

Early manifestations of type 1 Gaucher disease in presymptomatic children diagnosed after parental carrier screening

Amy C. Yang, MD¹, Louise Bier, MS¹, Jessica R. Overbey, MS², Jessica Cohen-Pfeffer, MD¹, Khyati Desai, MD¹, Robert J. Desnick, PhD, MD¹ and Manisha Balwani, MD, MS¹

Purpose: The overall published experience with pediatric type 1 Gaucher disease (GD1) has been based on ascertainment through clinical presentation of the disease. We describe the longitudinal follow-up in a presymptomatic pediatric cohort.

Methods: The cohort includes children diagnosed with GD1, either prenatally or postnatally by molecular genetic testing, and followed for clinical care at our center from 1998 to 2016. All patients' parents were *GBA* mutation carriers identified through carrier screening programs. Longitudinal clinical, laboratory, and imaging data were obtained through chart review.

Results: Thirty-eight patients aged 1–18 years (mean at last visit 6.9 ± 4.1 years) were followed, including 32 p.N409S homozygotes and 6 p.N409S/p.R535H compound heterozygotes. At the last evaluation, a minority had hematological (5%), bone (15%), or linear

growth (19%) issues. Only 12% had splenomegaly and 74% had moderate hepatomegaly. Chitotriosidase activity varied widely (6–5,640 nmol/hour/ml) and generally increased with age. Pediatric Gaucher severity scores (GSS) remained stable and within the mild-disease range for most (95%). Treatment for progressive disease during this period was recommended for four children.

Conclusion: Most children with the p.N409S/p.N409S and p.N409S/p.R535H GD1 genotypes have minimal disease manifestations and progression during childhood and can be monitored using limited assessments. Those with other mutations may require additional monitoring. These data are valuable for newborn screening and counseling.

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INTRODUCTION

Type 1 Gaucher disease (GD1) (OMIM 230800) is an autosomal-recessive lysosomal storage disorder caused by deficiency of the enzyme acid β -glucosidase, resulting from mutations in the *GBA* gene. This enzyme deficiency leads to progressive accumulation of glucosylceramide (GL-1), primarily in the liver, spleen, and bone marrow, causing hepatosplenomegaly, anemia, thrombocytopenia, and skeletal disease. GD1 is distinguished from types 2 and 3 by the lack of primary neurologic involvement.¹ Treatment is available with intravenous enzyme replacement therapy (ERT) or, for adults, substrate reduction therapy.²

GD1 is most common in the Ashkenazi Jewish (AJ) population, which has an estimated *GBA* carrier frequency of 1 in 14 to 18,^{3–6} although *GBA* mutations can occur in individuals of any ethnic background. Because of the high frequency of *GBA* mutations, prenatal screening for GD has become increasingly common among the AJ population^{4,7,8} and is recommended by the American College of Medical Genetics and Genomics and the American College of Obstetrics and Gynecology. The

increased proclivity for carrier screening has led to a greater number of children diagnosed with GD presymptotically because they were tested either prenatally or postnatally because their parents are known *GBA* carriers. With the expansion of screening panels to pan-ethnic carrier screening, the population of presymptotically diagnosed pediatric GD patients is likely to increase. Moreover, newborn screening for lysosomal diseases including GD is already being performed in Missouri, Illinois, and Pennsylvania. As more states move to include GD on newborn screening panels, the number of patients diagnosed is expected to increase. It is anticipated that questions will be raised regarding what to expect for these children identified presymptotically, including when and how symptoms will first develop, how these children should be monitored, and when to start treatment.^{9,10}

Symptom presentation and progression in GD1 is highly variable, especially among those homozygous for the most common p.N409S (previously known as p.N370S) mutation.^{6,11–14} Although the mean age at diagnosis for p.N409S homozygotes is 28 years, data from the International Collaborative Group

The first two authors contributed equally to this work.

