Assessment of Basal Metabolic Rate and Nutritional Status in Patients with Gaucher Disease Type III

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Abstract Gaucher disease type III (GD III) is a rare form of GD characterized by neurological involvement and severe systemic disease. The objective of this study was to assess the nutritional status and energy metabolism of patients with

GD III. **Methods:** The basal metabolic rate (BMR, measured by indirect calorimetry) and anthropometric parameters (height, weight, body mass index (BMI), and arm circumference) of three patients with GD III (p.L444P/L444P genotype) were assessed at different time points. The clinical severity of GD was assessed by means of physical examination, laboratory tests, imaging findings, and the severity scores proposed by Zimran (SSI) and Davies (SSNI). **Results:** The measured BMR of patients 1 (age 14 years, not on enzyme replacement therapy (ERT), SSI score 33, SSNI score 14.5), 2 (age 17 years, on ERT, SSI score 33, SSNI score 16), and 3 (age 20 years, on ERT, SSI score 33, SSNI score 7.5) was, respectively, 47%, 72%, and 15% higher than that estimated by the Harris–Benedict equation. Patients with a more severe phenotype had more marked hypermetabolism. Patients 1 and 2 had BMI-for-age z scores of -1.09 and -1.39 , respectively, and height-for-age z scores of -4.27 and -3.02 , respectively; patient 3 had a BMI of 24.7 kg/m^2 . **Conclusion:** All three patients showed hypermetabolism; however, the two patients with the highest BMR had more severe GD and were malnourished. Additional studies are warranted to assess whether hypermetabolism may be a biomarker of disease severity in GD.

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Abbreviations

BMR Basal metabolic rate
ERT Enzyme replacement therapy
GD Gaucher disease

Introduction

Gaucher disease (GD, OMIM 230800) is the most prevalent lysosomal storage disorder. It is the result of mutations in the

GBA gene, which codes for the enzyme glucocerebrosidase (GBA, EC 3.2.1.45), located on chromosome 1q21.31. GBA deficiency leads to a progressive buildup of its substrate, glucocerebroside, which in turn accounts for the clinical manifestations of Gaucher disease (Cox-Brinkman et al. 2008). Three forms of GD have been described: a) type I, the most prevalent form, characterized by visceral, hematological, and bone disease, with absence of neurological involvement; b) type II, or acute neuronopathic GD, with very early onset of clinical manifestations and major neurological involvement; and c) type III (OMIM: 231000), subacute or chronic neuronopathic GD, which is similar to type II but less severe (Schiffmann and Vellodi 2007).

Type III GD can be further divided into subtypes according to the nature and extent of neurological involvement: some patients have more severe neurological manifestations with progressive myoclonus epilepsy and mild visceral involvement (type IIIA), whereas others have severe visceral disease and oculomotor apraxia as the sole sign of neurological involvement (type IIIB) (Patterson et al. 1993). A third variant (type IIIC), characterized by oculomotor apraxia, moderately severe visceral involvement, and progressive cardiovascular calcifications, has also been described (Abrahamov et al. 1995). As GD III is even more rare than GD I, few patients have been studied, particularly with respect to nutritional status (Bembi et al. 1994; Erikson et al. 1995; Tylki-Szymanska and Czartoryska 1999; Altarescu et al. 2001). Assessments of the basal metabolic rate (BMR) of patients with Gaucher disease type III were not found in the literature.

The objective of this study was to assess the nutritional status and energy metabolism of patients with GD III treated at a reference center for Gaucher disease management in Rio Grande do Sul, Brazil.

Methods

This study included all three patients (two male, one female) with GD III followed at the Rio Grande do Sul State Referral Center for Diagnosis, Monitoring and Treatment of Gaucher Disease (CRDG), Brazil.

