Genetic and clinical characteristics of Filipino patients with Gaucher disease

Mary Anne D. Chiong, Marie Julianne C. Racoma, Mary Ann R. Abacan

Institute of Human Genetics, National Institutes of Health University of the Philippines Manila, Philippines
Department of Pediatrics, Philippine General Hospital, Manila, Philippines
University of Santo Tomas, Manila, Philippines
Newborn Screening Reference Center, National Institutes of Health, University of the Philippines, Manila, Philippines

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ABSTRACT

Gaucher disease (GD) is a lysosomal storage disorder caused by the deficiency of the β-glucocerebrosidase enzyme due to disease causing mutations in the GBA1 (glucosidase beta acid) gene, leading to the abnormal accumulation of the lipid glucocerebroside in lysosomal macrophages. This is a review of the clinical features and molecular profiles of 14 Filipino patients with GD. Five patients presented with type 1 disease, two had type 2 GD and seven had type 3 GD. The age of onset for all types was between 1 and 2 years of age but there was a delay of 2.2 years from the time of symptom onset to confirmation of diagnosis. Hepatosplenomegaly, anemia and thrombocytopenia were present in most of the patients. Stunting was seen in 63.6% and bone abnormalities were present in 63.6%. The most common mutant allele detected in this cohort was L483P (previously L444P), followed by F252I, P358A and G241R. IVS2+1 G > A, N409S and G416S mutations were reported singularly. There were 3 patients who were found to have N131S mutations and one patient with D257V mutation, mutant alleles that have only been reported among the Filipinos to date. Except for N409S, the mutations found in this cohort were generally severe and were congruent with the severe phenotypes found in most patients. Of the 14 patients, only 6 were able to undergo enzyme replacement therapy which significantly improved the hematologic parameters and decreased the sizes of the liver and spleen but did not consistently improve the growth and skeletal abnormalities nor alleviate the neurological manifestations of our patients with GD. Improved monitoring through recommended modalities for assessments and tools for evaluation should be implemented in order to fully appreciate the severity of the disease and accuracy of the response to treatment.

1. Introduction

Gaucher disease (GD) is a multisystemic disorder that results from the accumulation of undegraded glucocerebroside in lysosomes of tissue macrophages due to the deficiency of the enzyme β-glucocerebrosidase (EC 3.2.1.45) [1]. The deficiency of the enzyme is caused by autosomal recessive mutations in the GBA1 (glucosidase beta acid) gene located on chromosome 1 (1q21) [2].

Gaucher disease is traditionally classified into three broad phenotypic categories: Type 1, a non-neuropathic disease ranging from asymptomatic subjects to those who display childhood-onset disease. Type 2 GD is an acute neuroopathic form characterized by the early appearance of visceral signs, oculomotor abnormalities, brainstem involvement and limited survival to the first two or three years of life. Type 3 GD is a chronic neuroopathic disease characterized by neurologic symptoms that appear later in life. The appreciation that patients with type 1 may develop late-onset neurologic manifestations suggest that GD is a continuum of disease states [3,4].

The incidence is 1/40,000 to 1/60,000 births in the general population, but it can reach 1/800 births in the Ashkenazi Jewish population [5]. The diagnosis relies on the measurement of β-glucocerebrosidase activity in leukocytes, fibroblasts or the recently developed screening tool using dry blood spots. Almost 300 mutations and polymorphisms in GBA1 gene have been identified [6]. Treatment with macrophage-targeted mannose-terminated glucocerebrosidase enzyme replacement therapy (ERT) is the standard of care for patients with type 1 and 3 Gaucher disease [6]. Oral substrate reduction therapy in the form of Eliglustat has likewise been found to produce significant improvements in spleen and liver sizes, hematologic parameters, bone mineral density and disease biomarkers among adult patients with Gaucher disease type 1 [7].

In this review, we describe the clinical features, laboratory parameters and molecular characteristics of 14 Filipino patients with Gaucher disease, as well as the hematologic, skeletal, growth and neurologic responses of 6 patients who have undergone ERT.
2. Methods

2.1. Subjects

This study involved chart reviews of 14 Filipino patients confirmed to have Gaucher disease from 2003 to July 2017. The diagnosis was based on clinical findings and confirmed by low β-glucocerebrosidase activity in peripheral leukocytes or dried blood spots. The enzyme measurement was done at the National Taiwan University Hospital from 2004 to 2017. The first 2 patients diagnosed in 2003 had enzyme assays done at the National Referral Laboratory of the Women’s and Children’s Hospital in Adelaide Australia. The data during initial and follow up evaluations were gathered up to the latest month/year of consult. This study was approved by the institution’s ethical review board (2017-265-01).

