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CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Glycogen storage disease with massive left ventricular hypertrophy and increased native T1: a case report

Jie Wang[1†], Lutong Pu[1†], Yuchi Han[2], and Yucheng Chen [1,3]*

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [2]Wexner Medical Center, College of Medicine, The Ohio State University, USA; and [3]Center of Rare Diseases, West China Hospital, Sichuan University, Chengdu, Sichuan, China

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Background Glycogen storage disease (GSD) type Ⅲa is a rare autosomal recessive disorder resulting in the accumulation of abnormally structured glycogen in the liver, skeletal muscle, and cardiac muscle. Cardiovascular magnetic resonance (CMR) tissue characteristics in GSD have rarely been reported.

Case summary We report a 24-year-old male patient suffering from recurrent palpitation and atypical chest pain for 5 years with suspected hypertrophic cardiomyopathy. Laboratory tests revealed an elevated creatine kinase, and physical exam revealed hepatosplenomegaly. Cardiovascular magnetic resonance demonstrated asymmetrical massive left ventricular hypertrophy with a maximal thickness of 34.6 mm in the septum. In the regions with focal late gadolinium enhancement (LGE) in the anterior septum, both native T1 and extracellular volume (ECV) are elevated. However, in the LGE-negative regions of the myocardium, native T1 was elevated without elevation in ECV (septum, 22.7%; free wall, 20.9%). Whole exome sequencing revealed a novel pathogenic homozygous nonsense variant of the *AGL* gene (c.4284 T > G, p. Tyr1428*), confirming the diagnosis of the patients as GSD type Ⅲa.

Discussion This case showed increased diffuse native T1 but not ECV on CMR in LGE-negative myocardium in GSD, which indicates that the T1 value is increased with an accumulation of glycogen in the myocardium, but the ECV space was not expanded in this process. Genetic testing should be obtained in severe LV hypertrophy when multi-organ involvement is present, and myocardial tissue characterization is discrepant between T1 elevation and normal ECV to consider glycogen storage disorder.

Keywords Glycogen storage disease • Hypertrophic cardiomyopathy • T1 mapping • Late gadolinium enhancement • Case report

ESC curriculum 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy

Learning points

- To demonstrate the tissue characteristics of glycogen storage disease (GSD) type III by multimodality imaging.
- To understand the important role of cardiovascular magnetic resonance in the diagnosis of GSD.

* Corresponding author. Tel: +86 18980602149, Email: Chenyucheng2003@163.com
† The first two authors contributed equally to the study.
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Introduction

Glycogen storage disease (GSD) type Ⅲa is a rare autosomal recessive disorder with a pathogenic variant of the *AGL* gene resulting in the absence of the glycogen debranching enzyme and the accumulation of abnormally structured glycogen in the liver, skeletal muscle, and cardiac muscle.[1] Patients with GSD type Ⅲa may present with hepatomegaly, hypoglycaemia, hyperlipidaemia, and growth retardation. The severity of symptoms is related to the degree of liver disease and progressive muscle involvement, with a broad spectrum of clinical phenotypes. The pathological process involves cardiac muscle, often leading to left ventricular (LV) hypertrophy and progressive cardiomyopathy.[2–4]

Summary figure

Timeline	Events
Since infancy	Hypoglycaemia and hepatomegaly
19–24 years old	Recurrent palpitation and atypical chest pain
Initial presentation at 24 years old	(1) Hypoglycaemia and abnormal liver function in laboratory tests. (2) Prolonged Q-T interval and non-specific ST-T changes in the electrocardiogram. (3) Increased left ventricular (LV) ejection fraction and LV hypertrophy on echocardiography.
Initial cardiovascular magnetic resonance evaluation	(1) Asymmetrical massive LV hypertrophy. (2) Focal late gadolinium enhancement. (3) Increased native T1 and extracellular volume in the LGE-positive area but increased T1 and normal ECV in the LGE-negative area.
Further evaluation	A pathogenic variant of the *AGL* gene
After discharge	Supportive treatment
Follow-up at 27 years old	Died of hepatic failure

Case presentation

A 24-year-old male patient suffering from recurrent palpitation and atypical chest pain for 5 years was referred to cardiovascular magnetic resonance (CMR) with suspected hypertrophic cardiomyopathy (HCM) found on an echocardiogram (*Figure 1*). On physical exam, he had a blood pressure of 113/87 mmHg and a regular heart rate and rhythm. The thyroid was of normal size and consistency without nodules. He had no elevated jugular venous distention. He had no lymphadenopathy. His lungs are clear to auscultation bilaterally. He had no extra heart sounds or murmurs. An abdominal examination showed hepatomegaly and splenomegaly. He had no peripheral oedema. His skin had no special lesions. The patient had no family history of metabolic or cardiac disease but had a history of hypoglycaemia and hepatomegaly since infancy.

