFD	Osteopenia	Lucencies	DEXA Score, Mean *t* Score	DEXA Score, Mean *z* Score
1/M/21	N370S/L444P	B	T++	S8.9, H1.7	+	–	–	+	–	+	+
2/F/29	N370S/L444P	B	T+	NA	NA	NA	NA	NA	NA	NA	NA
3/F/17	N370S/N370S	–	–	S0.9, H1.0	+	–	NA	NA	NA	–	–
4/F/21	N370S/N370S	B, F	T+	S3.1, H0.9	+	–	+	+	–	+	+
5/F/21	N370S/N370S	–	A+P, T+	NA	NA	NA	NA	NA	NA	NA	NA
6/F/21	N370S/N370S	–	–	S3.9, H1.2	+	–	–	–	–	+	+
7/M/22	N370S/N370S	–	–	S3.1, H1.1	+	–	–	+	–	–	–
8/F/24	N370S/N370S	B	T++	S3.7, H1.0	+	–	–	+	–	–	–
9/M/26	N370S/N370S	B	–	S5.0, H1.1	+	+	+	–	–	+	+
10/F/27	N370S/N370S	–	–	S2.2, H1.3	+	–	NA	NA	NA	NA	NA
11/F/29	N370S/N370S	–	T+	NA	NA	NA	NA	NA	NA	NA	NA
12/F/30	N370S/N370S	B	T++	NA	NA	NA	NA	NA	NA	NA	NA
13/F/30	N370S/N370S	–	T+++	S4.2, H1.4	+	–	–	–	+	–	–
14/F/30	N370S/N370S	–	T+	S1.2, H1.0	+	+	+	–	–	+	+
15/F/31	N370S/N370S	B	T+	S6.6, H1.4	+	–	NA	NA	NA	+	+
16/F/31	N370S/N370S	–	–	S1.8, H0.9	+	+	+	–	–	NA	NA
17/F/31	N370S/N370S	–	–	NA	NA	NA	NA	NA	NA	–	–
18/F/32	N370S/N370S	B	–	S2.3, H1.1	+	–	NA	NA	NA	NA	NA
19/F/32	N370S/N370S	B	–	S4.9, H1.3	+	–	+	+	+	+	+
20/F/32	N370S/N370S	–	T++	S2.9, H1.1	+	–	+	–	–	+	+
21/M/32	N370S/N370S	–	T++	S4.0, H1.3	+	–	–	–	–	+	+
22/M/33	N370S/N370S	–	–	S3.0, H1.0	+	–	–	+	–	–	–
23/F/34	N370S/N370S	B	–	NA	NA	NA	NA	NA	NA	NA	NA
24/F/34	N370S/N370S	–	–	S1.9, H1.0	+	–	+	+	–	+	+
25/F/35	N370S/N370S	–	A+, T++	S14.6, H2.2	+	NA	+	+	+	NA	NA
26/F/35	N370S/N370S	–	–	S1.7, H1.2	+	–	NA	NA	NA	+	+
27/M/36	N370S/N370S	B, BP, F	A+	S4.2, H1.0	+	+	–	+	+	–	–
28/F/37	N370S/N370S	BP	–	S1.3, H0.9	+	–	–	–	–	–	–
29/F/37	N370S/N370S	–	T+	S1.9, H0.9	+	–	+	+	–	–	–
30/F/37	N370S/N370S	–	–	S1.3, H1.0	+	–	–	–	+	++, Fx	+, Fx
31/F/40	N370S/N370S	–	T+	S3.6, H1.1	+	–	+	+	–	+	–
32/F/40	N370S/N370S	–	–	NA	NA	NA	NA	NA	NA	NA	NA
33/F/40	N370S/N370S	–	–	S1.8, H1.1	+	–	NA	NA	NA	NA	NA
34/M/30	N370S/V394L	B, BP	T+	S3.9, H1.0	+	–	–	+	–	+	+
35/F/28	N370S/R496H	–	–	S2.5, H1.1	+	–	–	–	–	–	–
36/F/29	N370S/R496H	–	–	NA	NA	NA	NA	NA	NA	NA	NA
37/F/31	N370S/R496H	–	A+P	S2.6, H1.0	+	–	–	+	–	++, Fx	++, Fx
No. (%)		13/37 (35)	18/37 (49)	S28/29 (97) H16/29 (55)	29/29 (100)	4/28 (14)	10/23 (43)	13/23 (57)	5/23 (22)	15/25 (60)	14/25 (56)

Abbreviations: A, anemia; B, easy bruising and/or bleeding; BP, bone pain; DEXA, dual energy X-ray absorptiometry; EFD, Erlenmeyer flask deformity; F, fatigue; Fx, history of fracture; H, liver volume; HF, hematologic findings; MI, marrow infiltration; NA, not available; P, pregnant; RS, review of systems; S, spleen volume; T, thrombocytopenia; VM, visceromegaly.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; to convert platelet counts to $\times 10^9$/L, multiply by 1.0.