The diagnosis of GD had previously been established by the usual clinical, enzymatic, and molecular parameters. Energy metabolism was assessed by indirect calorimetry, performed between 7 and 9 a.m., after patients had been instructed to fast for 12 hours. The protocol recommended to all patients was the following: 8 hours of sleep, a restriction of physical activity and caffeine base products for 24 hours; 30 minutes of rest before the assessment; transportation by car; and assessment of gases for 30 minutes, discarding the first 10 minutes. All three patients underwent assessment in the same season. BMR was measured with a MedGraphics CPX-D breath-by-breath cardiopulmonary exercise testing

system, using manufacturer-recommended calibration and gas collection protocols, as well as the equation proposed by Weir (1949). Briefly, as the indirect calorimetry evaluates the respiratory quotient, there are 15–30 measurements per minute. Each patient was evaluated during 30 minutes, but the first 10 minutes were not taken into account, and the more stable period was chosen for analysis. Means were obtained after the exclusion of outliers. Results were converted into kcal/day and compared with BMR as estimated by the Harris–Benedict equation (Harris and Benedict 1919). Differences up to 10% between BMR and the values of Harris–Benedict equation were not considered clinically relevant because studies have reported that the reassessment of indirect calorimetry in healthy individuals can result in alterations by 3–5% when conducted after 24 hours or up to 10% when conducted after weeks or months (Compher et al. 2006).

Nutritional assessment was based on height-for-age and body mass index (BMI)-for-age z scores for the adolescent patients (1 and 2) and on BMI for the adult patient (3); arm circumference was measured in all three patients. The nutritional status was diagnosed in accordance with the World Health Organization guidelines (WHO 1995, 2006 and 2007) and arm circumference was measured as per Frisancho (1990). GD severity was assessed on the basis of the systemic involvement score proposed by Zimran et al. (1992) and the neurological severity score proposed by Davies et al. (2007). This study was approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee (project n. 08/204), and all patients (or their legal guardians) provided written informed consents for participation.

Results

All three patients present the p.L444P/L444P genotype, subtype 3b. A summary of the clinical profile of all three patients is shown in Table 1. Clinical, laboratory, and imaging findings were indicative of a more severe disease phenotype in patients 1 and 2 as compared to patient 3; this was corroborated by neurological examination. At the time of inclusion, patient 1 was untreated due to the development of allergic reactions to imiglucerase (Genzyme Corp., Allston, MA) after 10 years of enzyme replacement therapy (ERT) and taliglucerase alfa (Protalix, Carmiel, Israel) as well (Vairo et al. 2013). Patient 2 was on imiglucerase ERT (60 IU/kg/infusion), as was patient 3 (60 IU/kg/infusion until age 16 and 30 IU/kg/infusion thereafter). Patients 2 and 3 are siblings and had undergone splenectomy – at age 2.9 and 5.7, respectively – before starting ERT.

All patients had severe bone changes that hindered height measurement: Patient 1 had major thoracic kyphosis, thoracolumbar scoliosis, and coxa valga; Patient 2 had

Table 1 Summarized profile of patients with Gaucher disease type III included in this study

	Patient 1		Patient 2 ^a	Patient 3 ^a
	Assessment 1	Assessment 2		
Gender	Male		Male	Female
Genotype	p.L444P/L444P		p.L444P/L444P	p.L444P/ L444P
Age (years)	11.8	14.2	17	20
Age at start of treatment (years)	1.8 ^b		2.9	5.7
Treatment duration (years)	— ^{c1}	— ^{c2}	14	14
Imiglucerase dose (IU/kg/infusion)	—	—	60	30 ^d
Weight (kg)	26.1	29.7	42.7	56
Height (cm)	130.0	132.0	153.0	150.5
Body mass index (kg/m ²)	15.4	17.0	18.2	24.7
Splenectomy (Y/N)	No	No	Yes	Yes
Splenomegaly (Y/N)	Yes ^e	Yes ^e	—	—
Hepatomegaly (Y/N)	No	Yes ^e	No	No
Osteoporosis (Y/N) ^f	—	—	No	No
Respiratory involvement ^g	—	RLD + ILD	RLD + ILD	None
Respiratory rate (mean)	—	30	20	—
Hemoglobin (g/dL)	9.8	8.0	13.5	11.4
Platelets ($\times 10^3/\text{mm}^3$)	165	56	454	437
Chitotriosidase (nmol/mL/h).VR(a)	9939	19878	10409	10938
Albumin (g/dL)	—	2.9	4.3	4.6
SSI – Severity score ^h	25	33	33	33
SSNI – Neurological severity score ⁱ	—	14.5	16	7.5
Basal metabolic rate (kcal/kg/day)	43	51	52	28

