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Outcome of early-treated type III Gaucher disease patients

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ABSTRACT

Recombinant human acid β-glucosidase GBA (rhGBA) infusion is an effective therapy for non-neuropathic (type I) Gaucher disease (GD), but its effect on subacute neuropathic (type III) GD is still controversial. The most common genotype for type III GD is homozygous c.1448T>C (p.L444P) mutation, and in this study, we treated seven such patients starting from an early age (median 2.1 years; range 1–2.9 years). Before the start of treatment, all patients presented hepatosplenomegaly, anemia, and thrombocytopenia, but with no neurological signs. Normalization of hemoglobin levels and platelet numbers was achieved in all patients in one year. However, after a median treatment period of 7.6 years (2.2–12.0 years), two patients developed horizontal gaze palsy, one had seizures, four demonstrated mental retardation, and five showed kyphosis. Moreover, lymphadenopathy in the neck, thorax, or abdomen was observed in four patients. Therefore, the progression of neurological symptoms in these patients probably reflected the neurologic natural history of type III GD. Residual somatic symptoms, including kyphosis and lymphadenopathy, may be more common than what we thought. An additional treatment will be necessary to improve the outcome of type III GD.

Introduction

Gaucher disease (GD) is a sphingolipid storage disease, resulting from a deficiency in β-glucocerebrosidase (EC 3.2.1.45, acid β-glucosidase, GBA) activity [1]. A deficiency in GBA leads to accumulation of glucocerebroside in macrophages (Gaucher cell) in the bone marrow, liver, spleen, and brain. GD can be classified into 3 clinical types: type I, or the non-neuropathic form (MIM #230800); type II or the acute neuropathic form (MIM #230900); and type III, or the subacute neuropathic form (MIM #231000) [2]. Patients with type I GD usually manifest hepatosplenomegaly with or without bone deformity/crisis during adulthood. Enzyme replacement therapy (ERT) with recombinant human GBA (rhGBA) is an effective treatment for type I GD, which reduces hepatosplenomegaly, increases hemoglobin levels and platelet count, and increases bone mineral density [3]. Patients with type II GD typically exhibit neurodegeneration and hepatosplenomegaly before one year of age. ERT does not prevent neurodegeneration [4], and most type II GD patients die before early childhood.

Type III GD was originally reported from the province of Norrbotten in Sweden. At that time these patients exhibited both visceral and neurological manifestations from childhood to death which commonly occur before they reach adulthood [5], but now they respond to ERT with increased well-being [6]. The causative *GBA* gene mutation is c.1448T>C (p.L444P) [7]. Type III GD patients with myoclonic epilepsy and other *GBA* gene mutations were also reported [8]. The p.L444P mutation is the predominant mutation in type III GD [9–11]. Patients with homozygous p.L444P mutation frequently manifested severe systemic involvements but only mild neurological abnormalities including supranuclear horizontal gaze palsy and/or other eye symptoms, mental retardation, and seizures. These patients have also been classified as having type IIIB GD [12],

Abbreviations: GD, Gaucher disease; GBA, acid β-glucosidase; ERT, enzyme replacement therapy.

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as a means to differentiate them from the earlier recognized type III patients (now defined as type IIIA) and patients with progressive heart valve calcification (type IIIC) [13].

Although rhGBA infusion is an effective therapy for type I GD, effects of ERT on type III GD patients were variable. The European Task Force for Neuronopathic GD has reviewed the largest cohort (55 patients) of type III GD (40 with homozygous p.L444P mutation) [14]. However, there was considerable variation in the dose of ERT, as well as an uneven distribution of risk factors including age, genotype, and splenectomy.

In this study, we described seven type III GD patients who had a homogeneous genetic background (homozygous p.L444P mutation). We treated these patients from an early age but found that their neurological symptoms developed gradually. Residual somatic symptoms, including kyphosis and lymphadenopathy, are also common.

Methods

GBA activity was measured by 4-methylunbellyferal substrates, as previously described [15]. Genotyping was performed as described in our previous publication [9]. A total of seven GD patients who were homozygous for the p.L444P mutation were analyzed in this study (Table 1). Patient 2 was born prematurely at gestational age 29 weeks with a birth weight of 1340 g. The median age of the seven patients at diagnosis was 1.9 years and the median age at the start of ERT with Cerezyme® (Imiglucerase) was 2.1 years (Table 1). The dose of ERT used was 60 U/kg/2 weeks, with the exception of patient 2, whose dosage was increased to 120 U/kg/2 weeks when lymphadenopathy was found. The median treatment period was 7.6 years. Follow-up examinations of these patients were performed according to the recommendations from the Gaucher Registry, including regular studies for hemogram, chitotriosidase activity, CCL18 levels, the skeletal system, sizes of the visceral organs, and mentality. The degree of thoracic kyphosis was estimated by the traditional Cobb angle measured on lateral spine radiographs, and the definition of kyphosis was an angle ≧45°. An intelligence quotient (IQ) was obtained by using the Wechsler Intelligence Scale for Children. Data are presented as the means ± standard deviations. Statistical analyses were performed using the SPSS statistical package, version 11.5. The Wilcoxon signed rank test was applied for statistical analysis before and after treatment. A p value less than 0.05 was considered statistically significant.

