

Type 1 Gaucher Disease: Phenotypic Expression and Natural History in Japanese Patients

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Abstract: Gaucher disease is caused by a deficiency of glucocerebrosidase, resulting in hepatosplenomegaly, pancytopenia, growth retardation and skeletal involvement. We analyzed data on genotype and key clinical parameters in 35 Japanese patients with Gaucher disease type 1. Our data demonstrated that over 60% of patients had onset of Gaucher disease signs/symptoms at less than 5 years. Sixty percent and 46% of evaluable patients were splenectomized and developed severe bone involvement, respectively. Within mean follow-up periods of 8 years and 4 months, mean relative height and weight, severity score index and platelet count all worsened to a highly significant degree. These data suggest that type 1 Gaucher disease tends to be severe and progressive in Japanese patients, most of whom would be suitable for treatment and might indeed require earlier and more aggressive therapy.

Keywords: Gaucher disease, phenotype, natural history

INTRODUCTION

Gaucher disease is a relatively common, autosomal recessive lysosomal disorder. It is caused by deficiency of activity of the enzyme glucocerebrosidase (β -glucosidase) and consequent storage of the substrate glucocerebroside in cells of monocyte/ macrophage lineage. These cells become enlarged, long-lived and numerous, infiltrate and may damage and/or impair function of various tissues and organs.

Based on the presence and rate of progression of neurological symptoms, Gaucher disease is classified into three distinct variants -- types 1, 2 and 3. In type 1 Gaucher disease, the most common form, patients have no neurological

manifestations and a chronic clinical course. A clinical hallmark of type 1 Gaucher disease is variability in age of onset, severity and progression. The diagnosis can be established in infancy, adolescence or, rarely, as late as the eighth decade of life. Some patients have minimal signs or symptoms, while many have debilitating or disabling hematologic, visceral and/or skeletal involvement and/or have required splenectomy. The disease may be life-threatening or even fatal. Such clinical variation may be a function of genetic and/or environmental factors.

Recent advances make it feasible to successfully treat patients with type 1 Gaucher disease with enzyme replacement therapy or allogeneic bone marrow transplantation (1, 2).

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However, both modalities are expensive, and bone marrow transplantation also entails significant problems of donor availability, morbidity and mortality. Therefore it is important to determine which patients with type 1 Gaucher disease have the greatest need for treatment.

Thus it is useful to define the clinical severity of type 1 Gaucher disease among particular populations. Since their mutation prevalence differs from that of Jewish or other Caucasian patients (3), Japanese patients might be expected to have a different phenotype and natural history of type 1 Gaucher disease. This is the first report to describe the clinical expression of type 1 Gaucher disease in Japanese patients and to compare it to that of non-Japanese populations.

PATIENTS AND METHODS

Patients

We clinically evaluated and/or retrospectively analyzed the medical records of all Japanese cases of type 1 Gaucher disease known to us. Currently, our laboratory performs glucocerebrosidase activity assays and genotyping for all Gaucher disease cases in Japan.

This series includes four pairs of siblings (patients 5 and 6; 17 and 18; 22 and 23; 30 and 31), one pair of identical twins (patients 20 and 21) and two patients (2 and 29) with siblings with Gaucher disease who are excluded here because of unavailability of samples and medical records. Hence this series includes 35 patients from 30 different families; their genotypes also have been reported elsewhere (3,4).

Of the 35 patients, 14 have been treated with enzyme replacement therapy (cases 1, 3, 4, 5, 6, 8, 10, 11, 14, 19, 20 and 21) or bone marrow transplantation (9 and 13). In these patients, data at evaluation/analysis just before treatment were used to evaluate the natural history. In 5 fatal cases, the evaluation/analysis just before death was used when it was available. Children are defined as individuals ≤ 18 years old at

evaluation/analysis or death.

Diagnosis of Gaucher disease and of the type 1 variant was based on acid β -glucosidase assay and on physical findings, respectively. To exclude type 3b Gaucher disease, pediatricians and/or ophthalmologists ruled out the presence of horizontal supranuclear gaze palsy and strabismus (5). To further exclude neuronopathic disease, CT scan or magnetic resonance imaging (MRI) of the brain was performed in patients 3, 6, 8, 10, 19, 20, 21, 32 and 33 and auditory brain stem response (ABR) was evaluated in patients 3, 8, 10, 19, 20, 21 and 32. No patient showed neurological signs up through evaluation/analysis. Five patients (2, 7, 16, 24, 26) died without developing neurological signs (6).