2.2. Clinical characteristics

Data on the patients' anthropometrics, date of birth, date of diagnosis, date of the first symptoms and clinical features such as neurologic signs and organ measurements were obtained from the medical records of the Philippine General Hospital and the Institute of Human Genetics, National Institutes of Health-Manila (IHG-NIH). Hematologic, biochemical parameters and results of the ancillary investigations were also reviewed.

2.3. Mutation studies

Twelve patients who are enrolled in RegistryNXT (https://www.registynxt.com/) for Gaucher disease had the opportunity to have mutation testing done at the Molecular Development Laboratory of the University of Washington, USA after the families have undergone an informed consent process and pre genetic counseling at IHG-NIH. Sanger dideoxy sequencing of the entire coding region of the glucocerebrosidase (GBA1) gene was the reported method used for the identification of mutations. Post genetic counseling was given by geneticists at IHG-NIH upon receipt of the mutation results.

2.4. Method of data analysis

Quantitative patient characteristics are summarized by means and standard deviations (SDs). Qualitative characteristics such as clinical features and skeletal findings are presented as a frequency distribution.

3. Results

3.1. Demographic, clinical and laboratory characteristics

There were 14 patients with 3 sibling pairs from non-consanguineous pedigrees. There were 3 males and 11 females with ages that ranged from 1 month to 21 years. All were Filipinos except for Patient 12 and Patient 14. Five had type 1 disease who had no neurologic involvement at diagnosis and pre genetic counseling at IHG-NIH. The mean age of onset of clinical manifestations for type 1 ranged from 1 month to 21 years. All were Filipinos except for Patient 12 and Patient 14. Five had type 1 disease who had no neurologic involvement at diagnosis and pre genetic counseling at IHG-NIH. The mean age of onset of clinical manifestations for type 1 was 1.12 years (SD 0.56; 0.5–2 years) and the mean age for the confirmation of diagnosis was 3.35 years (SD 2.1; 0.25–5.5 years). For type 3, the mean age of onset of the signs and symptoms was 1.7 years (SD1.19; 1–4 years) and the diagnosis was confirmed at a mean of 3.9 years (SD 1.5; 2–6 years). Overall, it took an average of 2.2 years from the onset of clinical manifestations to confirmation of diagnosis for all types.

Hepatosplenomegaly as an initial presentation was seen in 12 patients (85.7%) while 2 patients presented with splenomegaly alone.
There was a delay of 1.2 years from the time of diagnosis to initiation of enzyme replacement therapy (ERT). Two had type 1 GD and 4 had type 3 GD. Two patients with type 2 GD and 1 with type 3 GD had no skeletal survey done.

Table 2
Distribution of signs and symptoms according to the type of GD.

| Signs and symptoms                  | Type 1 (n = 5) | Type 2 (n = 2) | Type 3 (n = 7) | Total |
|-------------------------------------|---------------|---------------|---------------|-------|
| Hepatosplenomegaly                  | 5             | 1             | 6             | 12 (85.7%) |
| Splenomegaly alone                  | 0             | 1             | 1             | 2 (14.2%)  |
| Hematological                       | Pallor        | 5             | 2             | 6     | 13 (92.8%) |
|                                    | Bleeding      | 2             | 1             | 3     | 6 (42.8)   |
| Eye findings                        | Strabismus    | 0             | 1             | 3     | 4 (28.5%)  |
|                                    | Gaze Initiation Defect | 0 | 1 | 4 | 5 (35.7%) |
| Neurologic                          | Seizures      | 0             | 0             | 5     | 5 (35.7%)  |
|                                    | Developmental delay | 0 | 1 | 5 | 6 (42.8%) |
|                                    | Intellectual disability | 0 | 0 | 4 | 4 (28.5)  |
| Failure to thrive                   | 1             | 0             | 4             | 5     | 5 (35.7%)  |
| Fatigue                             | 2             | 0             | 4             | 6 (42.8) |
| Bone Fracture                       | 0             | 0             | 1             | 1 (7.1%)  |
| Bone Pain                           | 0             | 0             | 1             | 1 (7.1%)  |
| Radiologic Bone Abnormalitiesa      | 3             | 0             | 4             | 7 (53.6%) |
|                                    | Erlenmeyer flask deformity | 3 | 2 | 5 (45.4%) |
|                                    | Osteopenia    | 1             |               | 1 (6.7%)  |
|                                    | Lytic changes | 1             |               | 1 (6.7%)  |
|                                    | Fracture      | 1             |               | 1 (6.7%)  |

