Molecular Genetics and Metabolism 109 (2013) 14–20

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Exercise intolerance in Glycogen Storage Disease Type III: Weakness or energy deficiency?☆,☆☆,★

Nicolai Preisler [a,*], Agnès Pradel [b], Edith Husu [a], Karen Lindhardt Madsen [a], Marie-Hélène Becquemin [c], Alix Mollet [d], Philippe Labrune [d,e], Francois Petit [f], Jean-Yves Hogrel [g], Claude Jardel [h], Francois Maillot [i], John Vissing [a], Pascal Laforêt [j]

[a] Neuromuscular Research Unit, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[b] Service Central d'Explorations Fonctionnelles Respiratoires, Assistance Publique — Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, F-75013 Paris, ER10 UPMC, Univ Pierre et Marie Curie, Sorbonne Paris Cité, France
[c] Service Central d'Explorations Fonctionnelles Respiratoires, Assistance Publique — Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, F-75013 Paris, ER10 UPMC, Univ Paris Diderot, Sorbonne Paris Cité, France
[d] APHP, Centre de Référence des Maladies Héréditaires du Métabolisme Hépatique, Service de Pédiatrie, Hôpital Antoine Béclère, Clamart, France
[e] Univ Paris Sud, UFR Kremlin Bicêtre, France
[f] Molecular Genetics and metabolic diseases laboratory, Antoine Béclère Hospital, Clamart, France
[g] Institut de Myologie, GH Pitié-Salpêtrière, Paris, France
[h] Service de Biochimie Métabolique, UF de biochimie des maladies neurométaboliques, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France
[i] CHRU de Tours, service de Médecine Interne, Université François Rabelais, INSERM U1069, Tours, France
[j] Centre de Référence de Pathologie Neuromusculaire Paris-Est, Institut de Myologie, GH Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France

ARTICLE INFO

Article history:
Received 12 February 2013
Accepted 12 February 2013
Available online 19 February 2013

Keywords:
Glycogen Storage Disease
Debrancher deficiency
Skeletal muscle
Exercise
Metabolism

ABSTRACT

Myopathic symptoms in Glycogen Storage Disease Type IIIa (GSD IIIa) are generally ascribed to the muscle wasting that these patients suffer in adult life, but an inability to debranch glycogen likely also has an impact on muscle energy metabolism. We hypothesized that patients with GSD IIIa can experience exercise intolerance due to insufficient carbohydrate oxidation in skeletal muscle. Six patients aged 17–36-years were studied. We determined VO_{2peak} (peak oxygen consumption), the response to forearm exercise, and the metabolic and cardiovascular responses to cycle exercise at 70% of VO_{2peak} with either a saline or a glucose infusion. VO_{2peak} was below normal. Glucose improved the work capacity by lowering the heart rate, and increasing the peak work rate by 30% (108 W with glucose vs. 83 W with placebo, $p = 0.018$). The block in muscle glycogenolytic capacity, combined with the liver involvement caused exercise intolerance with dynamic skeletal muscle symptoms (excessive fatigue and muscle pain), and hypoglycemia in 4 subjects. In this study we combined anaerobic and aerobic exercise to systematically study skeletal muscle metabolism and exercise tolerance in patients with GSD IIIa. Exercise capacity was significantly reduced, and our results indicate that this was due to a block in muscle glycogenolytic capacity. Our findings suggest that the general classification of GSD III as a glycogenosis characterized by fixed symptoms related to muscle wasting should be modified to include dynamic exercise-related symptoms of muscle fatigue. A proportion of the skeletal muscle symptoms in GSD IIIa, i.e. weakness and fatigue, may be related to insufficient energy production in muscle.

Abbreviations: GSD III, Glycogen Storage Disease Type III; GDE, glycogen debranching enzyme; VO_{2peak}, peak oxygen uptake; W_{peak}, peak work rate; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; FFA, free fatty acid; PFK, phosphofructokinase.

