Case Report

Evidence of cardiomyocyte necrosis in glycogen storage disease type II

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Abstract

Adult-onset glycogen storage disease type II (GSD-II), unlike the infantile form, is not normally associated with coexisting cardiovascular pathologies. In infantile onset GSD-II, cardiomyopathy is a common feature, and mutations in the genes for cardiac troponin T and I are likely to be involved. This case report describes a 39-year-old man with no classical risk factors for premature cardiac disease who presented with central chest pain and shortness of breath. Serum aspartate transaminase (AST) had been consistently elevated for 15 years. Adult GSD-II had been diagnosed two years previously by muscle biopsy. On presentation, there was an elevated serum creatine kinase and AST. Electrocardiography and echocardiography were both normal, and an acute coronary syndrome was ruled out. Cardiac Troponin T (cTnT) was found to be positive at 0.1 μg/L using a Cardiac Reader, subsequently confirmed on an Elecsys 1010 (both from Roche Diagnostics, Lewes, UK). cTnT may therefore be a useful biomarker in examining subclinical cardiac involvement in GSD-II patients.


Introduction

Glycogen storage diseases of muscle (glycogenosis) are rare autosomal recessive diseases, characterized by abnormal accumulation of glycogen in skeletal muscle. This is due to a specific biochemical defect in carbohydrate metabolism. The disease can be clinically mild or severe, as is the case with Pompe's disease (glycogen storage type II (GSD-II) disease). Pompe's disease is characterized by a deficiency of α-glucosidase (acid maltase, GAA, EC 3.2.1.20) enzyme. The enzyme degrades α-1,4 and α-1,6 linkages in glycogen, maltose and isomaltose. As a result of the enzyme deficiency, glycogen accumulates in the liver, nerve, cardiac and muscle tissues. The severity of the disease is directly proportional to the degree of enzyme deficiency. Patients are classified according to onset as infantile, juvenile or adult; however, a continuum of disease severity is suggested by the clinical phenotype of the disease. Infantile onset Pompe's disease presents in the first months of life and is characterized by hypotonia, cardiomegaly, macroglossia and mild hepatomegaly. There is a striking loss of cardiomyocyte myofibrils leading to systolic and diastolic dysfunction. Cardiac glycogenosis is observed electrocardiographically by a short PR interval which is pathogenic of infantile Pompe's disease. There are tall QRS complexes across the precordial and limb leads, and Q waves may be present. Inverted T waves and ST segment depression indicative of myocardial ischaemia are also observed. Myocardial mass index exceeds that of the most severe forms of familial hypertrophic cardiomyopathy. The resulting diminished cardiac output and thickening of the myocardium leads to fatal ischaemia or arrhythmia. In juvenile onset Pompe's disease, cardiac involvement is normally absent or mild with mortality due mainly to respiratory failure. The adult onset of the disease occurs in the third to sixth decade of life and is similar to the juvenile form.

Case study

A 39-year-old man was referred to the Accident and Emergency Department by his General Practitioner with central chest pain and increasing shortness of breath that predated the admission, was not worsened by the episode of chest pain and persisted during the subsequent admission. The patient was a life-long non-smoker and did not have a family history of cardiac disease. There were no demonstrable classical

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cardiovascular disease risk factors, and his total cholesterol was 4.6 mmol/L with a triglyceride of 1.1 mmol/L. His previous medical history included a 15-year history of weight loss (body mass index (BMI) at presentation was 18.1 kg/m²), diarrhoea, epigastric and abdominal pains. A peptic ulcer had been previously excluded by endoscopy, and the abdominal pains had first been attributed to irritable bowel syndrome. Aspartate transaminase (AST) had been consistently raised since the original presentation 15 years ago. Adult onset GSD-II was diagnosed two years previously by muscle biopsy following investigation for weak and wasted muscles. Upon examination, the cardiovascular system was normal, as was the respiratory system, without any clinical evidence of a primary respiratory disorder.

