

Case Studies

BIOCHEMICALLY SUPPORTED DIAGNOSIS OF FABRY DISEASE IN A YOUNG ADULT WITH UNEXPLAINED LEFT VENTRICULAR HYPERTROPHY: A DIAGNOSTIC CHALLENGE

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ABSTRACT

Fabry disease (OMIM #301500) is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, resulting in deficient activity of α -galactosidase A. This enzymatic defect leads to lysosomal glycosphingolipid accumulation and progressive multisystem dysfunction. The clinical manifestations are variable and non-specific, which may delay diagnosis. We report a 29-year-old Malay man who presented with recurrent palpitations, exertional chest pain, dyspnoea and fatigue. The physical examination was unremarkable, and there was no known relevant family history. Cardiac magnetic resonance imaging demonstrated significant concentric left ventricular hypertrophy with markedly reduced native myocardial T1 values. No significant coronary artery abnormalities were identified, raising suspicion of an infiltrative or metabolic cardiomyopathy. Plasma α -galactosidase A activity was markedly reduced at 0.3 nmol/mL/h (reference interval, 2.0–10.0 nmol/mL/h), which, together with the compatible cardiac imaging findings, strongly supported a diagnosis of Fabry disease, although molecular confirmation was unavailable. This case highlights a cardiac-predominant presentation strongly supportive of Fabry disease in a young Malaysian adult without documented classical extracardiac manifestations or a known relevant family history. It underscores the importance of considering Fabry disease in young patients with otherwise unexplained left ventricular hypertrophy and characteristic cardiac magnetic resonance findings. Early recognition is important to facilitate molecular confirmation, family screening and timely consideration of disease-specific management before irreversible organ damage develops.

KEYWORDS: Fabry disease, left ventricular hypertrophy, α -galactosidase A, cardiac magnetic resonance, cardiac-predominant presentation

INTRODUCTION

Fabry disease (FD) is a rare lysosomal storage condition inherited through an X-linked pattern, caused by alterations in the *GLA* gene that produce insufficient activity of the enzyme α -galactosidase A. This deficiency in the enzyme causes a slow accumulation of metabolic substrates, especially globotriaosylceramide and galactosylceramide, in lysosomes throughout various tissues in the body (1). The unusual aggregation of these substrates provokes cellular inflammation and fibrosis, which eventually causes dysfunction in multiple organ systems (2).

The clinical manifestations of Fabry disease are diverse and non-specific, frequently resulting in delayed diagnosis and irreversible organ damage if left unrecognised (3,4). In male individuals with the hemizygous variant, various systems such as the renal, skin, corneal, nervous, and cardiovascular systems are generally impacted (5). Cardiac abnormalities rank among the primary contributors to morbidity and mortality in Fabry disease, often manifesting as left ventricular hypertrophy (LVH) (6,7).

Enzyme replacement therapy (ERT) is an established disease-specific treatment for Fabry disease, although the cardiac response is influenced by the stage of myocardial involvement at treatment initiation (8). We report a cardiac-predominant presentation strongly supportive of Fabry disease in a 29-year-old Malaysian man with otherwise unexplained left ventricular hypertrophy, markedly reduced native myocardial T1 and severely deficient plasma α -galactosidase A activity. The clinical value of this case lies in the absence of documented classical extracardiac manifestations or a known relevant family history, illustrating the importance of targeted evaluation for Fabry disease in young patients with unexplained left ventricular hypertrophy.

CASE REPORT

A 29-year-old Malay man with no known medical comorbidities presented with recurrent episodes of palpitations, exertional chest pain, dyspnoea, and fatigue. The symptoms were exacerbated by physical activity and were accompanied by pain radiating to the neck, jaw and arms.

On admission, the patient was afebrile at 36.9°C, with a blood pressure of 130/80 mmHg, heart rate of 120 beats per minute and normal oxygen saturation. Physical examination did not reveal any significant abnormalities, including angiokeratomas. A targeted review found no documented history of acroparaesthesia or neuropathic pain, hypohidrosis or anhidrosis, heat intolerance, gastrointestinal symptoms, hearing impairment or tinnitus. Formal ophthalmological assessment for cornea verticillata was not documented. There was no known family history of consanguinity, renal failure, early-onset stroke, sudden cardiac death, inherited cardiac disease or unexplained cardiomyopathy.



