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CLINICAL REPORT

Cardiopulmonary assessment of patients diagnosed with Gaucher's disease type I

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Abstract

Background: Understanding the basis of the phenotypic variation in Gaucher's disease (GD) has proven to be challenging for efficient treatment. The current study examined cardiopulmonary characteristics of patients with GD type 1.

Methods: Twenty Caucasian subjects (8/20 female) with diagnosed GD type I (GD-S) and 20 age- and sex-matched healthy controls (C), were assessed (mean age GD-S: 32.6 ± 13.1 vs. C: 36.2 ± 10.6, $p > .05$) before the initiation of treatment. Standard echocardiography at rest was used to assess left ventricular ejection fraction (LVEF) and pulmonary artery systolic pressure (PASP). Cardiopulmonary exercise testing (CPET) was performed on a recumbent ergometer using a ramp protocol.

Results: LVEF was similar in both groups (GD-S: 65.1 ± 5.2% vs. C: 65.2 ± 5.2%, $p > .05$), as well as PAPS (24.1 ± 4.2 mmHg vs. C: 25.5 ± 1.3 mmHg, $p > .05$). GD-S had lower weight ($p < .05$) and worse CPET responses compared to C, including peak values of heart rate, oxygen consumption, carbondioxide production (VCO_2), end-tidal pressure of CO_2, and O_2 pulse, as well as HR reserve after 3 min of recovery and the minute ventilation/VCO_2 slope.

Conclusions: Patients with GD type I have an abnormal CPET response compared to healthy controls likely due to the complex pathophysiologic process in GD that impacts multiple systems integral to the physiologic response to exercise.

KEYWORDS

cardiopulmonary exercise testing, echocardiography, Gaucher's disease

1 | INTRODUCTION

Gaucher's disease (GD) is a hereditary deficiency of the lysosomal enzyme glucocerebrosidase (also known as glucosylceramidase) causing disruption in the breakdown of the sphingolipid glucocerebroside (glucosylceramide) (Gary et al., 2018; Stirnemann et al., 2017). As such, it is a form of sphingolipidosis and the most

Abbreviations: BMI, body mass index; C, controls; CPET, cardiopulmonary exercise test; GD, Gaucher's disease; GD-S, subjects with Gaucher's disease; HR, heart rate; HRR-3, heart rate after three minutes of recovery; LVEF, left ventricular ejection fraction; O_2 pulse, oxygen pulse; $PETCO_2$, end-tidal pressure of CO_2; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; VE, minute ventilation; VE/VO_2, ventilatory equivalent for oxygen; VO_2, oxygen consumption; WR, work rate.

common of the lysosomal storage diseases (Gary et al., 2018; Stirnemann et al., 2017). The disease is caused by a recessive mutation in the gene located on chromosome 1 and affects both females and males (Gary et al., 2018; Stirnemann et al., 2017). When glucocerebrosidase is defective, glucocerebroside accumulates in mononuclear leucocytes, particularly in macrophages. They transform into so-called "Gaucher's cells" which can collect in the liver, spleen, kidneys, lungs, brain, and bone marrow leading to malfunctions and disorders (Stirnemann et al., 2017). Based upon neuronopathic features, there are three types of GD: (1) type I, non-neuronopathic (95%); (2) type II, acute neuronopathic; and (3) type III, chronic neuronopathic (Biegstraaten et al., 2018; Elstein et al., 2018; Gary et al., 2018; Grabowski et al., 2015; Stirnemann et al., 2017). Type 1 and 3 are additionally characterized by direct involvement of the lungs and pulmonary vasculature dysfunction leading to pulmonary hypertension (Biegstraaten et al., 2018; Grabowski et al., 2015; Miller et al., 2003; Stirnemann et al., 2017). Furthermore, reports demonstrate cardiovascular disorders in type 3 GD, predominantly affecting the mitral and aortic valves (Gary et al., 2018; Kör et al., 2017). Given the pathophysiologic process and multisystem involvement of GD, assessment of potential cardiac abnormalities in other types of GD is highly warranted. The aim of the current study was to examine the potential utility of resting echocardiography and cardiopulmonary exercise testing (CPET) in the evaluation of patients with GD type 1.

2 | METHOD

2.1 | Patients

We prospectively studied 20 subjects (8/20 female) diagnosed with type 1 GD (GD-S). The diagnosis is made according to clinical features, analysis of lysosomal betaglucocerebrosidase activity and presence of changes at *GBA1* gene on chromosome 1q22 (MIM number 606463). Included subjects had the following changes: 2 subjects were homozygous for *N370S* mutation in the *GBA1* gene locus; 18 patients had complex heterozygous mutations with *N370S* mutation at one allele and diverse changes at the other allele (6 patients had *D409H* mutation, 4 patients had *R463H* mutation, 4 patients had *L444P* mutation, 1 patient had *R120W* mutation, 1 patient had *R47X* mutation, 1 patient had *deletion 1236_1317del82bp* and 1 patient had *deletion 1265_1319del55bp*). Measurements were performed before the initiation of treatment with enzyme replacement therapy in the GD-S. All subjects were clinically stable and did not exercise regularly.