[a] For anemia: +, men: hemoglobin level lower than 12 g/dL; women: hemoglobin level lower than 11 g/dL. Thrombocytopenia: platelet counts, +, mild (120-150 $\times 10^3$/μL); ++, moderate (60-119 $\times 10^3$/μL); +++, severe (<60 $\times 10^3$/μL). Visceromegaly: S: spleen volume × N; H: liver volume × N.

DEXA *t* and *z* test scores: –, mild or none (>–1) at all sites measured; +, moderate (>–2.5 to ≤–1) at 1 or more sites; ++, severe (≤–2.5) at 1 or more sites.

sified by CHIT 1 genotypes, were higher in the group of N370S homozygotes who were subsequently recommended ERT, suggesting a correlation with disease severity.

COMMENT

For over 2 decades, physician experts have suggested that up to two-thirds of AJ type 1 GD N370S homozygous patients were asymptomatic throughout life and eluded medical attention.[6,19] This presumption was based on studies that estimated the heterozygote frequency of the common N370S mutation in the AJ population to be approximately 1 in 14.5 to 17.5, which predicted that approximately 1 in 840 to 1225 AJ individuals were N370S homozygotes.[12,13] However, experts in North America and Israel noted that the frequency of N370S homozygotes in their clinics was less than expected.[6,12,19] Is homozygosity for N370S "benign'" or "low penetrant"?[23] Are "asymptomatic" GD homozygotes essentially "normal" throughout life,[20] or do they have clinical manifestations that progress? We addressed these issues by identifying asymptomatic N370S homozygotes diagnosed by prenatal carrier screening programs and evaluating their GD manifestations.

First, the heterozygote and homozygote frequencies were determined by testing for 6 common AJ type 1 GD mutations in over 8000 AJ individuals who sought pre-

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Table 3. Biomarkers of Gaucher Disease Homozygotes at Baseline Evaluation

Patient No./ Sex/Age, y	Genotype	CHIT 1 Dup24 Genotype	CHIT 1 G102S Genotype	Chitotriosidase Activity[a]
1/M/21	N370S/L444P	wt/null	NL/NL	3392
2/F/29	N370S/L444P	wt/wt	G102S/NL	3500
3/F/17	N370S/N370S	wt/wt	NA	2707
4/F/21	N370S/N370S	wt/null	NL/NL	854
5/F/21	N370S/N370S	NA	NA	1224
6/F/21	N370S/N370S	wt/wt	NL/NL	1370
7/M/22	N370S/N370S	wt/wt	NL/NL	1055
8/F/24	N370S/N370S	wt/wt	NL/NL	3054
9/M/26	N370S/N370S	wt/wt	NL/NL	4547
10/F/27	N370S/N370S	wt/null	NA	NA
11/F/29	N370S/N370S	wt/wt	NL/NL	1390
12/F/30	N370S/N370S	wt/null	NL/NL	988
13/F/30	N370S/N370S	wt/null	NL/NL	966
14/F/30	N370S/N370S	wt/wt	G102S/G102S	NA
15/F/31	N370S/N370S	wt/wt	NL/NL	6402
16/F/31	N370S/N370S	wt/wt	NL/NL	NA
17/F/31	N370S/N370S	wt/wt	G102S/G102S	1221
18/F/32	N370S/N370S	wt/wt	G102S/NL	665
19/F/32	N370S/N370S	wt/wt	NL/NL	5694
20/F/32	N370S/N370S	wt/wt	G102S/NL	NA
21/M/32	N370S/N370S	wt/wt	NL/NL	NA
22/M/33	N370S/N370S	wt/null	NL/NL	99
23/F/34	N370S/N370S	wt/wt	NL/NL	5054
24/F/34	N370S/N370S	wt/wt	NL/NL	1496
25/F/35	N370S/N370S	wt/null	NL/NL	NA
26/F/35	N370S/N370S	wt/null	G102S/NL	254
27/M/36	N370S/N370S	wt/wt	NL/NL	3420
28/F/37	N370S/N370S	null/null	NL/NL	0
29/F/37	N370S/N370S	wt/wt	NL/NL	471
30/F/37	N370S/N370S	NA	NA	104
31/F/40	N370S/N370S	null/null	NA	0
32/F/40	N370S/N370S	wt/null	NL/NL	1056
33/F/40	N370S/N370S	wt/null	NA	NA
34/M/30	N370S/V394L	wt/null	G102S/NL	1190
35/F/28	N370S/R496H	wt/wt	NA	40
36/F/29	N370S/R496H	NA	NA	10
37/F/31	N370S/R496H	null/null	NL/NL	0