For comparison with our cohort, we used two of the most recently reported series of non-Japanese patients with type 1 Gaucher disease (7,8).

Mutation Analysis

We detected seven common mutations, 1226G (N370S), 84GG, 754A (F213I), IVS2+1, 1448C (L444P), 1504T (R463C) and 1342C (D409H) by digestion of polymerase chain reaction (PCR) or mismatched PCR products. When mutations remained unidentified, single-stranded confirmation polymorphism (SSCP) analysis was performed. PCR products showing abnormal mobility on SSCP gel were subcloned using a TA cloning kit (Invitrogen, San Diego, CA, USA), then sequenced using a T7 sequencing kit (Pharmacia LKB, Uppsala, Sweden). Experimental conditions and results of the SSCP have been described elsewhere (4).

Clinical Evaluation/Analysis

We assessed all patients and/or analyzed their records for severe bone involvement, splenectomy and overall disease severity. For pediatric patients, we also assessed and/or analyzed their records for growth retardation in weight or stature. We performed and/or analyzed

records of standard physical, laboratory and radiological evaluations. These included measurements of white blood cells, platelets, hemoglobin, angiotensin-converting enzyme, tartrate-resistant acid phosphatase, transaminase and plain radiographs of the femora and symptomatic areas of bone. Physical growth was expressed as a function of the standard deviation (SD) or percentile relative to published standards for age-matched healthy Japanese children. We defined "severe bone involvement" as presence of avascular necrosis or fracture. The definition excluded bone crises, other bone pain or other clinical or radiological bone abnormalities.

To quantitate overall disease severity, we used the severity score index (SSI) (9). The SSI assigns point values according to age at diagnosis, degree of cytopenia, degree of

involvement of various organ systems and spleen status. The degree of severity correlates with higher score. Although some investigators consider the SSI subjective and difficult to interpret (10, 11), its use facilitates comparison of our and other series (7,8).

Statistical Analysis

Paired t-tests were used to analyze changes in relative physical growth, and Wilcoxon signed rank tests, to analyze changes in SSI and hematological measurements and correlation between genotype and clinical parameters. Statistical analysis was performed with PC-SAS Version 6.11 (SAS Institute, Inc., Cary, NC, USA).

Table 1. Japanese Patients with Type 1 Gaucher Disease: Characteristics and Findings

Patient No.	Sex	Age	Presentation/Diagnosis Principal Finding(s)*	SSI	Evaluation/Analysis				
					Age	SSI	Splenectomy	Severe Bone Involvement	Genotype
1	M	1 yr 8 mo	Petechiae	8	10 yr	15	-	-	1448C/1193A
2 [†]	F	7 yr	Hepatosplenomegaly [‡]	NA	17 yr [§]	NA	+	+	1448C/1213G
3	M	1 yr 10 mo	Abdominal distension	9	22 yr	19	+	+	1448C/1603T
4	M	2 yr 4 mo	Anemia	9	4 yr	20	+	+	1448C/1448C
5 [†]	M	3 yr	Bone pain	14	10 yr	17	+	+	1448C/754A
6 [†]	M	2yr 1mo	Hepatosplenomegaly [‡]	9	6 yr	11	-	-	1448C/754A
7	F	2 yr	Abdominal distension	NA	11 yr [§]	NA	+	+	1603T/1603T
8	M	2 yr	Abdominal distension	8	3 yr	9	+	-	1448C/754A
9	M	1 yr	Hepatosplenomegaly	NA	4 yr	11	+	-	1354C/1354C
10	M	2 yr 9 mo	Abdominal distension	8	6 yr	16	+	-	1448C/1448C
11	M	2 yr 11 mo	Abdominal distension	9	8 yr	11	-	-	1448C/1448C
12	M	31 yr	Bone pain	10	33 yr	NA	+	+	1448C/1246G
13	F	1 yr 1 mo	Hepatosplenomegaly	NA	3 yr	15	+	-	1448C/1448C
14	F	6 yr	Hepatosplenomegaly	8	12 yr	13	-	+	1448C/1414G