2.2 | Blood analysis

Beta-glucosidase and chitotriosidase activity were analyzed from leucocytes separated from 5 ml of whole blood collected by venous puncture in an EDTA tube. In order to measure chitotriosidase activity, plasma was incubated with 4-methylum belliferyl-β-D-NN,N′triacetylchitotriose as substrate in citrate/phosphate buffer pH 5.2, at 37°C. The result was expressed in μmol/L/h. Assay of acid β-glucosidase activity was performed by fluorogenic substrate 4-methyl-umbelliferyl-β-D-glucopyranoside in the presence of Triton X-100 and pure sodium taurocholate. Activity was expressed in μmol/g prot./h.

2.3 | Spirometry

Prior to the start of each CPET, subjects underwent forced spirometric assessments at rest using a Spirovit-SP-10 device (Schiller Health Care Ltd, Switzerland) in order to calculate forced expiratory volume in one second (FEV1).

2.4 | CPET

Patients performed CPET on a recumbent ergometer in the morning, 2 hr after awakening and in a fasting state, using a ramp increase in work rate (WR) (American Thoracic Society; American College of Chest Physicians, 2003). The test was terminated when the respiratory exchange ratio (RER) was ≥1.0. Breath by breath data was collected during CPET using a Cardiovit CS 200 device (Schiller, Baar, Switzerland). Blood pressure was measured using a standard cuff sphygmomanometer. Systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), oxygen consumption (VO_2), carbondioxide output (VCO_2), minute ventilation (VE), ventilatory equivalent for oxygen (VE/VO_2), O_2 pulse, and the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) were determined at rest, peak exercise and after three minutes of recovery from exercise. HR reserve (HRR-3) was calculated as the difference between HR peak and HR after three minutes of recovery from CPET. Peak VO_2 and the peak RER was the average of last 15s of CPET. VE and VCO_2 values, acquired from the initiation of exercise to peak were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope).

2.5 | Echocardiography

Standard B-mode echocardiography at rest was performed using Vivid 9 ultrasound device (BTO6, 1.5–3.6 MHz; GE Healthcare Technologies, Waukesha, WI, USA) to assess left ventricular ejection fraction (LVEF), according to

recommended criteria (Lang et al., 2015). Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography from the systolic right ventricular to right atrial pressure gradient using the modified Bernoulli equation. Right atrial pressure (assessed jugular venous pressure) was added to the calculated gradient to yield PASP (Rudski et al., 2010).

2.6 | Statistics

Results are expressed by mean and standard deviation. Correlations between variables were performed by Pearson`s correlation test and Spearman's rank correlation test. The differences between parameters were assessed by the Student's *t*-test. Binary logistic regression analysis was performed to identify the best model to predict probability of GD on CPET studies. Hierarchical models were defined considering the statistical significance and clinical relevance of independent variables, taking into consideration principal effects and second level interactions in each model. Statistical tests were considered significant when a *p*-value was <.05. The SPSS software package (SPSS version 17.0, SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

3 | RESULTS

All subjects diagnosed with GD demonstrated hepatomegaly; 16 patients had splenomegaly, whereas 4 of them underwent splenectomy. Of 20 patients, 15 had thrombocytopenia and 8 had osteopenia. Hemoglobin levels were normal in all patients. Subjects in the GD-S and C demonstrated a similar age and height; GD-S had a lower weight and BMI, as shown in Table 1. FEV_1, HR at rest, and SBP and DBP in all phases of CPET were normal in both groups and of similar values ($p > .05$). HR peak, HRR-3, O_2 pulse peak, as well as VO_2, VCO_2, and $P_{ET}CO_2$ at all phases of CPET were lower while the VE/VCO_2 slope was higher in GD-S compared to control.

Significant correlations between beta-glucosidase and chitotriosidase activity with cardiopulmonary and echocardiographic parameters in GD-S were not found, as shown in Table 2.

4 | DISCUSSION

The major finding of this study is that patients with GD type 1 demonstrated normal echocardiographic, but a worse overall CPET response compared to controls, including the chronotropic response, ventilatory efficiency, HRR, O_2 pulse, VO_2, VCO_2, and $P_{ET}CO_2$. Given the clinical importance of assessing cardiorespiratory fitness, now viewed as a vital sign (Ross et al., 2016), our findings potentially have important clinical implications for this patient population.