¹Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA; ²Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York, USA. Correspondence: Manisha Balwani (manisha.balwani@mssm.edu)

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Gaucher Registry show that some individuals may not be diagnosed until the 8th or 9th decade of life.^{11,12} It is estimated that as many as two-thirds of p.N409S homozygotes remain undiagnosed as a result of mild or subclinical symptoms.^{3,15} However, although p.N409S homozygotes tend to be less affected than p.N409S compound heterozygotes, the p.N409S homozygous state should not be considered an exclusively mild or adult-onset form of GD.¹⁶ p.N409S homozygotes have been observed to exhibit severe GD1-related disease manifestations in hematologic, visceral, and bone parameters.¹² Even among those diagnosed serendipitously via prenatal carrier screening, a majority of these “asymptomatic” patients exhibited some degree of disease manifestation.⁶ Further, registry data demonstrate that a few p.N409S homozygotes are diagnosed during childhood and can experience moderate to severe symptoms.^{12,17}

The *GBA* allele p.R535H (previously known as p.R496H) is found almost exclusively in the Ashkenazi Jewish population and has been part of our *GBA*-targeted mutation panel since 2006. This has been described as a “mild” allele, although limited information is available in the literature.¹⁸ In combination with p.N409S, this compound heterozygous genotype (p.N409S/p.R535H) generally confers mild, adult-onset GD1, although childhood presentation of disease has also been described.¹⁹

Because there is marked clinical variability in GD1, it is difficult to predict disease progression based on genotype alone. Because of the importance of early intervention to maximize response to treatment, current consensus guidelines recommend regular monitoring of symptomatic pediatric GD1 patients for evidence of visceral, hematologic, and bone involvement.^{16,20–23} Specifically, the most recently revised guidelines recommend physical examinations (including detailed history and careful monitoring of height and growth velocity) and hematologic assessments, including complete blood count (CBC) and biomarkers, such as chitotriosidase activity, every 6–12 months; monitoring of liver and spleen volumes every 6–12 months, preferably via volumetric magnetic resonance imaging (MRI); and skeletal assessments, including dual-energy X-ray absorptiometry (DXA) every 12 months and MRI of the spine and femur every 12–24 months.²¹

However, these guidelines were devised mainly for clinically affected children diagnosed as a result of symptom presentation. Although there is recognition that children diagnosed presymptomatically likely require less intensive monitoring,²¹ data specifically describing this cohort’s disease involvement and progression are not available. Here, we describe our 18 years of experience following 38 children with GD1 diagnosed presymptomatically through genetic testing to inform monitoring and counseling guidelines.

MATERIALS AND METHODS

Cohort and assessments

The study cohort consists of children diagnosed presymptomatically with GD1, either prenatally by chorionic villus sampling or amniocentesis or postnatally by molecular genetic testing. All parents were known *GBA* mutation carriers, of AJ

ethnicity, and identified through the Jewish Genetic Disease carrier screening program. All patients were referred for evaluation and management to the Comprehensive Gaucher Disease Treatment Center at the Icahn School of Medicine at Mount Sinai from 1998 to 2016.

Longitudinal data were obtained through a retrospective chart review protocol approved by the Mount Sinai Institutional Review Board. Patients were evaluated at baseline and at follow-up, typically every 1 to 2 years. Baseline disease burden and progression were monitored through clinical, laboratory, and imaging assessments. Medical and family histories, reviews of systems, and physical examinations were performed for all children by a physician with expertise in Gaucher disease (GD) (M.B., A.Y., and J.C.P.). Linear height was measured at each visit. For children aged 2 and older, their current height percentiles for age and sex on the Centers for Disease Control and Prevention growth chart were compared with expected midparental height percentiles, as outlined previously by Tanner *et al*.²⁴ Standard deviations from expected midparental height and prior height measurements were calculated based on Z-scores. Laboratory studies included CBC and chitotriosidase activity at each visit; coagulation studies, hepatic function tests, immunological studies, and iron indexes were performed for older children as needed. Organ volumes were measured every 1–2 years using a limited abdominal ultrasound typically starting at approximately age 4–6 years and abdominal MRI was performed starting at approximately age 10 years; these values were converted to multiples of normal (MN) based on body weight.²⁵ Bone mineral density was assessed by DXA starting at approximately age 6 years because of a paucity of well-established norms below this age group; these values were assessed approximately every 2 years for children aged 6 and older. All assessments were performed as part of clinical standard of care and recommendations for imaging studies varied based on the individual patient’s ability to tolerate those procedures and/or concerning signs or symptoms.