Patient No.	Sex	Age	Presentation/Diagnosis Principal Finding(s)*	SSI	Evaluation/Analysis				
					Age	SSI	Splenectomy	Severe Bone Involvement	Genotype
15	M	33 yr	Asymptomatic thrombocytopenia	6	35 yr	6	-	-	1448C/1504T
16	F	3 yr	Bone pain	NA	29 yr [†]	21	+	+	1213G/1213G
17 [†]	F	26 yr	Asymptomatic thrombocytopenia	5	39 yr	6	-	-	?/?
18 [†]	F	29 yr	Asymptomatic thrombocytopenia [‡]	5	44 yr	6	-	-	?/?
19	F	1 yr 1 mo	Hepatosplenomegaly	8	4 yr	10	+	-	1448C/754A
20 [†]	M	2 yr 11 mo	Hepatosplenomegaly	7	4 yr	8	-	-	1448C/754A
21 [†]	M	2 yr 11 mo	Hepatosplenomegaly	7	4 yr	8	-	-	1448C/754A
22 [†]	M	3 yr 2 mo	Abdominal distension	7	9 yr	7	-	-	1448C/683T
23 [†]	F	1 yr 7 mo	Hepatosplenomegaly [‡]	7	8 yr	7	-	-	1448C/683T
24	F	5yr	Abdominal distension	NA	7 yr [§]	NA	+	+	?/?
25	F	7 yr	Bone pain	7	40 yr	14	+	+	1448C/754A
26	F	1 yr 6 mo	Hepatosplenomegaly	NA	7 yr [§]	NA	+	-	1448C/1390G
27	F	5 yr 3 mo	Hepatosplenomegaly	11	24 yr	14	+	+	1448C/1448C
28	M	57 yr	Hepatosplenomegaly	5	63 yr	5	+	-	1603T/1603T
29 [†]	F	11 yr	Hepatosplenomegaly [‡]	5	24 yr	12	-	+	1448C/754A
30 [†]	M	3 yr 9 mo	Hepatosplenomegaly	8	14 yr	16	+	+	1448C/754A
31 [†]	F	1 yr 9 mo	Hepatosplenomegaly [‡]	8	12 yr	16	+	+	1448C/754A
32	F	4 yr	Records Unavailable	NA	27 yr	8	+	-	1448C/1448C
33	F	2 yr 4 mo	Hepatosplenomegaly	17	4 yr	17	-	+	?/?
34	M	2 yr 2 mo	Hepatosplenomegaly	9	4 yr	11	-	-	754A/?
35	M	8 yr	Hepatosplenomegaly	6	19 yr	18	+	+	1504T/?

*Principal finding(s)=Gaucher disease sign(s) or symptom(s) that led to diagnosis.

†known family involvement: patients 5 and 6, 17 and 18, 22 and 23, and 30 and 31, respectively, are siblings, patients 20 and 21 are identical twins and patients 2 and 29 had siblings with Gaucher disease who were excluded here because of unavailable samples and medical records.

‡diagnosed after diagnosis of a sibling; finding was present at this time

§deceased

- =absent

+ =present

? =unknown allele

NA =not available

SSI =severity scoring index; degree of severity correlates with higher score (9)

RESULTS

Japanese Patients: Characteristics and Findings (Table 1)

The 35 patients in this series included 18 males and 17 females. At latest evaluation/analysis or death, the cohort comprised 23 children and 12 adults. The series showed considerable genetic heterogeneity at least 15 genotypes and 12 alleles), but 25 patients (71%) had at least one 1448C allele. In descending order of frequency, the most common genotypes were: 1448C/754A, 10 (29%) patients, 1448C/1448C, 6 (17%) patients, unknown/unknown, 4 (11%) patients, 1448C/683T and 1603T/1603T, 2 (6%) patients each. In descending order of

frequency, the most common alleles were: 1448C, 31 (44%) of 70 alleles; 754A, 11 (16%) alleles; unknown, 10 (14%) alleles; 1603T, 5 (7%) alleles and 1213G, 3 (4%) alleles.

At diagnosis, mean age was 8 years (range: 1 to 57 years). As their principal finding at diagnosis, 25 (71%) patients had hepatosplenomegaly, which was massive enough to cause abdominal distention in 7 individuals (20%). Five patients (14%) had abnormal hematologic findings, i.e., thrombocytopenia, anemia or petechiae as their chief finding. Four patients (11%) principally experienced bone pain. Six (17%) patients (2, 6, 18, 23, 29, 31) were diagnosed by testing after diagnosis of a sibling. In all such cases, some signs of Gaucher disease sign were found.