Figure 1. Electrocardiogram demonstrating sinus rhythm with a PR interval of 120 ms with left ventricular hypertrophy.

The electrocardiogram (ECG) showed sinus rhythm, a PR interval of 120 ms and features of left ventricular hypertrophy (Figure 1). Repeated electrocardiograms showed no progressive changes. Echocardiography demonstrated concentric left ventricular hypertrophy with preserved or near-normal systolic function. Cardiac magnetic resonance (CMR) imaging confirmed significant concentric left ventricular hypertrophy (Figure 2) and markedly reduced native myocardial T1 values. No significant coronary artery abnormalities were identified during the CMR assessment, raising suspicion of an infiltrative or metabolic cardiomyopathy, including Fabry disease.

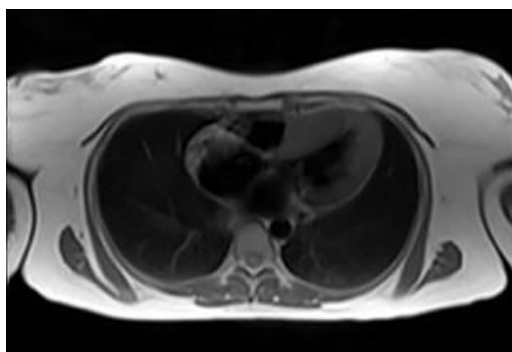


Figure 2. Cardiac magnetic resonance imaging demonstrating concentric left ventricular hypertrophy.

Laboratory investigations revealed an increased level of high-sensitivity cardiac troponin I of 25 ng/L (reference interval, <20 ng/L). The full blood count was within the reference intervals: haemoglobin, 141 g/L (138–172 g/L); total white cell count, $7.3 \times 10^9/\text{L}$ ($4.0\text{--}11.0 \times 10^9/\text{L}$); and platelet count, $226 \times 10^9/\text{L}$ ($150\text{--}450 \times 10^9/\text{L}$). Serum creatinine was within the laboratory reference interval at 65 $\mu\text{mol/L}$ (reference interval, <100 $\mu\text{mol/L}$), corresponding to a retrospectively calculated estimated glomerular filtration rate (eGFR) of approximately 126 mL/min/1.73 m² using the 2021 race-free CKD-EPI creatinine equation, indicating preserved glomerular filtration. However, urinalysis and quantitative urine albumin-to-creatinine or protein-to-creatinine ratios were unavailable from the retrospective clinical record; therefore, early or subclinical renal involvement could not be excluded. The lipid profile showed triglycerides of 1.7 mmol/L (reference interval, <1.7 mmol/L), HDL cholesterol of 1.0 mmol/L (reference interval, >1.0 mmol/L), LDL cholesterol of 1.56 mmol/L (reference interval, <3.0 mmol/L) and total cholesterol of 3.33 mmol/L (reference interval, <5.2 mmol/L).

Plasma α -galactosidase A activity was measured using an in-house fluorometric lysosomal enzyme assay. Plasma separated from EDTA-anticoagulated whole blood (10 μL) was incubated in duplicate with 20 μL of 1 mmol/L 4-methylumbelliferone- α -D-galactopyranoside in 0.1 mol/L acetate buffer containing 0.3 mol/L N-acetyl-galactosamine at pH 4.8. N-acetyl-galactosamine was included to inhibit α -galactosidase B activity. After incubation at 37°C for 90 minutes, the reaction was stopped with 200 μL of carbonate buffer. Liberated 4-methylumbelliferone was measured using a fluorescence microplate reader at excitation and emission wavelengths of 366 nm and 442 nm, respectively. Enzyme activity was expressed as nmol/mL/h. Each analytical run included a reagent blank and in-house normal- and low-level plasma internal quality controls, and the laboratory participated in the ERNDIM external quality-assurance scheme for lysosomal enzymes.

The patient's plasma α -galactosidase A activity was markedly reduced at 0.3 nmol/mL/h (laboratory reference interval, 2.0–10.0 nmol/mL/h). Total β -hexosaminidase A+B activity, the reference enzyme for plasma lysosomal enzyme assays, was within its reference interval of 270–1529 nmol/mL/h, supporting specimen integrity and reducing the likelihood that the low α -galactosidase A activity resulted from specimen deterioration. Together with the compatible cardiac imaging findings, the biochemical results strongly supported a diagnosis of Fabry disease.