Abbreviations: NA, not available; NL, normal; null, nonfunctional 24 base-pair duplication allele; wt, wild-type.
[a]Normal level is less than 180 nmol/h/mL.

Table 4. Chitotriosidase Levels and Enzyme Replacement Therapy (ERT)[a]

	ERT Not Recommended		ERT Recommended	
Chitotriosidase Genotype	Patients, No.	Chitotriosidase Level (Range), nmol/h/mL	Patients, No.	Chitotriosidase Level (Range), nmol/h/mL
wt/wt	8	1760 (471-2710)	6	4081 (1370-6400)
wt/null	4	599 (99-1060)	2	910 (854-970)

Abbreviations: null, nonfunctional 24 base-pair duplication allele; wt, wild-type.
[a]Data are based on the numbers of patients who had available levels.

natal genetic carrier screening. The overall heterozygote frequency in this population was 1 in 15; the heterozygote frequency for the most common mutation, N370S, was 1 in 17, representing 92% of the GD alleles detected. Notably, the predicted homozygote frequency for the common mutations of 1 in 949 was, in fact, essentially that observed; 9 previously undiagnosed GD homozygotes were detected, or 1 in 897. Of these, 8 were N370S homozygotes, an observed frequency (1 in 1009) that also was close to that expected (1 in 1129), based on the carrier frequency (P=.94). Thus, our ascertainment of AJ GD homozygotes in this population was complete.

Second, what proportion of GD homozygotes detected by prenatal carrier screening were symptomatic or asymptomatic? Of the 37 GD homozygotes detected by our or other prenatal carrier screening programs, 13 of 37 (35%) reported symptoms consistent with type 1

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GD, including bruising, bone pain, and fatigue. As might be expected, the 2 previously undiagnosed patients with the N370S/L444P genotype, which typically manifests in childhood,[35] were both symptomatic, reported easy bruisability, had clinically significant disease manifestations, (Table 2) and were referred for ERT. Notably, 24 of 37 (65%) were asymptomatic for GD on review of systems, consistent with previous expert predictions of the proportion of asymptomatic patients.[6,19,20] However, clinical, laboratory, and/or imaging studies of all 37 patients revealed GD manifestations ranging from mild to relatively severe at a mean age of 30 years, with the youngest, and mildest, a 17-year-old female with the N370S/N370S genotype who had only marrow infiltration (Table 2). Even the 3 patients identified with the mildest N370S/R496H genotype had disease manifestations.

Third, what are the manifestations in these previously undiagnosed homozygotes? All 37 patients had bone marrow infiltration, which is evidence of GD and is the precursor of future irreversible bone involvement. Notably, of the 29 patients who had imaging studies, 10 of 23 (43%) had the Erlenmeyer flask deformity, 4 of 28 (14%) had a bone infarction, and 5 of 23 (22%) had bone lucencies on imaging. Among the others, the manifestations ranged from splenomegaly, thrombocytopenia, anemia, marrow infiltration, bone infarctions, osteoporosis, and pathologic fractures.

In postmenopausal women, osteopenia is a well-established risk factor for fracture, particularly of the hip.[36] However, the relationship between osteopenia and fracture risk in young premenopausal women and in men has not been defined. The guidelines for treatment of osteopenia/osteoporosis in postmenopausal women with low BMD values are not applicable to premenopausal women with osteopenia.[37] Moreover, there are limited data on the use of standard pharmacologic therapy (eg, bisphosphonates) in women who are planning a pregnancy. These findings highlight the need to recognize and closely monitor young patients with GD with low BMD. Bone mineral density should be monitored annually, and supplementation with calcium and cholecalciferol for patients with GD who are osteopenic is recommended. Early detection of disease manifestations in these patients will facilitate monitoring and therapeutic intervention prior to the development of irreversible complications.