Gaucher severity scoring

An overall disease-severity score was assigned for each patient at each annual evaluation using the pediatric Gaucher Severity Score (GSS) developed by Kallish and Kaplan.²⁶ The GSS is a validated, objective, and comprehensive measure of disease involvement that allows comparisons to the potential symptom spectrum. Using this severity scoring system, patients were evaluated across four major domains, growth, hematologic symptoms, visceral enlargement, and bone involvement, and assigned scores as outlined in the system. The GSS was applied retrospectively for visits prior to 2013, and prospectively thereafter.

Statistical analyses

Demographic, medical history, and laboratory data are displayed as mean and standard deviation for continuous variables and as proportions for categorical variables. To explore changes in laboratory values over time and to present panel plots of each

Table 1 Patient demographics

	Number of patients (<i>n</i> = 38)
Age at diagnosis (years)	
Prenatally	20 (53%)
0 to <1	8 (21%)
1 to <2	4 (10%)
2 to <3	3 (8%)
>3	3 (8%)
Genotype	
p.N409S/p.N409S (N370S/N370S)	32 (84%)
p.N409S/p.R535H (N370S/R496H)	6 (16%)
Age at last evaluation (years)	
1 to <6	12 (31%)
6 to <12	20 (53%)
12 to 18	6 (16%)
Sex	
Male	17 (45%)
Female	21 (55%)

individual, LOESS plots were created to explore the cohort's mean at each age. All analyses were conducted using SAS version 9.4 (SAS, Cary, NC).

RESULTS

A total of 38 patients—17 males and 21 females aged 1 to 18 years (mean age at last visit was 6.9 ± 4.1 years)—were evaluated at baseline and at follow-up, for a mean of 5.2 years (± 4.6). This cohort comprised 32 p.N409S homozygotes (84%) and 6 p.N409S/p.R535H compound heterozygotes (16%). Twenty children were diagnosed through prenatal testing (53%), and 18 were presymptomatically tested at various ages after birth (47%) (**Table 1**). Most were diagnosed before age 3 years, with only 2 children diagnosed at age 3 years; 1 child was diagnosed at age 5 because the parents deferred testing.

Hematological and visceral assessments

Hematological manifestations were minimal in this cohort. No patient had a history of significant bruising or bleeding. None had persistent anemia. One child had transient microcytic anemia due to iron deficiency, which was corrected with iron supplementation. Only two children (5%) had thrombocytopenia in the moderate range (60 to $<120 \times 10^3/\mu\text{l}$) (**Table 2**). Sixteen children had coagulation testing; four of them (25%) had mildly elevated partial thromboplastin time (PTT) (maximum value at last evaluation was 38 s) but a normal international normalized ratio (INR). The mean PTT for 16 children at their last evaluation was 34.3 ± 3.7 s (normal range 25.4–34.9).

No imaging studies were performed for children younger than age 4 unless organomegaly was noted on examination. At the last visit, only two children at age 4 underwent abdominal ultrasound, and neither had significant spleen or liver enlargement. Sixteen of 20 children aged 6 to 11 (80%) underwent abdominal ultrasound at their last visit; one could not complete

Table 2 Hematologic findings and organ volumes at last evaluation

	Age range, years			
	0 to <6	6 to <12	12 to 18	Total
Hemoglobin (g/dl)	<i>N</i> = 11	<i>N</i> = 20	<i>N</i> = 6	<i>N</i> = 37
Anemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenia ($10^3/\mu\text{l}$)	<i>N</i> = 11	<i>N</i> = 20	<i>N</i> = 6	<i>N</i> = 37
Severe (<60)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate (60 to <120)	1 (9%)	1 (5%)	0 (0%)	2 (5%)
Mild/normal (≥ 120)	10 (91%)	19 (95%)	6 (100%)	35 (95%)
Liver volume (MN)	<i>N</i> = 2	<i>N</i> = 15 ^a	<i>N</i> = 6	<i>N</i> = 23 ^a
Severe (>2.5)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate (>1.25–2.5)	0 (0%)	14 (93%)	3 (50%)	17 (74%)
Mild/normal (≤ 1.25)	2 (100%)	1 (7%)	3 (50%)	6 (26%)
Spleen volume (MN)	<i>N</i> = 2	<i>N</i> = 16 ^a	<i>N</i> = 6	<i>N</i> = 24 ^a
Severe (>15)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate (>5–15)	0 (0%)	2 (12%)	1 (17%)	3 (12%)
Mild/normal (≤ 5)	2 (100%)	14 (88%)	5 (83%)	21 (88%)