☆ Statistical analysis: Statistical analysis was conducted by Nicolai Preisler, MD.

☆☆ Funding: The study was supported by the AFM [no. 15205], the Association Francophone des Glycogénoses, and the Sara and Ludvig Elssas Foundation.

★ Disclosure statement: The authors have nothing to disclose pertaining to the present work, however, three authors report disclosures unrelated to the present work: NP, PL and JV report having received research support, honoraria, and travel funding from the Genzyme Corporation. PL and JV are members of the Genzyme Pompe Disease Advisory Board. JV works as a consultant for Lundbeck Pharmaceutical Company.

* Corresponding author at: Neuromuscular Research Unit, Dept. of Neurology, University of Copenhagen, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Fax: + 45 3545 6138.

E-mail addresses: npreisler@hotmail.com (N. Preisler), agnes-francoise.pradel@psl.aphp.fr (A. Pradel), edithhusu@gmail.com (E. Husu), karen_lindhardt@hotmail.com (K.L. Madsen), marie-helene.becquemin@psl.aphp.fr (M.-H. Becquemin), alix.mollet@abc.aphp.fr (A. Mollet), philippe.labrune@abc.aphp.fr (P. Labrune), francois.petit@abc.aphp.fr (F. Petit), jy.hogrel@institut-myologie.org (J.-Y. Hogrel), claude.jardel@psl.aphp.fr (C. Jardel), maillot@med.univ-tours.fr (F. Maillot), vissing@rh.dk (J. Vissing), pascal.laforet@psl.aphp.fr (P. Laforêt).

1096-7192/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2013.02.008

1. Introduction

Glycogen Storage Disease Type III (GSD III) is an inborn error of metabolism, which is caused by glycogen debranching enzyme (GDE) deficiency [1,2]. GDE is expressed in most tissues and plays a central role in glycogen catabolism [3,4]. In 85% of patients with GSD III, the GDE activity is absent in both skeletal muscle and liver (GSD IIIa) while 15% of patients have only liver involvement (GSD IIIb) [5,6].

Skeletal muscle glycogen is an essential source of energy to support muscle contraction, especially at high intensities of exercise [7,8]. Due to the defect in muscle glycogen breakdown in GSD III, it could therefore be expected that exercise-related symptoms occur in patients with GSD III, due to an energy crisis in muscle, similar to what is observed in myophosphorylase deficiency (McArdle disease, GSD V). The forearm exercise test has been used to examine exercise tolerance in patients with GSD III. However, exercise tolerance to more prolonged aerobic types of exercise involving larger muscle groups, has not yet been quantified in an experimental setting in patients with GSD III [9,10].

The aim of the present study was to determine the response and tolerance to exercise in patients with GSD IIIa without major permanent muscle weakness. We questioned the current description of this disorder as being mainly associated with static muscle involvement in adults [9,11,12]. We hypothesized that in young patients with GSD IIIa, without major weakness or muscle wasting, we would observe exercise intolerance, as a consequence of an impaired skeletal muscle glycogenolytic capacity. In an attempt to unmask skeletal muscle metabolic derangements, we provoked muscle metabolism with moderate- and high-intensity exercise.

We determined peak work capacity on a cycle-ergometer, and the response to static forearm exercise. We observed whether or not a second-wind phenomenon occurred, and measured pulmonary gas-exchange, and plasma metabolites and hormones during cycle-ergometer exercise at 70% of VO_{2peak} (peak oxygen uptake). Finally, in an attempt to circumvent the metabolic block in skeletal muscle, the patients were allocated to receive either saline (placebo) or a glucose infusion during constant load cycling. This test was performed because we hypothesized that supplying energy below the metabolic block could improve exercise tolerance, as it has been observed in GSD V, which is similar in that the enzyme deficiency affects glycogenolysis [13].

2. Subjects and methods

Please refer to the Supplemental Data for additional details of the methods.

2.1. Subjects

Six patients with biochemically or genetically confirmed GSD IIIa were included (Table 1).