The electrocardiogram showed a prolonged Q-T interval (QTc 548 ms) and non-specific ST-T changes (*Figure 2*). Pre-excitation was not observed on a 24-h Holter electrocardiogram. Laboratory tests showed decreased early morning fasting blood glucose (3.0–4.0 mmol/L), significantly elevated creatine kinase (CK, 2210 IU/L, normal reference value: 19–226 IU/L), alanine aminotransferase (61 IU/L, normal reference value: <50 IU/L), aspartate aminotransferase (179 IU/L, normal reference value: <40 IU/L), and glutamyl transpeptidase (181 IU/L, normal reference value: <60 IU/L), indicating liver injury, but normal alkaline phosphate (110 IU/L, normal reference value: 51–160 IU/L). Abdominal ultrasound showed hepatomegaly and splenomegaly. Echocardiography showed an increased LV ejection fraction (76%), enlargement of the left atrium (37 mm), and markedly thickened interventricular septum (31–34 mm).

Cardiovascular magnetic resonance was performed and demonstrated asymmetrical massive LV hypertrophy with a maximal thickness of 34.6 mm in the septum (*Figure 3 A and B*). There was focal late gadolinium enhancement (LGE) in the anterior septum (*Figure 3 C and D*) with increased native T1{1421.2 ms [normal T1 = 1193.2 (1124.9–1265.1) ms at 3 T]; *Figure 3E*} and extracellular volume (ECV) (38.8%; *Figure 3F*) in the LGE-positive area. In the LGE-negative area, native T1 was elevated (septum, 1370.0 ms; free wall, 1317.5 ms) without an increase of ECV (septum, 22.7%; free wall, 20.9%). Myocardial oedema was presented with an elevated T2 time of 43 ms [normal T2 = 35.9 (30.9–41.0) ms at 3 T] (*Figure 3G and H*).

His symptoms initially abated after treatment with metoprolol but recurred soon after. We conducted whole exome sequencing and confirmation using the Sanger sequencing method. Genetic analysis revealed a novel pathogenic homozygous nonsense variant of the *AGL* gene (c.4284 T > G, p.Tyr1428*) (*Figure 4A*), confirming a diagnosis of GSD type Ⅲa. In addition, the patient's father and daughter were genetically tested after written consents were obtained, and they were confirmed to have a heterozygous variant with *AGL* (c.4284 T > G, p. Tyr1428*; *Figure 4B*). Supportive treatment was initiated. However, the patient died of hepatic failure after 3 years of follow-up.

Discussion

Many single-site variations of the *AGL* gene have been previously reported in GSD type III, including missense, nonsense, splice sites, small frameshift deletions and insertions, and large gene deletions and duplications.[1,5] In addition, a previous study reported a large phenotypic heterogeneity among individual GSD Ⅲ patients.[6] In this case, our patient had clinical and biochemical signs of liver, heart, and skeletal muscle involvement with GSD type Ⅲa.

Myocardial hypertrophy is a common phenotype of cardiac involvement and generally progresses over time,[7] in 32–71% of the patients.[5] There has only been one case report in the literature describing CMR findings in patients with GSD type Ⅲa with myocardial fibrosis.[3] Morphological analysis of muscle biopsies in some GSD type III cases also found significant fibrosis.[8] However, the tissue characteristic by T1 mapping was not previously reported in patients with GSD type III.

In this case, the young male patient with GSD Ⅲa presented with massive LV hypertrophy and LV fibrosis. In addition, an elevated CK and hepatosplenomegaly were also present in this patient, which raised suspicion for an HCM phenocopy with multi-organ involvement.[9] However, unlike other HCM mimics, this case showed increased diffuse native T1 but not ECV on CMR in LGE-negative areas, indicating that the T1 value increased with an accumulation of glycogen in the myocardium without expansion of extracellular volume. A similar finding in the discrepancy in the T1 and ECV values in LGE-negative areas was also recently reported in a GSD patient with Danon disease.[10]