— not measured/unavailable

^a Patients 2 and 3 are siblings

^b Patient discontinued enzyme replacement therapy after 10 years of treatment due to a severe allergic reaction (Vairo et al. 2013)

^c At the time of assessment, the patient had been off ERT for (1) 8 months; (2) 38 months

^d 60 IU/kg/infusion until age 16 and 30 IU/kg/infusion thereafter

^e Spleen and liver assessed by ultrasound (volume):

Spleen: 1 evaluation = 306.5 cm³; 2 evaluation = 2484.5 cm³

Liver: 1 evaluation = 2,169 cm³; 2 evaluation = 5,370 cm³

^f Assessed by bone density scanning. Not performed in patient 1

^g Characterized by restrictive lung disease (RLD, assessed by spirometry) and interstitial lung disease (ILD, assessed by computed tomography). Lung function tests (spirometry) of patient 1 showed mild, proportionate reduction of FVC and FEV1 and intact air flow at assessment 1, which had progressed to severe restrictive lung disease unresponsive to bronchodilator therapy by assessment 2

^h Zimran et al. 1992

ⁱ Davies et al. 2007

kyphoscoliosis and lumbosacral hyperlordosis; and Patient 3 had thoracolumbar hyperkyphosis and wedge-shaped vertebrae due to a history of pathological fractures.

Basal Metabolic Rate

Patient 1 underwent two assessments: at month 8 and month 38 after treatment discontinuation. In these assessments, BMR was, respectively, 14% and 47% higher than that estimated by the Harris–Benedict equation, corresponding to 43 and

51 kcal/kg/day. Patients 2 and 3 had a BMR 72% and 15% higher than that estimated by the Harris–Benedict equation, corresponding to 52 and 28 kcal/kg/day, respectively.

Nutritional Status

Before ERT, the weight-for-age z scores of patients 1, 2, and 3 (at age 1.8, 2.9, and 5.7 years, respectively) were −2.28, −1.20, and −4.45. Patient 1 had a height-for-age z score of −4.11. At initial assessment, patient 1 had

BMI-for-age and height-for-age z scores of -1.16 and -2.54 , respectively, versus -1.09 and -4.27 , respectively, at the second assessment. Patient 2 had BMI-for-age and height-for-age z scores of -1.39 and -3.02 , respectively, and patient 3 had a BMI of 24.7 kg/m^2 (height-for-age z score at age 19 years: -1.93). Arm circumference was below the 5th percentile in patients 1 and 2 and between the 50th and 75th percentiles in patient 3.

Discussion

The findings of this study showed that hypermetabolism is very frequent in GD type III, regardless of the current status of ERT. This was expected since many chronic diseases are associated to hypermetabolism (Schols 2003; Kao et al. 2011). Indeed, one patient had a BMR 70% higher than the estimated rate despite treatment, which may explain the malnutrition diagnosis. Patient 1, who was not on ERT, underwent repeated metabolic assessments, which showed a marked increase in BMR concomitantly with a deterioration in the clinical status: worsening blood cell counts, development of hepatomegaly, progression of splenomegaly from mild to severe, and deterioration of airflow from intact to severe restrictive respiratory disease (Table 1). The organomegaly identified on the physical examination and imaging tests was also reflected in an increase in BMI during the assessment period despite frank malnutrition.

The pulmonary manifestations present in these three patients are consistent with data available in the literature, which reports an increased risk of these manifestations in patients homozygous for the p.L444P mutation (Santamaria et al. 1998; Kraoua et al. 2011). One hypothesis for this hypermetabolic state involves the pulmonary manifestations these patients experience. Lung compliance is affected by kyphoscoliosis, as shown by the evidence of restrictive lung disease on spirometry. The only patient with normal spirometry in this sample had relatively mild hypermetabolism. In previous studies, malnourished patients with chronic obstructive pulmonary disease were found to have BMRs 18% higher than those of healthy controls (Baarends et al. 1997; Schols 2003; Kao et al. 2011). This increase is explained chiefly by the increased respiratory rate that occurs secondary to alveolar involvement, medication use, and a chronic inflammatory state. However, in our series, patients experienced BMR increases of up to 70%, which suggests that pulmonary involvement may be a contributing factor to these abnormalities in energy metabolism rather than their sole cause. Studies have shown that patients with GD type I also exhibit a hypermetabolic state, the causes of which remain unclear (Barton et al. 1989; Corssmit et al. 1995; Doneda et al. 2011, 2013). The two patients in our

series with pulmonary involvement and a more severe phenotype also had comparatively marked hypermetabolism. Within this context, hypermetabolism appears to be a biomarker of disease severity.