2.2. Outcome measures

The patients were studied during 4 separate exercise interventions. 1) Peak exercise capacity: In this test, the primary outcome was to measure W_{peak} (peak work rate), VO_{2peak}, and change in plasma lactate concentration. 2) Non-ischemic forearm exercise test: Outcomes were changes in plasma lactate and ammonia concentrations. 3) The placebo (saline) infusion study: The primary outcomes of the placebo infusion trial were to observe whether a second-wind phenomenon occurred, and to describe changes in plasma lactate and glucose during exercise. 4) The glucose infusion study: The primary outcome measures of the glucose infusion study were changes in heart rate, RPE (ratings of perceived exertion) and changes in W_{peak} compared to placebo.

2.3. Exercise testing

2.3.1. Peak exercise capacity (day 1)

W_{peak} and $VO_{2\ peak}$ were determined on the first test day. The subjects exercised on a cycle ergometer on which workload was gradually increased until exhaustion. Pulmonary gas-exchange and heart rate were monitored continuously and blood samples were drawn at rest and at time of exhaustion. The results of this test were compared to 12 healthy (6 women and 6 men) gender- and age-matched (28 ± 7 years) sedentary controls, tested with the same peak protocol on a different occasion.

2.3.2. Non-ischemic forearm exercise testing (day 1)

This test was performed using a hand-grip dynamometer. The method has been described in detail elsewhere [14]. The subjects squeezed the grip handle continuously, applying a force corresponding to 70% (isometric work) of their maximal hand-grip strength, for 30 s. Blood samples were drawn according to Fig. 2.

2.3.3. Infusion trials (placebo and IV glucose, days 2 and 3, Fig. 1)

Each patient was randomized and blinded to receive a 10% glucose solution intravenously on one day and an isotonic saline (placebo) infusion the other day. The infusion was delivered as a 125 mL bolus, followed by a constant rate infusion (5 m per minute), which was given until exhaustion. On day one, three patients received the

Table 1
Clinical and molecular characteristics of the patients.

Patients	Age (years)	BMI (kg m^2)	*AGL*-gene mutation	Enzyme activity (nmol min^{-1} h^{-1})†	Age of onset	Muscle weakness§	Plasma CK (U L^{-1})	Cardiac involvement	Vital capacity (% of normal)
♠1♂	19	25	c.664+1G>A c.664+1G>A	Blood: 0	Childhood	No	780	HCM EF = normal	93%
♠2♂	17	26	c.664+1G>A c.664+1G>A	Not done	Childhood	LL proximal weakness (MRC 4)	2450	HCM EF = normal	93%
3♀	36	37	ND	Liver: 0	15 years	No	2600	HCM EF = normal	97%
4♂	34	28	c.3216_3217delGA c.3216_3217delGA	Blood: 0	16 years	No	5000	HCM EF = normal	97%
5♀	33	25	c.2229delT c.3486_3488delGAA	Blood: 0	Childhood	UL proximal weakness (MRC 4)	1731	No HCM EF = normal	ND
6♀	24	23	c.752A>G c.1736-11A>G	Blood: 0.86	Childhood	LL proximal weakness (MRC 4)	828	No HCM EF = normal	100%
Mean	27.2	27.2	NA	NA	NA	NA	2232	NA	96.0
SD	8.2	5.1					1561		3.0

Legend ♂ = male and ♀ = female. ♠ = Subject nos. 1 and 2 were brothers. SD = standard deviation. BMI = body mass index. † = Enzyme activity was based on the incorporation of ^{14}C-glucose into glycogen. ND = not done. § = Muscle strength was graded using the Medical Research Council Scale (5 point scale). LL = lower limb. UL = upper limb. CK = Plasma creatine kinase, reference values <280 UL^{-1}. HCM = hypertrophic cardiomyopathy. EF = ejection fraction, above 65% was defined as normal. NA = non-applicable. None of the subjects took any medications.