* Two patients with type 2 GD and 1 with type 3 GD had no skeletal survey done.

(Patients 9 and 14). Hepatosplenomegaly was accompanied by bleeding in 1 patient (7.1%), pallor in one (7.1%) and neurologic symptoms in 3 patients which manifested as either developmental delay, esotropia or seizures (21.4%). Of the type 2 patients, patient 13 presented with ocular abnormalities, hyperextension of the neck, developmental regression, microcephaly, spasticity, and tonic clonic seizures apart from hepatosplenomegaly. She succumbed at 2.5 years of age. Patient 14 had colloidon ichthyosis at birth accompanied by hepatosplenomegaly, anemia and thrombocytopenia. He died at 2 months of age due to massive bleeding. At baseline, 9 (64.3%) patients were stunted (height for age z score – 2) and 5 (35.7%) were underweight (weight for age z score – 2). Patients 9 and 10 were splenectomized before the confirmation of diagnosis. The distribution of other clinical manifestations are in Table 2.

The initial mean hemoglobin for all types was 85.3 g/L (SD 35; range 10.9–16.4) and mean platelets were at 93 × 109/L (SD 75; range 27 – 144.0). ALT was slightly elevated in 2 of the 12 (16.7%) (Table 3). None were tested for hepatitis virus infection.

Table 3
Summary of baseline laboratory findings.

| Laboratory Parameters | Frequency | Mean | SD  | Min | Max |
|-----------------------|-----------|------|-----|-----|-----|
| Hemoglobin (g/L)      | 14        | 85.3 | 35.0 | 53.0 | 164.0 |
| Type 1                | 5         | 84.2 | 15.9 | 66.1 | 109.0 |
| Type 2                | 2         | 144.0 | 28.3 | 124.0 | 164.0 |
| Type 3                | 7         | 83.3 | 19.3 | 53.0 | 108.0 |
| Platelet (×10^9/L)    | 14        | 92.9 | 75.4 | 9.0  | 228.0 |
| Type 1                | 5         | 121.6 | 96.7 | 9.0  | 226.0 |
| Type 2                | 2         | 71.0 | 37.0 | 45.0 | 97.0  |
| Type 3                | 7         | 78.6 | 69.2 | 31.0 | 228.0 |
| WBC (×10^9/L)         | 14        | 8.0  | 4.9  | 2.7  | 19.7  |
| Type 1                | 5         | 9.2  | 7.0  | 3.2  | 19.7  |
| Type 2                | 2         | 12.6 | 0.4  | 12.3 | 12.9  |
| Type 3                | 7         | 5.9  | 2.8  | 2.7  | 10.1  |
| AST (IU/L)            | 12        | 103.2 | 130.9 | 24.0 | 513.0 |
| Type 1                | 3         | 89.9 | 5.3  | 84.0 | 94.0  |
| Type 2                | 2         | 291.0 | 313.9 | 69.0 | 513.0 |
| Type 3                | 7         | 55.1 | 21.3 | 24.0 | 91.0  |
| ALT (IU/L)            | 12        | 32.3 | 9.2  | 22.1 | 50.0  |
| Type 1                | 4         | 32.3 | 11.9 | 24.0 | 50.0  |
| Type 2                | 1         | 24.0 | –    | –    | –     |
| Type 3                | 7         | 33.5 | 8.5  | 22.1 | 49.0  |
| Chitotriosidase nmol/ml/ b<sup>-1</sup> | 8          | 11,138.5 | 11,185.0 | 322.5 | 27,128.9 |
| Type 1                | 3         | 17,238.8 | 14,448.1 | 658.9 | 27,128.9 |
| Type 2                | 2         | 10,888.0 | 14,924.2 | 322.5 | 21,454.0 |
| Type 3                | 3         | 5204.1 | 2959.4 | 2344.4 | 8253.9 |

* Chitotriosidase done in 12 patients but 4 were noted to have CHIT gene duplication.