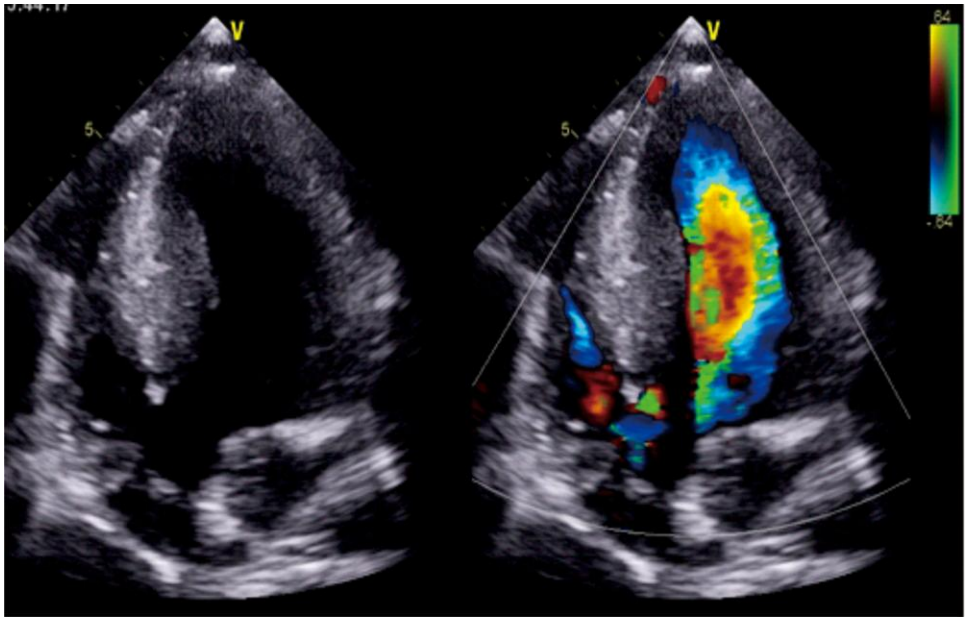

Figure 1 Echocardiography on the admission of the young male patient with glycogen storage disease type Ⅲa.

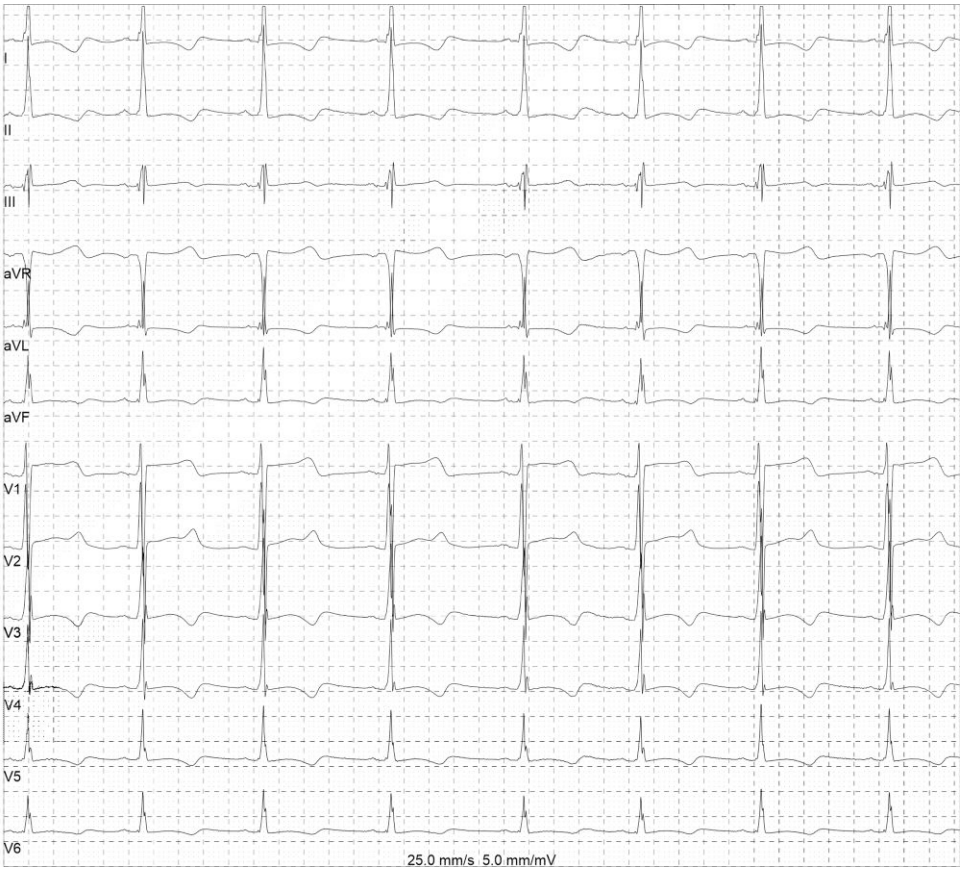

Figure 2 Electrocardiography on the admission of the young male patient with glycogen storage disease type Ⅲa.