On admission, he had an elevated serum creatine kinase (CK) of 904 U/L (upper reference limit <195 U/L) and an AST of 115 U/L (upper reference limit < 35 U/L). Electrocardiography (ECG) revealed sinus bradycardia, with high T-wave take off in lead V2–V6 (Figure 1). There was no ECG evidence of acute myocardial ischaemia. Echocardiography demonstrated both right and left ventricles were within normal dimensions with no abnormality in contractility. Both atria were normal. There was no evidence of valve thickness, and all were mobile with no regurgitation. Normal Doppler flow was observed. From the history, clinical examination or ECG, there was no evidence suggestive of an acute coronary syndrome.

By point-of-care testing, cardiac troponin T (cTnT, Cardiac Reader, Roche Diagnostics, Lewes, UK) was reported as positive at 0.1 μg/L. Subsequently, an aliquot of serum was frozen at −20°C and referred for cTnT measurement by a laboratory-based method. The sample was analysed using the Elecsys 1010 (Roche Diagnostics, Lewes, UK). The assay coefficient of variation was 5.5% at 0.32 μg/L and 5.4% at 6.0 μg/L; the detection limit was 0.01 μg/L with an upper limit of 25 μg/L. The cTnT concentration was confirmed as 0.1 μg/L.

The patient was admitted for a 24 h period of observation and subsequently discharged without readmission or development of coronary artery disease to date.

**Discussion**

Troponin T and I are proteins located on the tropomyosin strand within the sarcomere of muscle cells. Tissue-specific isoforms of both troponin T and troponin I exist in skeletal (sTnT and sTnI) and cardiac (cTnT and cTnI) muscle cells. The measurement of cardiac troponin is now considered the ‘Gold Standard’ test for myocardial necrosis due to the sensitivity and specificity of the test, and the evidence base for outcome prediction.

The presence of an elevated serum cTnT on two assay platforms suggests cardiomyocyte necrosis in our patient with adult onset GSD-II. Unfortunately, cTnI was not measured during this admission. At the time of investigation, the second-generation cTnT assay was in routine clinical use. This assay employed two cardiac-specific monoclonal antibodies (M7 and M11.7) to human cTnT and had been shown not to demonstrate cross-reactivity with skeletal troponin T.10 Baum et al.,11 who conducted a multicentre evaluation, did not observe any falsely positive second-generation cTnT concentrations in patients with

![Figure 1](image-url)  
*Figure 1  Electrocardiogram of a 39-year-old male with shortness of breath and Pompe’s disease. There is a sinus bradycardia, with high T-wave take off in lead V2–V6*
skeletal muscle damage, including multiple trauma, non-cardiac surgery and marathon runners. In particular, they studied 33 patients with Duchenne muscular dystrophy, which showed markedly lower second-generation cTnT concentrations (24% detectable < 0.2 μg/L) compared with 76% of samples where cTnT concentrations were greater than 0.2 μg/L when using the first-generation assay.11

Cardiac myocyte necrosis is most severe in the infantile form of GSD-II. It is a result of a restrictive cardiomyopathy, often in the presence of cardiomegaly, and is due to excessive glycogen storage in cardiac muscle. The condition is often fatal 2–3 weeks from onset. Echocardiographically, there is enlargement of both left and right ventricles, and two-dimensional imaging confirms the concentric nature of the hypertrophied ventricles.12 Papillary muscle hypertrophy may be present,12 and valvular involvement occurs in approximately 20% of patients13 but is not always present.12 Metabolic hypertrophic cardiomyopathies may be due to mutations in sarcomeric proteins,14 including troponin and β-myosin. Molecular analysis of troponin mutations to define clearly the pathophysiology of the cardiomyopathy in such cases is warranted. It is currently not known, however, how the mutated forms of cTnT and cTnI are detected by commercial immunoassay methods.

It is thought that cardiac involvement is either absent or mild in the adult form of the disease.2 The presence of cTnT in the serum of the patient presented in this case study with adult onset GSD-II challenges this view. The use of cardiac troponin T measurement as a marker of myocardial necrosis in the absence of an acute coronary syndrome may be useful in assessing subclinical cardiac pathology in GSD-II.

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