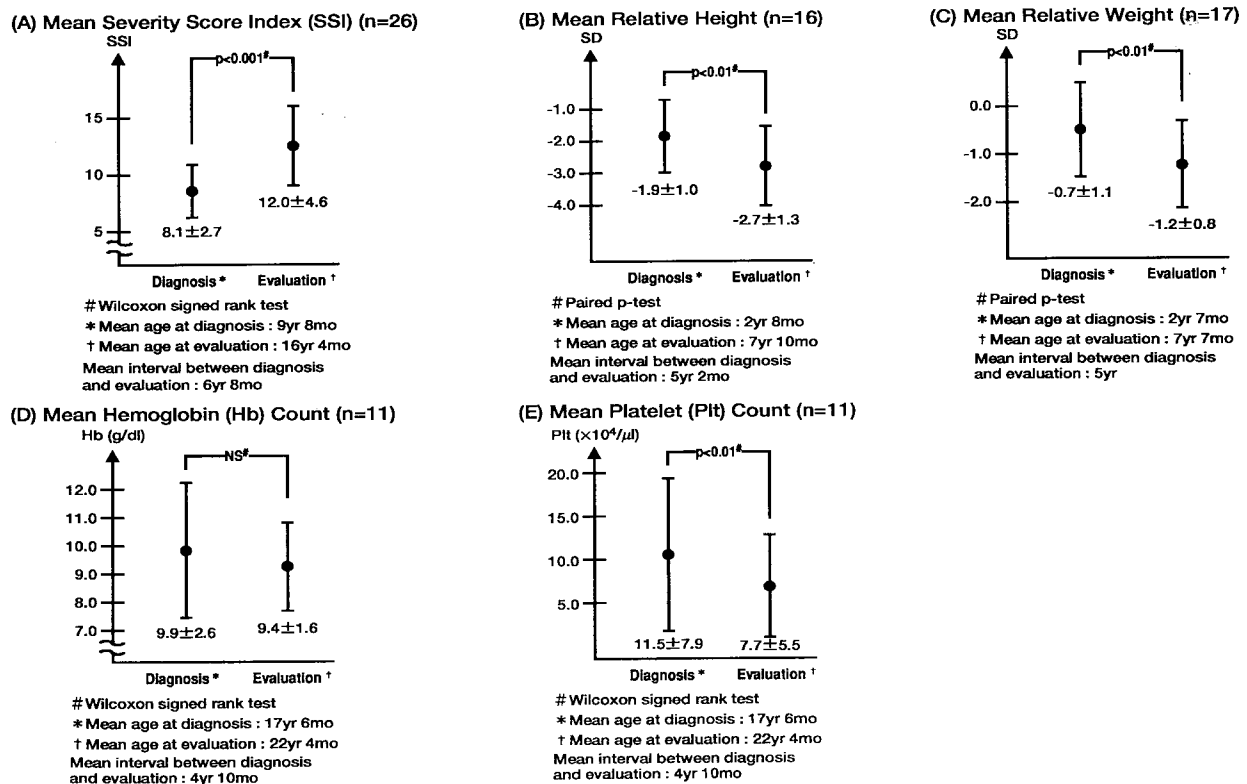


Figure 1. Natural history of Japanese patients with type 1 Gaucher disease: Statistical analysis of selected parameters.

Natural History of Type 1 Gaucher Disease in Japanese Patients (Figure 1)

To characterize the natural history of type 1 Gaucher disease in this series, we compared certain clinical and biochemical parameters at diagnosis and at evaluation/analysis. Within a mean interval of 8 years, 4 months \pm 7 years, 8 months for the entire series, 21 patients (60%) were splenectomized. Of these 21 patients, five (cases 8, 9, 12, 13 and 28; 24% of splenectomized patients; 14% of all patients) were splenectomized to facilitate diagnosis and to prepare for bone marrow transplantation. Sixteen (46%) patients developed severe bone involvement. In 26 evaluable patients, over a mean interval of 8 years, 1 month \pm 7 years, 5 months between diagnosis and evaluation/analysis, mean SSI increased from 8.1 ± 2.7 to 12.0 ± 4.6 . This increase was highly significant ($p = 0.0001$, Wilcoxon signed rank test) (Figure 1A).

