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Cross-sectional retrospective study of muscle function in patients with glycogen storage disease type III

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Abstract

Glycogen storage disease type III is an inherited metabolic disorder characterized by liver and muscle impairment. This study aimed to identify promising muscle function measures for future studies on natural disease progression and therapeutic trials. The age-effect on the manual muscle testing (MMT), the hand-held dynamometry (HHD), the motor function measure (MFM) and the Purdue pegboard test was evaluated by regression analysis in a cross-sectional retrospective single site study. In patients aged between 13 and 56 years old, the Purdue pegboard test and dynamometry of key pinch and knee extension strength were age-sensitive with annual losses of 1.49, 1.10 and 0.70% of the predicted values (%pred), respectively. The MFM score and handgrip strength were also age-sensitive but only in patients older than 29 and 37 years old with annual losses of 1.42 and 1.84%pred, respectively. Muscle strength assessed by MMT and elbow extension measured by HHD demonstrated an annual loss of less than 0.50%pred and are thus unlikely to be promising outcome measures for future clinical trials. In conclusion, our results identified age-sensitive outcomes from retrospective data and may serve for future longitudinal studies in which an estimation of the minimal number of subjects is provided.

Keywords: Glycogen storage disease type III; Debranching enzyme deficiency; Metabolic myopathy; Outcome measures

1. Introduction

Glycogen storage disease type III (GSDIII) or Cori Forbes disease is an inborn error of metabolism caused by mutations in the 85-kb *AGL* gene on chromosome 1p21 [1]. This gene codes for the glycogen debranching enzyme (GDE), which releases glucose from glycogen branches in two reactions catalysed by oligo-1,4-1,4-glucantransferase and amylo-1,6-glucosidase activities at two distinct sites on the protein. In approximately 85% of patients, the GDE activity is absent in the liver and skeletal muscle (GSDIIIa subgroup), and symptoms are mainly hepatic and muscular, whilst 15% of patients only have liver involvement (GSDIIIb subgroup). A rare group of patients present a deficiency of either the glucosidase or the transferase activity of the enzyme and are classified as GSDIIIc or GSDIIId, respectively [2].

GSDIII most often develops during the first months or years of life with fasting hypoglycaemia, massive hepatomegaly, and markedly elevated transaminases. These signs predominate with short stature during childhood, but spontaneously improve around puberty in most patients. In GSDIIIa, muscle involvement is generally minimal in childhood, although an elevated creatine kinase level is frequent [3–7]. Conversely, myopathy may constitute the main symptom in adults with the

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presence of proximal and distal muscle weakness above the age of 30 years [8] and occurrence of exercise intolerance [9]. However, the muscle phenotype is poorly documented, with no further details concerning the weakness and muscle wasting in lower limbs and hands [5], and may appear heterogeneous. Kiechl et al. [10] describe 4 patients illustrating 4 different phenotypes: adult onset distal myopathy, subacute myopathy of respiratory muscles, severe generalized myopathy and minimal variant myopathy. A myogenic profile is generally observed via EMG [7,11], although a neurogenic component has also been described in some cases [7,10]. The only common muscle phenotype features in GSDIIIa appear to be elevated serum creatine kinase [7,10,12] as well as vacuoles and increased Periodic acid–Schiff (PAS) labelling in muscle biopsies [5,12]. However, quantification of strength and muscle function loss has not been documented.

Cardiac involvement is frequent. Increases in wall thickness and left ventricular mass are often observed on echocardiography in GSDIIIa and can remain asymptomatic or progress towards hypertrophic cardiomyopathy [13–16].

Current treatment consists of dietary modifications as detailed in Ref. [17]. In order to prevent hypoglycaemia, small and frequent meals during the daytime and corn starch have long been prescribed [2,18] but this does not limit other complications [17]. A high fat, high protein and low carbohydrate diet was more recently introduced as it may stimulate neoglucogenesis, limit glycogen storage and favour muscle protein synthesis and growth in children [2,19]. The modified Atkins or ketogenic diet has been shown to improve muscle and cardiac symptoms [20,21] and fructose may favour exercise tolerance [22]. However, despite guidelines [2], case reports and small cohort studies, there is currently no consensus and diet remains as per individual patient tolerance [17].

Recently, animal models of the disease were developed [23,24] and preclinical treatments with rapamycin [25,26] or enzyme replacement therapy [27] are emerging. For future clinical trials, identification of robust muscle, cardiac and hepatic outcome measures to assess treatment efficacy is necessary. Data on natural history of skeletal muscle weakness in GSDIII remain scarce [8]. The present work is a retrospective single site study of quantified measurements of muscle performance in GSDIII patients. The aim of this study was to improve the knowledge base concerning the evolution of muscle involvement in GSDIII. In particular, the objectives were to identify the most promising outcome measures sensitive to disease progression from existing preliminary data and to estimate the minimum number of subjects required in a future longitudinal study using the same outcome measures with a larger cohort.

2. Methods

2.1. Study design and participants

This is a cross-sectional retrospective single site study of the motor function data of GSDIII patients assessed during their neurological outpatient consultation between 2006 and 2010 (more than 80% of the patients were assessed between February 2006 and July 2007) in the East Paris Neuromuscular Centre, Institute of Myology, Paris. A follow-up of the patients is still ongoing. This study focuses retrospectively on their baseline data, explaining the long time between the data acquisition and their present publication. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study was declared to the *Commission Nationale de l'Informatique et des Libertés (CNIL)* and an information letter was sent to the patients eligible for the study, indicating the choice for their data not to be included in the study. Requirement for written informed consent was not mandatory for this retrospective single site study. The study was also approved by the Local Ethics Committee (CPP-Ile de France VI; La Pitié-Salpêtrière).

Patient data were eligible for the study if debrancher enzyme deficiency was confirmed. Enzymatic diagnostic was performed either by biochemical assay of labelled glucose incorporation into glycogen [28,29] on liver or erythrocyte samples or by spectrophotometric assay on leukocytes using phosphorylated limit dextrin (PLD) [4]. Non-eligibility criteria included pregnancy or breastfeeding.

Samples for DNA analysis of the *AGL* gene were obtained from all patients after signed informed consent. DNA was extracted from peripheral leukocytes. The 35 exons of the *AGL* gene [1] and the flanking intron–exon junctions were amplified by PCR and double strand sequenced to be compared to the reference sequence (GenBank Accession: NM_000028.2).

2.2. Motor function measure (MFM)

The motor function measure (MFM) was developed to assess ambulant or non-ambulant patients with neuromuscular diseases between 6 and 60 years of age [30]. The MFM-32 consists of 32 task items distributed into 3 dimensions: dimension 1 (D1, standing and transfers); dimension 2 (D2, axial and proximal motor function); and dimension 3 (D3, distal motor function). The scoring of each item is based on a 4-point scale. Scores are summed and expressed as a percentage of the maximum possible score for D1, D2, D3 and the total. Starting position, the tasks and scoring instructions are detailed in the MFM manual (http://www.motor-function-measure.org).

2.3. Manual muscle testing (MMT)

Manual muscle testing (MMT) was performed using the modified Medical Research Council scale (MRC) with subdivision of the five grades as detailed in Ref. [31]. Muscle strength was assessed bilaterally.

2.4. Dynamometry

In addition, elbow and knee extension strength was measured by handheld dynamometry (HHD) with the Nicholas dynamometer (Lafayette Instruments, Lafayette, Indiana) in the same position as for the MMT: knee extension was assessed in sitting with the hip and knee at 90° of flexion, whilst elbow extension was evaluated in the supine position, shoulder in 0°