ERT. The mean age of starting ERT was 4.1 years (SD 1.1; 2.6–5.5 years) with a mean dose of 58.3 units/kg (SD 4.1). The mean duration of ERT at the time of this report was 6.45 years (SD 5.52; 0.08–14 years). Three patients (Patients 4, 5 and 6) died of pneumonia while on the 3rd year, 4th year and 1st month of ERT respectively. Two of the 6 patients, Patients 1 and 2, achieved normal growth parameters during the 2nd and 1st years of ERT respectively. One patient had normal height at the outset (Patient 5). Patient 3 who is on the 6th year of treatment continues to be stunted as of this report. Patients 4 and 6, who died while receiving treatment, did not achieve normal height. Normal hemoglobin [10] was achieved in Patients 1–5 at a mean of 7.8 months after initiation of ERT (SD 6.06). Patient 6 who died 1 month after ERT initiation had no normalization of hemoglobin. Platelet count increased by 1.5% in patients 1–5 at a mean of 6.2 months (SD 5.8), but normal
levels (150–350 × 10^9/L) were achieved in only 4 of them at a mean of 18 months (SD 5.03). Patients 5 and 6 remained to have low platelet counts at the time of their demise. Patients 1 and 2 achieved normal splenic volumes at a mean of 4.2 years (SD 2.2). Patient 3 had a 50% decrease in spleen volume after 3.75 years of treatment, however she remains to have an enlarged spleen even while on the 6th year of treatment. Patient 4 and 5 had enlarged spleen at the time of demise. All five patients achieved normal liver size by physical examination and ultrasound at a mean of 4.9 years after starting ERT (SD 2.8). Patients 1, 2 and 5 developed thoracic scoliosis while on the 14th, 12th, and 5th year of treatment respectively. Patients 3 and 4 still showed Erlenmeyer flask deformity after 6 and 2 years of ERT respectively.

There was note of increase in the frequency of seizures in two patients on ERT (Patients 4 and 5), while stabilization was seen in two (Patients 1 and 2). There was evolution of seizures to myoclonic jerks for Patient 4 on the 7th month of ERT. Patient 2 had cholelithiasis on the 11th year of treatment.

3.2. Mutation analysis of the GBA gene

Using the current nomenclature for GBA1 mutations from the Human Genome Variation Society (http://varnomen.hgvs.org/), the most common mutant allele was L483P (previously L444), followed by F252I, P358A and G241R. IVS2 + 1 G > A, N409S, R159W and G416S mutations were reported singularly. There were 3 patients who had the N131S mutation, a mutant allele that has only been reported among the Filipinos. Another novel mutation D257V was seen in one patient. The reported severe mutations L483P, F252I, G241R, G416S, R159W and IVS2 + 1 G > A were seen in patients with Types 2 and 3 disease (Table 1). However, the 2 patients homozygous for F252I (Patients 3 and 7) are clinically presenting with type 1 disease. N409S was found in patient 12 with Type 1 disease. The novel mutations N131S and D257V were found in patients who had Types 2 and 3 disease. Two patients (Patients 6 and 11) were not able to undergo mutation testing. They were classified to have type 1 disease; however, the possibility that they had severe mutations could not be discounted as their early demise and severe manifestations implied a possible type 3 GD.

4. Discussion

This is the first review done among Filipino patients with Gaucher disease. The age of onset of clinical manifestations is in keeping with what has been reported in the literature. Most patients with type 1 disease have onset during the first decade of life, while patients with type 3 present at around 12 months old [11]. Despite early manifestations, diagnostic delay is one of the most significant observations in this study. Majority had severe manifestations early but the delay in diagnosis was most probably due to the failure to include GD in the differential diagnosis because of lack of awareness. Another reason could be the lack of local facilities for patients with rare diseases that can comprehensively assess these patients.

Hepatosplenomegaly was seen as the most common finding across all types in association with hematologic and bone abnormalities and is congruent with what have been reported in previous studies [12,13]. Many of our patients presented with near normal liver function. The neurologic, ocular and other manifestations of our patients with types 2 and 3 GD are likewise similar with other registry reports [11,14,15].