^aOne patient could not complete the full ultrasound study and only spleen measurements were obtained.

the entire radiological study. All children aged 12 years and older underwent abdominal ultrasound or MRI. Two of 16 (12%) children aged 6 to 11 and 1 of 6 (17%) children aged 12 to 18 had moderate splenomegaly (>5–15 MN). Of note, 14 of 15 (93%) children aged 6 to 11 had moderate hepatomegaly (>1.25–2.5 MN) based on abdominal ultrasound; however, in the older age group, only 3 of 6 (50%) children had moderate hepatomegaly. None had severe hepatomegaly (>2.5 MN) or splenomegaly (>15 MN). At age 3, patient 17 had thrombocytopenia and a palpable splenomegaly on examination following a febrile illness with mononucleosis attributed to an Epstein–Barr viral infection. Initially, the spleen volume was 13.8 MN on ultrasound. After 6 months, the spleen had decreased to 6.2 MN; after 2 years, it had decreased and remained stable at 2.8 MN.

Skeletal assessment and linear growth

Five of 38 patients (13%) reported mild, self-limited bone or joint pain not impacting daily activities that parents attributed to “growing pains” or excessive exercise. None had significant bone pain, bone crises, or fractures. Eight of 20 children aged 6 to 11 (40%) underwent DXA bone scan at the last visit. Of these, only 1 (13%) had an abnormal bone mineral density Z-score between -1 and -2 standard deviations below average. Similarly, five of six children aged 12 years and older underwent DXA bone scan. Of these, only 1 child (17%) had a Z-score between -1 and -2 . (**Table 3**) Linear growth was assessed at each visit. For children aged 2 years and older, 95% (35 of 37) were above the 5th percentile for height and showed no decline in their overall height percentiles; 81% (30 of 37) were growing along expected percentiles based on midparental height. Overall, 7 of 37 (19%) children had a height 1 standard deviation (SD) below the expected midparental height and none had

Table 3 Linear growth and bone density at last evaluation

	Age range, years			
	2 to <6	6 to <12	12 to 18	Total
Height percentile (CDC, 2–18 years)	N = 11	N = 20	N = 6	N = 37
<5 th	1 (5%)	1 (5%)	0 (0%)	2 (5%)
5–25 th	5 (45%)	5 (25%)	1 (17%)	11 (30%)
>25 th	5 (45%)	14 (70%)	5 (83%)	24 (65%)
Comparison to expected midparental height	N = 11	N = 20	N = 6	N = 37
2 SD below expected	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1 SD below expected	2 (18%)	4 (20%)	1 (17%)	7 (19%)
Same or increased	9 (82%)	16 (80%)	5 (83%)	30 (81%)
Change in height percentile	N = 8	N = 18	N = 6	N = 32 ^a
Declined 2 SD	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Declined 1 SD	0 (0%)	1 (6%)	1 (17%)	2 (6%)
Same or increased	8 (100%)	17 (94%)	5 (83%)	30 (94%)
Bone mineral density (Z-score)	N = 0	N = 8	N = 5	N = 13
< -2	n/a	0 (0%)	0 (0%)	0 (0%)
-1 to -2	n/a	1 (13%)	1 (20%)	2 (15%)
> -1	n/a	7 (87%)	4 (80%)	11 (85%)

^aChange in height percentile could not be determined for those who were only examined once or for those whose height percentile determination was switched from the WHO growth chart (before age 2 years) to the CDC growth chart (after age 2 years).

CDC, Centers for Disease Control and Prevention.

a height 2 SD below the expected midparental height. Only 1 child at age 10 and 1 child at age 13 exhibited a decline of more than 1 SD for height percentile.