In 16 evaluable pediatric patients, over a

mean interval of 5 years, 2 months \pm 3 years, 5 months between diagnosis and evaluation/analysis, mean relative height changed from -1.9 ± 1.0 SD to -2.7 ± 1.3 SD from healthy age-matched norms. This change was highly significant ($p = 0.0061$, paired t-test) (Figure 1B). In 17 evaluable pediatric patients, over a mean interval of 5 years \pm 3 years, 5 months, mean relative weight changed from -0.7 ± 1.1 SD to -1.2 ± 0.8 SD from healthy age-matched norms. This change also was highly significant ($p = 0.0083$, paired t-test) (Figure 1C).

In 11 evaluable non-splenectomized patients, over a mean interval of 4 years, 10 months \pm 5 years, 5 months, mean hemoglobin values worsened from 9.9 ± 2.6 g/dl to 9.4 ± 1.6 g/dl. This change was not significant ($p = 0.5771$, Wilcoxon signed rank test) (Figure 1D). Mean platelet counts worsened from $11.5 \pm 7.9 \times 10^4/\mu\text{l}$ to $7.7 \pm 5.5 \times 10^4/\mu\text{l}$. This change was highly significant ($p = 0.0078$, Wilcoxon signed rank test) (Figure 1E).

Japanese (n=35)	Age at Presentation/Diagnosis	Non-Japanese (n=53)
1	< 1 year	1
24	1 ~ 5 years	17
4	6 ~ 10 years	10
1	11 ~ 25 years	6
4	26 ~ 50 years	12
1	51 years >	7

Figure 2. Age at presentation/diagnosis of Japanese and non-Japanese patients. The data on non-Japanese patients as from Zimran et al. (8).

Japanese Versus Non-Japanese Patients; Age of Onset (Figure 2)

We compared age of onset of signs/symptoms in our series versus that reported in the series of Zimran et al. (8). The Zimran series comprised 53 American patients with Gaucher disease type 1: 24 males, 29 females, 9 children and 44 adults. Thirty-nine (74%) were Ashkenazic Jewish, 1 (2%), half Ashkenazic Jewish. The age of onset was <5 years in 25 (71%) Japanese patients, whereas it revealed two peaks in the American patients. In 18 (34%) cases, the age of onset was ≤5 years and in 19 (36%) cases, it was >26 years.

Japanese Versus Non-Japanese Patients; Disease Severity in the Pediatric Population (Table 2)

To exclude the influence of age distribution, we compared pediatric patients in our series with

those of Zevin et al. (7). This Israeli series comprised 34 pediatric patients with Gaucher disease, 18 males and 16 females, 26 (76%) of whom were Ashkenazic Jewish and 4 (12%), part Ashkenazic Jewish.

Frequency of splenectomy and of severe bone involvement was 57% and 39% in 23 evaluable Japanese patients, respectively, versus 9% each in the 34 Israeli patients. Among 19 evaluable Japanese patients, 14 (74%) were below the 3rd percentile, i.e., severely growth-retarded, in height. Among the Israeli patients, height also was stunted, but less severely than in our series: 10 (33%) of 30 evaluable patients were below the 3rd percentile. Severe growth retardation in weight, however, was less prevalent in the Japanese [2 (10%) of 20 evaluable patients] than in the Israeli series [8 (26%) of 31 evaluable patients]. Mean SSI at evaluation was over 2 points higher in 20 evaluable Japanese than in 34 evaluable Israeli children.

Table 2. Pediatric Patients with Type 1 Gaucher Disease. Japanese versus Non-Japanese Series

Japanese	Parameter	Non-Japanese (7)
13/23(57%)	Number (percentage) of splenectomized patients	3/34(9%)
9/23(39%)	Number (percentage) of patients with severe bone involvement*	3/34(9%)
	Number (percentage) of patients with severe growth retardation†	
14/19(74%)	height	10/30(33%)
2/20(10%)	weight	8/31(26%)
12.8	Mean severity score index‡ at evaluation/analysis	10.6
(n=20)	(number of patients)	(n=34)

*Severe bone involvement=presence of avascular necrosis or fracture.

†Severe growth retardation=parameter below the 3rd percentile for age group.

‡Severity score is calculated according to reference 9. Degree of severity correlates with higher score.