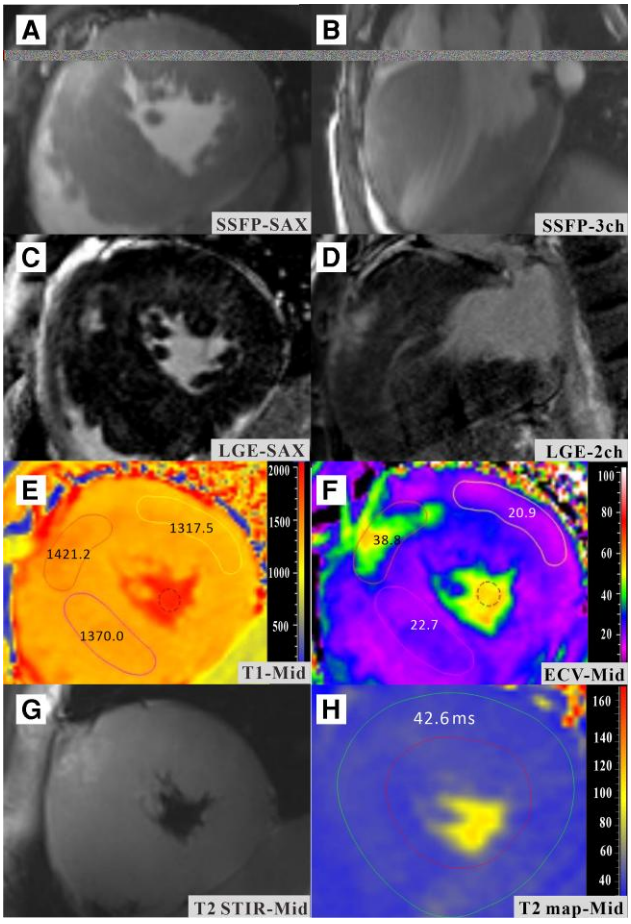

Figure 3 Cardiovascular magnetic resonance (CMR) finding of a young male patient with a GSD type Ⅲa. Mid-cavity short-axis (*A*) and three-chamber cine image (*B*); mid-cavity short-axis (*C*) and two-chamber late gadolinium enhancement (LGE) image (*D*); native T1 values of the region of interest (ROI) in the septum (1370.0 ms), LGE area (1421.2 ms), and left ventricular (LV) free wall (1317.5 ms) on mid-cavity short-axis T1 map (*E*); ECV values of the ROI in the septum (22.7%), LGE area (38.8%), and LV free wall (20.9%) on mid-cavity short-axis ECV map (*F*); mid-cavity short-axis T2-STIR image (*G*) and T2 mapping image (*H*).

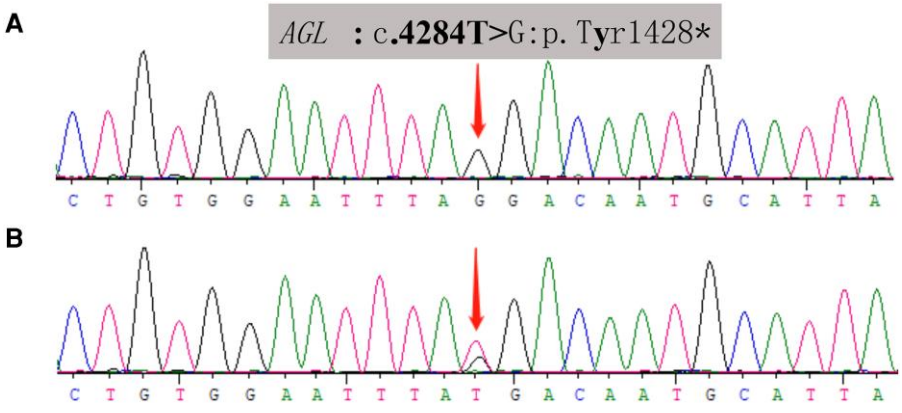

Figure 4 Sanger sequencing results. A novel pathogenic homozygous variant of the *AGL* gene (c.4284 T > G, p.Tyr1428*) was detected in a young male patient with glycogen storage disease type Ⅲa (*A*). His father and daughter were confirmed to have a heterozygous variant with *AGL* (*B*).

Conclusion

This case illustrated that genetic testing should be obtained in severe LV hypertrophy when multi-organ involvement is present, and myocardial tissue characterization is discrepant with T1 elevation and normal ECV to consider glycogen storage disorder.

Lead author biography

Dr Jie Wang worked in the Centre for Computational Bioinformatics at the University of Birmingham, UK, from September 2019 to April 2021 as a sponsored researcher. He specializes in the diagnosis and treatment of cardiomyopathies and cardiac magnetic resonance imaging characterization of cardiomyopathies. He has published more than 15 original articles as the first or co-first author in the past 5 years, including cardiomyopathy-related publications in *Radiology*, *JACC Cardiovasc Imaging*, *Can J Cardiol*, *Eur Radio*, and so on.

Consent: The authors confirm that written consent was obtained from the patient and his father for submitting and publishing this case report by the Committee on Publication Ethics (COPE) guidelines.

Conflict of interest: None declared.

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Data availability

Data generated or analysed during the study are available from the corresponding author by request.

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