Chitotriosidase and pediatric GSS

Chitotriosidase activity varied markedly among patients (6 to 5,640 nmol/hr/ml) and generally increased with age (Figure 1a). Of a maximum GSS of 20.4, as outlined by Kallish and Kaplan (2013), 36 of 38 children (95%) had scores within the mild range (0–6), with most remaining stable. Patients 2, 10, 13, 25, 26, and 30 had GSS that increased past 3 at the last visit. Patients 17 and 19 had scores that trended into the moderate range (6–9), with a maximum GGS of 6.7 and 7.2, respectively (Figure 2). Chitotriosidase activity and total GSS from each evaluation appeared to be positively correlated. However, interpretation is limited by the small sample size (Figure 1c).

To date, only 4 of 38 (11%) children have received or were recommended to undergo ERT. Patient 17 was recommended to undergo ERT at age 7 due to persistently low height percentile (<5th percentile for age) below 1 SD when compared with expected midparental height, persistent mild to moderate thrombocytopenia, mild to moderate splenomegaly over the course of three follow-up visits, and osteopenia on DXA bone scan. Patient 19 started ERT at age 14 due to decreased height percentiles greater than 1 SD, below 1 SD for midparental height expectations, and

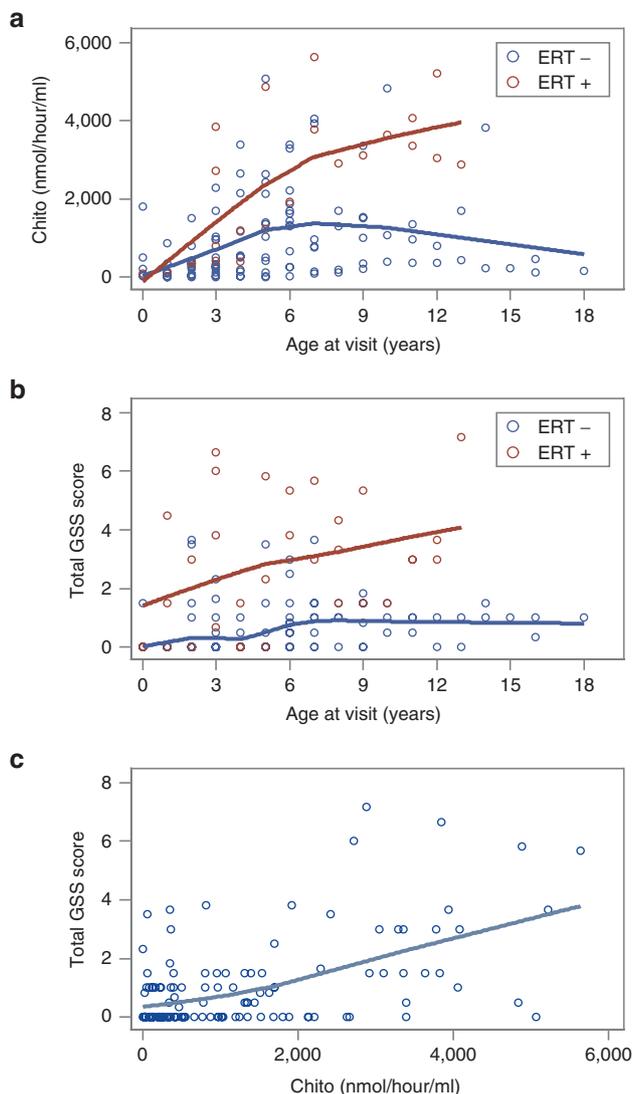


Figure 1 Chitotriosidase activity and Gaucher severity scores (GSS) at each visit. Chitotriosidase (chito) activity (nmol/hr/ml) and calculated GSS at each visit for each patient are represented by a circle. LOESS plots were created to illustrate the mean of the cohort. Panels a and b show chito activity and GSS for patients who were recommended to start enzyme replacement therapy (ERT) (in red) and for those who were not recommended ERT (in blue), respectively. Panel c shows the correlation between the chito activity and GSS at each visit.

moderate hepatosplenomegaly. There was osteopenia on DXA, but MRI of the femur showed no significant findings. Patient 25 was started on ERT at age 9 at another center for growth delay, short stature that was below expected midparental height, and moderate hepatosplenomegaly. Patient 30 was started on ERT at another center because of concerns of poor linear growth and joint pain. When comparing pre-treatment chitotriosidase activity and GSS trends between children who were and were not recommended ERT, children who were recommended to start ERT appeared to have higher trends for both, although statistical testing was not possible given the limited numbers (Figure 1a,b).