GD type 1 encompasses complex pathophysiology leading to clinical findings that portend a poor prognosis (Biegstraaten et al., 2018). Understanding the basis for the clinical variation in GD type I is rather challenging, as neither the quantity of lipid stored nor the amount of residual enzymatic activity has correlated well with the patient's phenotype and responses to treatment (Biegstraaten et al., 2018). GD type 1 does not carry any neuronopathic features and is characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, lung, and pulmonary vasculature dysfunction (Biegstraaten et al., 2018). Cardiopulmonary complications have been rarely described in GD type I, but appear to encompass restrictive cardiomyopathy, pulmonary hypertension, calcifications of the valves and mitral regurgitation (Roghi et al., 2017). Our results did not show any structural cardiac changes or increased PASP in GD-S, suggesting that there were no echocardiographic signs of pulmonary hypertension at rest. Moreover, ventilatory function at rest and during effort appeared to be normal. However, lower values of $PETCO_2$ during CPET and a higher VE/VCO_2 slope in GD-S are suggestive of the potential for vascular disturbances and impaired gas exchange at the level of alveolocapillary membrane characteristic of pulmonary hypertension (American Thoracic Society; American College of Chest Physicians, 2003). The chronotropic response and HRR-3 were also worse in GD-S, demonstrating possible autonomic dysfunction in these patients (Kawasaki et al., 2010). A lower peak O_2 pulse in the GD-S group, is suggestive of an inability to increase cardiac output during exercise, which is common for all heart failure phenotypes, and particularly useful for the detection of heart failure with preserved EF (Popovic et al., 2018). Furthermore, decreased peak VO_2 in GD-S demonstrates a systemic impairment (cardiopulmonary, skeletal muscle, and autonomic dysfunction) due to combination of complex pathophysiological mechanisms in GD type I that may have prognostic value (American Thoracic Society; American College of Chest Physicians, 2003; Lin and Radin, 1973). Finally, due to clinical features, deconditioning is not excluded as contributing mechanism for VO_2 decrease. The lower VCO_2 output is suggestive of possible alternate metabolic paths in ceramidase metabolism that may characterize patients with GD giving the hope that CPET measurements can be useful tool to assess the intensity of metabolic derangements in accordance with the disease activity and responses to therapy (Guazzi et al., 2016). Additional finding of the current study was lower BMI in GD-S, which was in accordance to previous reports demonstrating lower prevalence of overweight in untreated GD than in the general population. This finding was explained by metabolic abnormalities such as high resting energy expenditure in these patients (Langeveld et al., 2008). In support, treatment with

TABLE 1 Clinical, echocardiographic, and CPET parameters in subjects with Gaucher's disease and healthy control population

	GD-S ($n = 20$)	C ($n = 20$)	p
Age (years)	32.6 ± 13.1	36.2 ± 10.6	.366
Height (m)	1.7 ± 0.1	1.8 ± 0.1	.302
Weight (kg)	65.2 ± 12.1	75.9 ± 13.1	.014
BMI (kg/m^2)	22.1 ± 3.1	24.6 ± 3.0	.015
PAPS (mmHg)	24.1 ± 4.2	25.5 ± 1.3	.229
LVEF (%)	65.1 ± 5.2	65.2 ± 5.2	.991
FEV1 (L)	3.4 ± 0.8	3.8 ± 0.7	.115
RER peak	1.05 ± 0.07	1.07 ± 0.03	.301
VO_2 rest (ml/min/kg)	3.5 ± 1.9	3.9 ± 0.5	.326
VO_2 peak (ml/min/kg)	24.8 ± 7.2	31.6 ± 9.3	.002
VO_2 recovery (ml/min/kg)	6.7 ± 2.5	7.8 ± 2.5	.188
VCO_2 rest (ml/min)	203.5 ± 114.0	255.0 ± 56.9	.092
VCO_2 peak (ml/min)	1737.0 ± 678.8	2750.6 ± 1083.5	.001
VCO_2 recovery (ml/min)	600.0 ± 226.6	872.7 ± 404.3	.013
$P_{ET}CO_2$ rest (mmHg)	33.6 ± 3.6	34.4 ± 3.6	.497
$P_{ET}CO_2$ peak (mmHg)	41.8 ± 5.0	46.4 ± 4.4	.005
HR rest (beats/min)	74 ± 11	69 ± 16	.253
HR peak (beats/min)	149 ± 18	161 ± 18	.045
HRR-3 (beats/min)	51 ± 10	63 ± 12	.002
O_2 pulse peak	11.0 ± 3.7	15 ± 4.9	.007
VE/VO_2 peak	26.4 ± 3.8	26.8 ± 3.6	.411
VE/VCO_2 slope	30.3 ± 0.1	22.7 ± 2.1	<.0001
Chitotriosidase (μmol/L/h)	8471.4 ± 6423.7	–	
Beta-glucosidase (μmol/g/h)	1.7 ± 0.7	–	

Note: The values are expressed as mean ± *SD*.