Molecular analysis of the *GLA* gene was not performed because the test was unavailable and was not offered at the time of the patient's evaluation owing to financial and resource limitations. Accordingly, the diagnosis was considered strongly supported by the markedly reduced α -galactosidase A activity and compatible cardiac imaging findings but was not molecularly confirmed.

The patient was referred to a metabolic specialist for further evaluation and management. Information regarding subsequent *GLA* molecular testing, initiation of enzyme replacement therapy, genetic counselling, cascade family screening and longer-term clinical outcome was not available to the authors from the retrospective clinical record. Migalastat eligibility could not be assessed because an amenable *GLA* variant had not been identified.

DISCUSSION

Fabry disease is a progressive X-linked disorder, first described independently by Johannes Fabry and William Anderson in 1898, with an estimated prevalence of 1 in 40,000–117,000 individuals (2,9). Its manifestations vary by phenotype, sex, and residual α -galactosidase A activity. The classic phenotype usually affects males with <1% enzyme activity and presents early, whereas later-onset disease occurs in males with residual activity >1% and in females, whose enzyme levels may be normal because of variable X-chromosome inactivation (2,5,10,11,12).

Early manifestations commonly involve the skin and gastrointestinal system, progressing to ocular, auditory, neurological, renal, cerebrovascular, and cardiac complications (13). Cardiac manifestations, including ventricular hypertrophy, conduction abnormalities, valvular dysfunction, and arrhythmias are major causes of morbidity and mortality (7,14,15,16). In Malaysia, limited epidemiological data, clinical awareness, and access to specialised testing may contribute to under-recognition and delayed diagnosis, highlighting the need for improved awareness and diagnostic services (3,5,11).

Fabry disease may be diagnostically challenging when cardiac involvement occurs without the classical extracardiac manifestations commonly associated with the disease. In the present case, the patient presented predominantly with palpitations, exertional chest pain, dyspnoea and fatigue, together with concentric left ventricular hypertrophy. These findings are not specific to Fabry disease and may initially suggest more common cardiac conditions, particularly sarcomeric hypertrophic cardiomyopathy. Diagnostic suspicion was further reduced by the absence of documented classical extracardiac manifestations and a known relevant family history. Nevertheless, the absence of an apparent family history does not exclude Fabry disease because its X-linked inheritance, variable clinical expression, incomplete recognition of mildly affected relatives and limited family medical information may obscure the hereditary pattern (5,11). Although cardiac-predominant Fabry disease is a recognised phenotype, this case is clinically noteworthy because it occurred in a young Malaysian adult whose cardiac findings prompted targeted evaluation despite the absence of the usual diagnostic cues (12,14).

Distinguishing Fabry cardiomyopathy from sarcomeric hypertrophic cardiomyopathy is clinically important because the two conditions differ in pathophysiology, inheritance, management and implications for family screening. Sarcomeric hypertrophic cardiomyopathy is generally associated with pathogenic variants affecting cardiac contractile proteins, whereas Fabry cardiomyopathy results from deficient α -galactosidase A activity and progressive lysosomal glycosphingolipid accumulation within cardiomyocytes and other cardiac tissues (7,15,17,18). In this patient, the concentric pattern of left ventricular hypertrophy and markedly reduced native myocardial T1 were important diagnostic clues. Reduced native myocardial T1 is a recognised feature of Fabry cardiomyopathy and may help distinguish it from other causes of left ventricular hypertrophy, although it is not diagnostic when interpreted in isolation (7,19).

The CMR findings shifted the diagnostic consideration from a primary sarcomeric disorder towards a possible metabolic cardiomyopathy. The imaging findings did not independently establish Fabry disease; instead, the combination of concentric left ventricular hypertrophy and markedly reduced native myocardial T1 justified targeted biochemical testing. This case therefore demonstrates the complementary roles of cardiac imaging and specialised biochemical analysis in evaluating otherwise unexplained left ventricular hypertrophy.