The application of indirect calorimetry, nonetheless, shows some limitations. It requires specific conditions for reproducibility of results, such as the following: a) adhesion to a protocol establishing fasting period, intake restriction of some substances, such as caffeine, ethanol and nicotine, as well as restriction to physical activities previously to the assessment; b) a physically comfortable place under temperatures between 20°C and 25°C ; and c) patients must rest for 10 to 20 minutes before assessment, and then they must lay still in supine position for the collection of respiratory gases, whose quotient must be located in the interval >0.7 and <1 (Compher et al. 2006). This strict protocol for the assessment of BMR and the difficulties showed by some GD III patients in remaining in supine position may compromise its application as a biomarker of the disease. In relation to the patients assessed in this study, the protocol for assessing BMR through indirect calorimetry was strictly followed, and they showed no difficulties remaining calm.

Nutritional assessment of patients with GD III can be quite complex, due to the presence of skeletal deformities. Height could not be measured adequately in any of the three patients, thus making the BMI an unreliable indicator. Likewise, assessment of waist circumference is hindered by the presence of organomegaly, and subscapular skinfold measurement, by bone deformity. We were unable to find any published literature on the nutritional assessment of GD III patients; therefore, we are unaware of whether such patients treated at other centers present similar skeletal abnormalities or are similarly predisposed to malnutrition, as are two of the patients managed at our service. The patients reported herein have very severe disease, and, accordingly, were quite severely malnourished at the start of treatment. As treatment progressed, their weight z scores improved, although only patient 3 achieved an adequate weight. After a period of catch-up growth early in the course of treatment, the weight z scores of patients 1 and 2 appear to have plateaued at an unsatisfactory level.

On reviewing the literature, we found four studies that assessed the growth of children and adolescents with GD III, among other parameters. In the first study, three patients with GD III experienced substantial catch-up growth and two experienced catch-up weight gain after 12 months of ERT (Bembi et al. 1994). In the second study, the authors reported that patient growth returned to normal after ERT (Erikson et al. 1995). The third study reported the outcome of eight patients (five of whom children) after 28 months of ERT with alglucerase. Three non-splenectomized pediatric patients exhibited improved growth dynamics as compared

to the other two children; improvement in weight was less marked, probably due to the presence of visceromegaly and ascites at baseline (Tylki-Szymanska, Czartoryska 1999). The fourth study reported the weight and height outcomes of patients with GD III. According to the authors, ERT-responsive patients exhibited normal or accelerated growth during the study period (Altarescu et al. 2001).

These studies detected improvements in organomegaly, cell counts, and growth – similar to those seen in patients with type I disease – over the course of the observation period. However, we were unable to find any studies that addressed whether the improvements in weight and height seen in the early stages of therapy remain over time and whether such patients achieve adequate BMI and height by the end of the growth period. In this study, we observed that nutritional status indicators initially improved, but later plateaued at inadequate levels in two of the three patients.

Conclusion

Assessment of BMR showed that all three patients were in a hypermetabolic state, which was particularly marked in the patients with more severe disease. Whether hypermetabolism contributes to disease severity or severe disease leads to hypermetabolism is still unclear. Nutritional status assessment showed that the two GD III patients who were malnourished had more severe hypermetabolism, which may have had an adverse impact on their clinical condition. We believe evaluation of metabolism in this patient population may contribute to the development of nutritional guidance that is better suited to patients' real needs, and that an understanding of the causes of hypermetabolism may aid management of GD. Further studies are required to elucidate the causes of hypermetabolism and malnutrition in patients with GD III.

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Summary

Assessment of nutritional status and energy metabolism by indirect calorimetry in patients with Gaucher disease type III.

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