DISCUSSION

The present series would appear to comprise the vast majority of Japanese patients known to have type 1 Gaucher disease. Four factors render this series particularly representative of this patient population. First, in a country where 1226G, the major mutations associated with more mild disease, never have been documented (3, 4), few Gaucher disease patients are likely to remain free of disease manifestations. Indeed, "asymptomatic" cases may occur almost exclusively in 1226G homozygotes (10). Second, the Japanese health care system, with its very strong emphasis on preventive medicine, would tend to detect most patients with hepatosplenomegaly, hematologic abnormalities or other Gaucher disease findings. Third, our group is unlikely to remain unaware of many Gaucher disease cases in Japan, since only our laboratory can perform genotyping in Japan. And fourth, with 35 patients, the size of this series is in line with a 1996 Health Ministry survey that identified at least 50 surviving patients with Gaucher disease of any type in Japan. For these reasons, generalizations can be made with some confidence from observations in this series.

Our data clearly demonstrate that type 1 Gaucher disease tends to be severe and progressive in Japanese patients. Over 70% of our series had signs or symptoms of the disorder at <5 years of age, and 14% (5 of 35) had fatal disease (6). Within a mean follow-up of just 8 years, 4 months, 60% of the series had been splenectomized, and 46% had developed severe bone involvement. Within shorter follow-up intervals, mean relative height and weight, mean SSI and mean platelet count all worsened to a highly significant degree.

The severity of type 1 Gaucher disease in the Japanese population is underlined by comparison of the phenotypical characteristics of our series with those of an American (8) and an Israeli series (7). Both these series largely (>70%) comprise Ashkenazic Jews, in whom Gaucher disease may be relatively mild. On average, age

at presentation is younger, physical growth in height is more retarded, incidence of splenectomy or severe bone involvement is greater, and SSI is higher in the Japanese than in the non-Japanese series.

The increased severity of type 1 Gaucher disease in our patients at least in part may be attributable to the apparent absence of the 1226G allele in Japan (3, 4). This mutation may protect against neurologic involvement, and 1226G homozygotes tend to have a later onset -- by two to three decades -- and a milder course of disease than patients with other genotypes (10). Patients with other genotypes generally have much more severe disease with hepatic, splenic and osseous involvement, as well as a higher incidence of splenectomy at an earlier age. Although our series exhibited marked molecular heterogeneity, with at least 15 genotypes and 12 alleles, >70% of patients had at least one 1448C allele, which has been linked to more severe phenotypic expression.

Enzyme replacement therapy with the placental preparation α glucosidase (Ceredase, Genzyme Corporation, Cambridge, MA, USA) or the recombinant preparation imiglucosidase (Cerezyme, Genzyme Corporation, Cambridge, MA, USA) has been shown to arrest or reverse hematologic, visceral and skeletal involvement, to diminish physical growth retardation and to improve quality of life in patients of a variety of genotypes, ethnicities and ages (11-14). In a much more limited number of individuals, bone marrow transplantation also has ameliorated type 1 Gaucher disease manifestations (2, 15). However, this procedure is expensive and entails considerable problems of donor availability, morbidity and mortality. Therefore, in light of the efficacy, safety and lesser invasiveness of enzyme replacement therapy, bone marrow transplantation may have a limited role in type 1 Gaucher disease (16).

In view of the high cost of enzyme replacement therapy and the clinical heterogeneity of type 1 Gaucher disease, varying criteria have been proposed for starting treatment. Some

investigators have suggested administering enzyme replacement therapy to patients with advanced bone or marked visceral involvement or pulmonary disease (17). Others have proposed treating all symptomatic patients, including those with anemia, thrombocytopenia, leukopenia, spleno- or hepatomegaly, lung or clinical or severe radiologic bone involvement, and have suggested strongly considering enzyme replacement therapy in all pediatric patients with any sign of bone involvement (16). Based on earlier studies (6), we have advocated early, vigorous treatment for patients with a 1213G allele, liver or lung involvement, dyspnea or clubbing or history of splenectomy. Based on the data from this series, we conclude that most Japanese patients would be suitable for treatment, and indeed, might require earlier and more aggressive therapy.

In summary, in this communication, we demonstrated the severe and progressive nature of type 1 Gaucher disease in Japanese patients, as well as the importance of conducting and considering studies of phenotype and natural history in particular patient populations in developing treatment strategies for this genetic disease.

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