Results

Somatic responses to ERT

Hepatosplenomegaly and thrombocytopenia were observed in all patients at the time of diagnosis, and five patients (except patient 6 and 7) showed failure to thrive (Table 1). The mean HgB level increased from 8.6 ± 1.6 (g/dl) to 12.4 ± 0.77 (g/dl) after 1 year of treatment ($p = 0.028$). The platelet count increased from 89.32 ± 31.971.6 (k/cumm) to 215.94 ± 33.58 (k/cumm) after 1 year of treatment ($p = 0.028$). After a median treatment period of 7.6 years (2.2–12.0 years), none of them had an enlargement of the liver or spleen. Chitotriosidase activity decreased adequately in response to ERT, though a transient rise of chitotriosidase activities was noted during the period of drug shortage [15]. None of the 7 patients had bone crisis or avascular necrosis of the hip during the follow-up period. Bone mineral density measured using dual-energy X-ray absorptiometry revealed osteopenia ($Z < 1$) only in patient 2 ($Z = -4.1$) and patient 3 ($Z = -1.8$).

However, at the latest follow up, four (patients 1–4) showed short stature and three (patiens 2, 3, and 6) had a low body weight. Moreover, five of the seven patients exhibited kyphosis, although none of them complained of pain or discomfort (Table 1). Their spines felt rigid during physical examination, and patient 2 showed an acute angle over the thoracolumbar junction.

Progression of neurological symptoms

All patients, throughout the following period, had normal muscle power and muscle tone, normal deep tendon reflex, and no cerebellar sign. However, horizontal gaze palsy was observed in two patients (patients 2 and 5), although this symptom did not interfere with the daily activity of the patients. Patient 7 exhibited absence seizures since 10 years of age. Moreover, mild mental retardation was noted in patient 2 (FIQ 66), patient 5 (FIQ 55), and patient 7 (FIQ 70). Patient 1 had a borderline FIQ score (FIQ 88), but scores

Table 1
Clinical characteristics of p.L444P/p.L444P Gaucher disease patients.

Patient no.	1	2	3	4	5	6	7
Gender	M	M	F	M	F	F	F
Age at diagnosis	10 m	1 y, 2 m	2 y, 7 m	1 y, 10 m	1 y, 3 m	1 y, 9 m	2 y, 3 m
Age at ERT start	11 m	1 y, 2 m	2 y, 9 m	2 y	2 y, 1 m	2 y, 1 m	2 y, 4 m
GBA activity[a]	0.16	1.42	1.43	3.58	0.79	0.91	0.9
ERT dose (U/kg/2 weeks)	60	60[b]	60	60	60	60	60
Age at last survey	8 y, 5 m	4 y, 11 m	9 y, 2 m	4 y, 2 m	13 y, 5 m	14 y,1 m	13 y, 1 m
Hemoglobin (g/dl)[c]	12.5 ± 0.6	13.0 ± 0.5	12.6 ± 0.5	11.8 ± 0.2	13.1 ± 0.5	11.0 ± 0.6	13.0 ± 0.6
Platelet (k/cumm)	162.2 ± 31.7	182.6 ± 62.4	213.0 ± 41.9	228.0 ± 33.9	226.0 ± 45.9	260.7 ± 57.1	239.8 ± 69.9
BMD (age, Z score)	0.581 (8.1 y, −0.1)	0.345 (5.5 y, −4.1)	0.565 (9.6 y, −1.8)	0.502 (4.6 y, 0.5)	0.826 (14 y, −0.7)	1.123 (14.5 y, 0.2)	1.005 (13.6 y, −0.2)
Gaze palsy	−	+	−	−	+	−	−
Seizure	−	−	−	−	−	−	+
Mental retardation	− (FIQ 88)[d]	+ (FIQ 66)	−	−	+ (FIQ 55)	−	+ (FIQ 70)
Kyphosis (degree, age, area)	+ (48°, 7 y 5 m, thoracic)	+ (53°, 2 y 2 m, thoracolumbar)	−	−	+ (54°, 13 y 6 m, thoracic)	+ (45°, 14 y 2 m, thoracic)	+ (56°, 13 y, thoracic)
Lymphadenopathy[e]	+ (8 y 3 m, abdomen)	+ (3 y 6 m, neck, thorax, abdomen)	+ (7 y 8 m, thorax, abdomen)	+ (2 y, thorax, abdomen)	−	−	−

[a] GBA activity N > 5.1 nmol/mg/h.
[b] Increased to 120 U/kg/2 weeks when lymphadenopathy occurred.
[c] Hemoglobin and platelet values are mean ± (SD) after 1 year of treatment.
[d] Scores of Verbal Comprehension index (VCI) and Processing Speed Index (PSI) were below the normal ranges.
[e] Lymphadenopathy (age detected, location).