The stunting in our patients could be due to the large mass of Gaucher’s cells in the liver and spleen which exert an excessive metabolic burden leading to higher resting energy expenditure and increase in caloric requirements which manifested as a height-for-age z score less than zero [16]. The reported bone abnormalities such as osteopenia and lytic lesions are related to the accumulation of Gaucher cells in the bone marrow which lead to vascular occlusion and localized bone defects [1,4].

The results of β glucocerebrosidase assay did not reliably enable prediction of disease severity or subtype [17]. Some of our patients who were classified as having a milder disease even had lower levels than patients with severe types. Our patients who had elevated chitotriosidase reflect the presence of lipid-laden macrophages due to GD [18]. However due to limited resources, this was not utilized to monitor the response to therapy. Four patients who were deficient in chitotriosidase were assumed to have the common 24 bp duplication polymorphism in the CHIT gene which is reported to be highest among Asians [19]. It was observed from the laboratory parameters of the 14 patients that hemoglobin levels for types 1 and 3 were almost similar, but platelets and WBC were higher in type 1. There is usually a significant correlation between the degree of splenomegaly and cytopenias but this proved to be clinically negligible [20]. It is difficult to make observations for other parameters according to type because of the small number of affected patients.

Only 6 of our patients were able to avail of compassionate ERT. Normal hemoglobin was achieved at an average of 7.8 months and is in keeping with a reported collaborative study that anemic patients usually normalized within 6–12 months [21]. All patients who underwent ERT had severe thrombocytopenia (< 120,000/μL) at baseline which improved 1.5 fold at a mean of 6 months. It is expected that platelet counts increase to 1.5-fold by year 1, and continue during the next 2 to 5 years, however restoration to normal is not usually expected [22]. The 2 patients who did not achieve normal platelets had significant splenomegaly at baseline. Although liver and spleen volumes were not routinely done during treatment monitoring, the liver sizes for 5 patients fell within the observed timeline for improvement of 5 years [23]. The decrease in spleen sizes have not been uniform among our patients on ERT. Three patients had slower response which could be due to prior splenic infarctions or fibrosis [23]. None had bone crisis or bone pain among our patients on ERT. However, 3 patients developed thoracic scoliosis and 2 were still found to have Erlenmeyer flask deformity years after initiating ERT. It has been reported that after 2 to 4 years of ERT, bone involvement improved in 30% to 40% of pediatric patients while there was progression in < 5% [22]. The scoliosis could be linked to abnormal bone density [24].

Cholelithiasis seen in Patient 2 has been reported to have increased prevalence in GD due to bile acid composition abnormalities [15]. The neurologic symptoms of our patients, as with other reports [25–27] were not reversed by ERT because the enzyme does not cross the blood-brain barrier.

The most common mutation seen in our population, L483P, is a mutation known to cause a severe disease [28–30]. It is also the most common mutation seen in other Asian populations [31–33]. In these populations, this mutant allele was associated with types 1,2 and 3 phenotypes in heterozygous or homozygous forms. In two of our patients who are siblings (Patients 1 and 2), L483P was seen in heterozygous combination with a rare allele P358A (previously P319A) of unknown severity [31]. Since these 2 patients presented with a chronic neurogenopathic phenotype, P358A can be classified as severe. Patient 5 who had type 3 disease also had a severe allele G241R (previously G202R) in association with L483P. The parents’ genotype showed that the father is a carrier for L483P/wild type while the mother has G241R/wild type. The L483P and G241R mutations are known to occur in cis, and this is likely the case in this patient thereby accounting for the two G241R mutations as well as L483P. The “gene conversion” event between the active gene and pseudogene has probably been in the paternal side of the family for generations. G241R mutation destroys a NeI restriction site in the GBA gene and has been reported in a patient who died of type 2 disease [28]. Patient 12 who had L483P as an heteroallele together with N409S (previously N307S) had a type 1 disease. N409S is known to be mild and even a severe or lethal mutation inherited with it results in type I disease [28,34]. F252I (previously P213I) is a severe mutation seen among Asians with types 2 or 3 disease. Patients homozygous or heterozygous for this mutant allele presented primarily with oculomotor apraxia and mental retardation.
had type 2 GD was a heterozygote for a splicing null mutation IVS β

families from the ICGG Gaucher registry, Am. J. Hematol. 86 (1) (2011) 110–115.

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