Of the 29 GD homozygotes who had complete GD evaluations, imaging studies revealed that 28 of 29 (97%) had splenomegaly and 18 of 37 (49%) had abnormal hematologic values. Two women needed treatment during pregnancy owing to progressive thrombocytopenia. There was no correlation between the hematologic and/or visceral involvement and the presence or severity of bone manifestations among AJ type 1 GD patients, as previously noted.[38] In fact, of our 19 patients with normal blood counts, 15 of 19 (79%) had imaging studies that showed varying degrees of bone involvement, including 2 patients with bone infarcts (13%) and 5 with osteopenia/osteoporosis based on DEXA studies (42%).

Finally, do GD homozygotes remain mostly "asymptomatic" throughout life, or do they become the patients who are diagnosed and treated later in life as the disease progresses? Of this cohort, 21 patients continue to be followed by our center and have been evaluated annually or biannually. The oldest patient in our group was 50 years old at her last evaluation, which showed no evidence of disease progression since her initial evaluation 10 years earlier that had revealed mild splenomegaly and minimal bone involvement. Her plasma chitotriosidase activity was low at 564 nmol/h/mL. Contrary to the variable progression observed over years in the other N370S/N370S homozygotes, this patient's experience suggests that a small subset of N370S homozygotes may remain stable for years with minimal disease progression. In contrast, ERT has been recommended for 13 of the N370S homozygotes (42%) who had clinically significant disease at diagnosis or evidence of disease progression over a 9-year observation period. These results indicate that this disease genotype is not low penetrant but manifests in adulthood and is often progressive. In fact, the later-onset of manifestations in N370S homozygotes may contribute to its diagnostic delay, which may be associated with irreversible complications.[39]

Our findings are in contrast to those reported by Azuri et al,[40] who suggested that asymptomatic patients or those with mild symptoms do not require frequent monitoring. The fact that all 31 N370S homozygotes detected by carrier screening had GD manifestations at midlife solves the perception about the genotype being benign. Clearly, these patients should be identified as early as possible, a likelihood if future genome (exome) sequencing becomes commonplace. A comprehensive baseline evaluation based on GD consensus recommendations should be performed to assess disease involvement for these homozygotes on an annual or biannual basis.[26] Based on our experience, at least 40% will become candidates for ERT or future therapies.[41,42]

In summary, the evaluation of AJ GD homozygotes identified serendipitously by prenatal carrier screening revealed that these young to middle-aged homozygotes actually had disease manifestations, particularly bone involvement, that progressed with age in many homozygotes, often requiring therapeutic intervention. Our findings indicate that homozygosity for the common N370S mutation does not result in a benign or low penetrant disease and emphasizes the importance of early recognition and appropriate treatment to minimize or prevent future irreversible disease complications.

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the application process and postapproval, be publicly available. The FDA also must have authority and the will to withdraw device approvals if postmarketing data requirements are not met *or* if the postmarketing data show safety or effectiveness problems. Mechanisms for collecting postmarketing data must be made user friendly and publicly accessible. Registries such as the National Cardiovascular Data Registry and others are an important step in that direction. Currently, only 5% to 10% of all adverse events are actually reported. We have had many recent reminders that even those adverse events that are reported are not readily publicly available or turned over to the FDA in a timely fashion. The FDA recently sent another 12-page warning letter to Pfizer about delays in reporting adverse events dating back 6 years. The recent Avandia firestorm highlighted the importance of transparency of data. The problem is even more pressing and urgent for devices as seen in high-profile device recalls (Fidelis) as well as the recent Boston Scientific alert of serious problems with some of their implantable cardioverter-defibrillators.[11]

While we all appreciate the potential advantages of medical devices, prudent policy requires high-quality clinical data showing that the benefits outweigh the risks, before and after FDA approval. Holding manufacturers to these standards will enhance, not hinder, innovation and advancement of the science of medical devices.

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Editor

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Correction

Error in "Comment" Section. In the article titled "Type 1 Gaucher Disease: Significant Disease Manifestations in 'Asymptomatic' Homozygotes" by Balwani et al, published in the September 13 issue of the *Archives* (2010; 170[16]:1463-1469), in the next to the last paragraph of the article, the second sentence should have read, "The fact that all 31 N370S homozygotes detected by carrier screening had GD manifestations at midlife solves [instead of "agrees with"] the perception about the genotype being benign."

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