According to current international recommendations, including GeneReviews® and the Taiwan Society of Cardiology (TSOC) Expert Consensus on Fabry disease, measurement of α -galactosidase A activity is an appropriate first-line biochemical investigation in symptomatic male patients with suspected Fabry disease (5,11). In this case, plasma α -galactosidase A activity was markedly reduced at 0.3 nmol/mL/h compared with the laboratory reference interval of 2.0–10.0 nmol/mL/h. When interpreted together with the compatible CMR findings, this result provided strong biochemical support for Fabry disease and substantially strengthened the diagnostic impression raised by the markedly reduced native myocardial T1. Normal total β -hexosaminidase A+B activity, used as the reference enzyme for the plasma lysosomal enzyme assay, supported specimen integrity and reduced the likelihood that the low α -galactosidase A activity resulted from specimen deterioration or a general loss of lysosomal enzyme activity (13).

Nevertheless, α -galactosidase A activity testing cannot identify the causative *GLA* variant, establish genotype–phenotype correlations, facilitate variant-specific family testing or determine eligibility for mutation-specific treatment. Molecular analysis of the *GLA* gene was unavailable and was not offered at the time of the patient’s evaluation owing to financial and resource limitations. Consequently, the diagnosis in this case was strongly supported clinically, biochemically and by cardiac imaging but was not molecularly confirmed. This limitation precludes classification of the patient as having a genetically established “atypical cardiac variant”; therefore, the presentation is more appropriately described as cardiac-predominant (3,5,11,17).

The available renal findings should also be interpreted cautiously. Serum creatinine was 65 μ mol/L, corresponding to a retrospectively calculated eGFR of approximately 126 mL/min/1.73 m² using the 2021 race-free CKD-EPI creatinine equation. Although this finding did not indicate reduced glomerular filtration, urinalysis and quantitative urine albumin-to-creatinine or protein-to-creatinine ratios were unavailable from the retrospective clinical record. Therefore, early or subclinical renal involvement could not be excluded based on serum creatinine and eGFR alone.

Early recognition is important because Fabry disease is a potentially treatable cause of left ventricular hypertrophy. Disease-specific options include enzyme replacement therapy and, for patients with an amenable *GLA* variant, migalastat. Evidence suggests that treatment may provide greater cardiac benefit when initiated before advanced myocardial fibrosis and irreversible organ damage have developed, although response varies according to disease stage and pre-existing cardiac involvement (7,8,18,19,20,21,22). Recognition also permits molecular confirmation, genetic counselling and cascade screening of potentially affected relatives (5,11). In the present case, the patient was referred to a metabolic specialist; however, subsequent molecular testing, treatment status, family screening and longer-term outcome were unavailable from the retrospective record.

Overall, this case demonstrates the importance of integrating clinical assessment, CMR and specialised biochemical testing in young patients with otherwise unexplained left ventricular hypertrophy. The cardiac-predominant presentation, concentric hypertrophy, markedly reduced native myocardial T1 and severely reduced plasma α -galactosidase A activity strongly supported Fabry disease despite the absence of documented classical extracardiac manifestations or a known relevant family history. Greater awareness of this presentation may reduce diagnostic delay and enable timely confirmatory investigation and disease-specific management.

CONCLUSION

In conclusion, this case highlights the importance of considering Fabry disease in young patients with otherwise unexplained left ventricular hypertrophy, particularly when CMR demonstrates markedly reduced native myocardial T1. The combination of compatible cardiac imaging and markedly reduced plasma α -galactosidase A activity strongly supported Fabry disease in this patient, although the diagnosis was not molecularly confirmed. Whenever feasible, *GLA* molecular analysis should complement biochemical testing to identify the causative variant, support family screening and guide management. Early recognition may enable disease-specific intervention before irreversible cardiac and other organ damage develops.

Supplementary Materials: Not applicable.

Data Availability: The data supporting the findings of this study are not publicly available due to patient confidentiality and institutional data protection policies but are available from the corresponding author upon reasonable request, subject to approval by the relevant institutional authority.

Author Contributions: NMFO, SSN and AA conceived and designed the case report. HI and SMN collected the clinical data. RHYM performed the enzymatic analyses. NMFO drafted the manuscript. All authors critically revised the manuscript, approved the final version and agreed to be accountable for all aspects of the work.

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of this case report and the use of fully anonymised clinical data. All personal identifiers have been removed to

protect patient confidentiality and privacy. No identifiable images or personal information are included in this report.

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