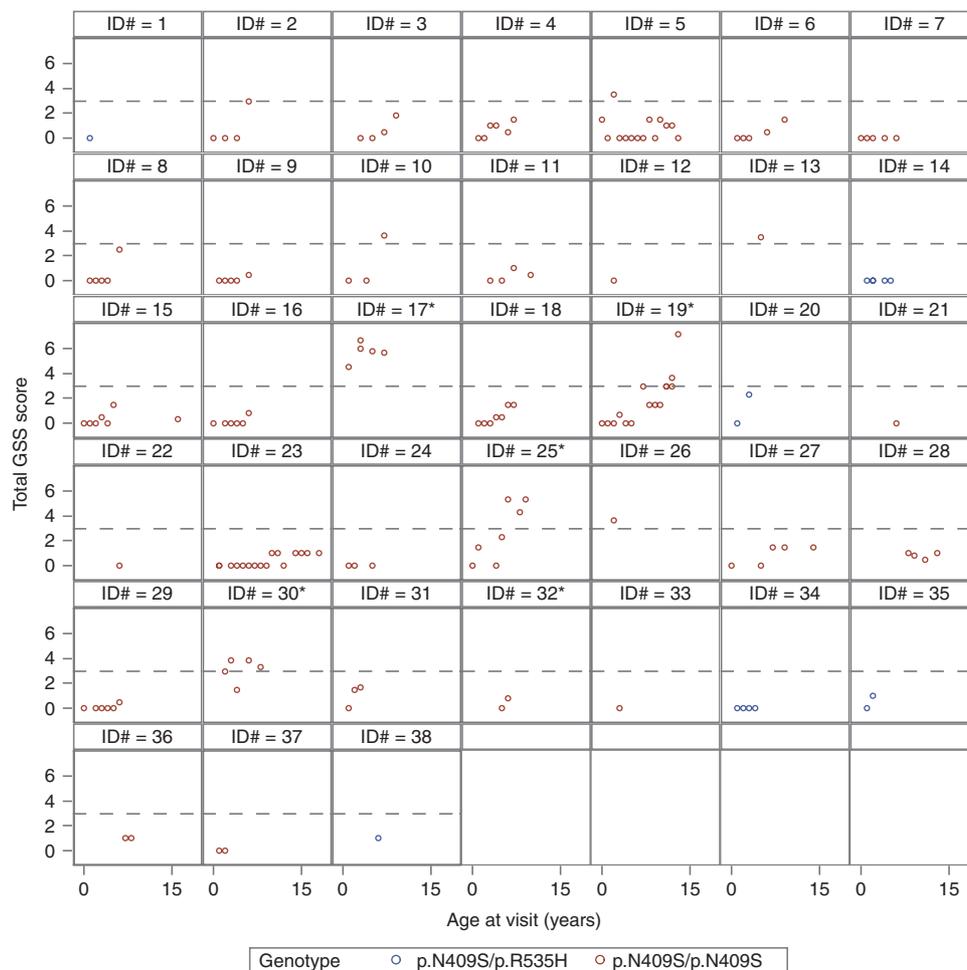


Figure 2 Gaucher severity scores (GSS) plot for each patient. GSS at each visit is represented by a circle. Genotypes p.N409S/p.N409S are designated by red circles and p.N409S/p.R535H by blue circles. *Subjects who were recommended to start enzyme replacement therapy. A dotted line is drawn across GSS 3.

DISCUSSION

The carrier frequency for the common allele p.N409S is approximately 6%,⁴ and the ICGG Gaucher Registry data estimate that 45% of US patients with GD1 are homozygous for p.N409S (Genzyme, Cambridge, MA; data available on request). With increased availability of carrier screening and movement toward newborn screening for lysosomal disorders in the United States, more children with these *GBA* genotypes will be ascertained presymptomatically. Because genotype information alone is not predictive of disease onset or progression, annual follow-up assessments have been proposed for presymptomatic children until disease burden warrants treatment.²¹ However, it is unclear which clinical, laboratory, or imaging assessments will be most informative in the decision to start treatment.