Abbreviations: BMI, body mass index; C, healthy control population matched by sex and age; FEV1, forced expiratory volume in the 1st second; GD-S, subjects with Gaucher's disease; HR, heart rate; HRR-3, heart rate reserve after three minutes of recovery; LVEF, left ventricular ejection fraction; O_2 pulse, oxygen pulse; PAPS, systolic pulmonary artery pressure; $P_{ET}CO_2$, end-tidal partial pressure of carbondioxide; RER, respiratory exchange ratio; VE/VO_2, ventilatory equivalent for oxygen; VO_2, oxygen consumption; VCO_2, carbondioxide output; VE, minute ventilation.

enzyme replacement therapy leads to a decrease in resting energy expenditure, increase of body weight, and possible insulin resistance. These metabolic alterations may contribute to overall functional capacity, as well.

The lack of significant correlations of chitotriosidase and beta-glucosidase activity with echocardiographic and CPET findings suggest that these blood markers are not sufficient for overall assessment and follow up of patients with GD.

Altogether, in the current study CPET was found to be informative in terms of revelation of overall body impairment in patients diagnosed with GD. It gives an insight in particular clinical aspects of this rare disease, enabling early detection of characteristic features. CPET allows detection of incipient changes in alveocapillary membrane and pulmonary hypertension even before resting echocardiography. It also allows diagnosis of heart failure before manifest reduction of ejection fraction. It gives an insight in metabolic and hematologic changes specific to GD. Thus, early CPET is highly recommendable in patients diagnosed with GD, both for pro-diagnostic reasons and for gauging effects of therapy.

4.1 | Limitation

The small sample size was a key limitation to the present study. As such, future studies should be conducted in larger cohorts allowing for the prognostic assessment of CPET measures in patients with GD. Of note, the current study was performed in native patients, before specific treatment. Further studies should emphasize CPET changes due to therapeutic interventions in patients diagnosed with GD.

TABLE 2 Correlations between beta-glucosidase and chitotriosidase activity and echocardiographic and CPET parameters in subjects with Gaucher's disease

	Chitotriosidase		Beta-glucosidase	
Parameter	***r***	***p***	***r***	***p***
LVEF	0.1	.808	−0.4	.103
PASP	−0.3	.290	−0.2	.412
FEV1	0.2	.494	−0.2	.389
HR peak	−0.1	.830	0.3	.150
HRR-3	−0.1	.672	0.2	.429
VO_2 peak	0.1	.565	0.1	.929
VCO_2 peak	0.1	.960	−0.4	.185
$P_{ET}CO_2$ rest	0.1	.673	−0.2	.513
$P_{ET}CO_2$ peak	0.2	.407	−0.2	.516
O2 pulse peak	0.1	.798	−0.4	.058
VE/VCO_2 slope	−0.2	.506	−0.2	.456

Abbreviations: FEV1, forced expiratory volume in the 1st second; GD-S, subjects with Gaucher's disease; HR, heart rate; HRR-3, heart rate reserve after three minutes of recovery; LVEF, left ventricular ejection fraction; O_2 pulse, oxygen pulse; PAPS, systolic pulmonary artery pressure; $P_{ET}CO_2$, end-tidal partial pressure of carbondioxide; VO_2, oxygen consumption; VCO_2, carbon dioxide output; VE, minute ventilation.

5 | CONCLUSION

The results of the present study demonstrate that patients with GD type I have an abnormal CPET response compared to healthy controls. These findings are likely due to the complex pathophysiologic process in GD that impacts multiple systems integral to the physiologic response to exercise. Future research should be conducted to further determine the clinical value of CPET in patients with GD.

CONFLICT OF INTERESTS

The authors have nothing to disclose.

AUTHOR'S CONTRIBUTION

Marija Bjelobrk drafted the paper. **Milan Lakocevic** collected data. **Svetozar Damjanovic** analyzed data. **Milan Petakov** collected data. **Milan Petrovic** collected and analyzed data. **Zoran Bosnic** performed statistical analysis. **Ross Arena** revised the paper. **Dejana Popovic** designed, drafted, and revised the paper.

ETHICS COMPLIANCE

Subjects provided written informed consent before participation. The study was approved by the local Ethics Committee.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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