The longitudinal data from our cohort are the first to describe the early natural history of GD1 disease in p.N409S homozygous and p.N409S/p.R535H patients diagnosed at birth or during early childhood. In contrast to patients reported in the ICGG Gaucher registry who were diagnosed when they presented with GD symptoms, our cohort consists of presymptomatic patients diagnosed by genetic testing. For our cohort of 38

children aged 1 through 18, the majority (>80%) displayed few, if any, signs or symptoms of GD in all parameters except for liver volume and had only mild GD burden, with GSS below 6 (95%). Based on our experience, most will not require treatment during childhood. This experience reinforces prior observations that most patients with p.N409S/p.N409S or p.N409S/p.R535H genotypes as a group tend to have milder GD compared with other genotypes, although a subgroup of individuals can still experience clinically significant symptoms, even during childhood.^{6,12,16,17} This finding is especially useful, and hopefully reassuring, when counseling parents of affected children with these genotypes in the prenatal and newborn screening setting.

The most common and earliest signs of GD1 in this cohort were associated with linear growth issues (not meeting expected midparental height or change in height percentile), osteopenia as evidenced on DXA scan, moderate hepatomegaly and/or splenomegaly, and increasing levels of chitotriosidase activity over time. Hematologic indexes were mostly normal; only one child had transient anemia due to iron deficiency and 5% of the children exhibited thrombocytopenia. Chitotriosidase activity levels tended to vary widely from one patient to the next, even

within a sibship. However, the chitotriosidase activity trend for each patient may be predictive of GD progression because it appears to correlate with the GSS, reinforcing its use as a GD biomarker. It is important to note that chitotriosidase activity cannot be used as a biomarker in approximately 6% of patients due to mutations in the *CHIT1* gene.²⁷ Recently, plasma glucosylsphingosine (lyso-GL1) has been proposed as potential biomarker and may be considered for clinical use in the near future.²⁸

Overall, the need for closer monitoring and potentially starting ERT in our cohort can be ascertained by a relatively few noninvasive methods, such as linear height measurements, abdominal ultrasound, CBC, and chitotriosidase. Although the decision to commence ERT was based on clinical experience, retrospectively, two of the four who required ERT in our cohort developed a GSS of more than 6; another had a maximum GSS of 5.3 at the last visit at our site. The decision to initiate treatment for the two patients currently followed at our center was made after repeated evaluations showed disease progression. When the decision to initiate treatment was also based on growth failure, the patient was first evaluated by an endocrinologist to rule out other causes. Both chitotriosidase activity and GSS trended higher in children who were recommended to start ERT than in those who were not.

We recognized that not all children in our cohort would be able to undergo the recommended assessments based on published guidelines. Thus, we have tailored our annual assessments on a case-by-case basis. Phlebotomy can be difficult and anxiety-provoking, especially for younger children, and sedation may be required for MRI studies if a child cannot remain still for the duration of imaging. Although liver and spleen volume estimation via ultrasound is not as accurate as that by an MRI study, a limited abdominal ultrasound with estimated liver and spleen volumes is easier to perform, more readily available, and helps improve patient compliance. If the physical examination is not concerning for organomegaly, we now initiate abdominal ultrasound studies at age 6, performed every 1–2 years, with transition to abdominal MRI after age 11 or older as tolerated. If the patient has been relatively stable, we suggest abdominal imaging every other year. DXA scan is initiated at age 6 and performed every 2 years. We recognize that at medical centers with normative data for children younger than age 6, DXA scan can be initiated at an earlier age. However, from our experience with this cohort, DXA scan at an earlier age is likely to be low-yield. X-ray of the femur and bone age studies were generally not ordered unless there were concerns regarding linear growth delay or bone or joint pain.

It is also important to recognize that various common pediatric concerns can arise in these patients. We consider a workup for iron deficiency if we notice anemia in this cohort because we typically will not expect the anemia to be GD-related. Sudden enlargement of the spleen from one year to the next is also not typical for these children, and a concurrent infectious etiology such as cytomegalovirus or Epstein–Barr virus should be considered. Because vitamin D deficiency is quite prevalent

in the United States, and because bone health maintenance is an important part of GD management, we have been regularly monitoring vitamin D levels and prescribing supplementation if needed.

We also noticed several trends in our cohort. First, there was a high prevalence of moderate hepatomegaly (>1.25 to 2.5 MN) on ultrasound between the ages of 6 and 11 (93%) but a lower incidence in the older age group (50%). This may be related, in part, to the difference in volume calculations from the imaging modalities. For example, in one patient who transitioned from abdominal ultrasound to MRI, liver volume decreased from 1,613 to 1,275 ml in 1 year's time. In another patient, the transition between the two imaging modalities did not change the liver-volume calculation. Ultrasound calculation is based on the maximum length, width, and depth of the liver using the formula for the volume of a prolapsed-ellipse model. This does not take into account the actual shape of the liver. On MRI, liver volume is a computer-generated calculation from the summation of the area and thickness of each image. Second, there may be some discordance in the interval growth of the child and the organ volumes. Longer-term studies are needed to follow-up this finding. Chitotriosidase levels also fluctuate widely in this cohort, presumably due to intercurrent infections or other unknown factors. These observations highlight the importance of not making decisions based on a single time point. In most cases, organ volumes (calculated as MN) and chitotriosidase levels stabilized with longitudinal follow-up. Decisions regarding follow-up and treatment in our cohort were based not on individual parameters such as organ volume or biomarkers but on an overall assessment of the child.

Limitations of this study include the small sample size, limited data on radiologic assessments, and the relatively young age of the patient cohort (mean age of 7 years). A longer follow-up period will help characterize GD progression through adolescence in this cohort. In addition, all the children in this study were Ashkenazi Jewish. Although the predominant disease-causing allele in the US non-AJ population is also p.N409S,^{29,30} some caution is necessary when extrapolating these data to non-AJ p.N409S/p.N409S patients because of various potentially differing genetic backgrounds and other factors that may impact disease onset and severity. Little information exists in the literature about the p.N409S/p.R535H genotype.^{18,19} The six children in our cohort appeared to have minimal manifestations, even compared with the p.N409S homozygotes, consistent with the previously described experience.¹⁹ None of the patients with this genotype required closer follow-up or treatment. Importantly, patients with p.N409S in combination with a more severe mutation, such as p.L483P (p.L444P), c.84dupG (84GG), or c.115+1G>A (IVS2+1G>A), typically present in early childhood with symptomatic disease and should have a different schedule of assessments with earlier and more frequent screening.

Parental anxiety about GD1 manifestations was significant in our cohort, due primarily to the paucity of literature on early manifestations in these children and the lack of objective

criteria for treatment initiation. Each patient visit included extensive counseling and a detailed interpretation of results. Families were generally compliant with annual follow-up, although a few patients transferred to local sites over time.

Conclusion

Although childhood complications of GD in patients with p.N409S/p.N409S or p.N409S/p.R535H genotypes are rare, a small subset of this population will experience clinically significant signs and symptoms during childhood and possibly require ERT. Annual age-based monitoring with a limited set of radiologic and laboratory assessments, including height measurements, liver and spleen imaging, DXA bone scan, CBC, and chitotriosidase activity, is appropriate for the presymptomatically diagnosed child. These assessments, along with GSS, can help with early identification of children developing a higher Gaucher disease burden.

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DISCLOSURE

M.B. is a member of the North American Gaucher Registry Advisory Board and has received honoraria from Genzyme and Shire. J.C.-P. is currently an employee of Biomarin Pharmaceutical Inc. R.J.D. serves as a consultant to Genzyme/Sanofi and receives royalties from Genzyme and Shire for the treatment of Fabry disease. L.B. is currently at the Institute for Genomic Medicine of Columbia University Medical Center in New York, New York. K.D. is currently affiliated with University of Texas Southwestern Medical Center in Dallas, Texas. The other authors declare no conflict of interest.

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