The Value of Advanced Cardiac Magnetic Resonance Imaging Technologies in Detecting the Characteristics of Cardiac Involvement in Anderson-Fabry Disease

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Keywords: Anderson-Fabry disease, Cardiac magnetic resonance, Echocardiography, LGE, T1 Mapping, Enzyme replacement therapy

Posted Date: July 20th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3157434/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of the American Society of Nephrology on November 1st, 2023. See the published version at https://doi.org/10.1681/ASN.20233411S1951d.
Abstract

Introduction: Anderson-Fabry disease (AFD) is a genetic disorder associated with cardiac involvement. Advanced cardiac magnetic resonance (CMR) technologies, including T1 mapping and gadolinium-enhanced CMR, have been used to detect and evaluate cardiac involvement in AFD patients. However, there is limited information on the characteristic CMR manifestations of cardiac involvement in Chinese AFD patients.

Methods: In this cross-sectional study, clinical data were collected from patients with AFD diagnosed at this center from January 2022 to March 2023. Compared with echocardiography, CMR was used to evaluate cardiac function, the degree of cardiac structural lesions, and to analyze characteristic CMR findings of cardiac involvement in AFD.

Results: 20 patients with AFD from nine families were included. This study showed that left ventricular hypertrophy (LVH) was detected in 85% of patients (18.41 ± 4.56 mm) by CMR, whereas echocardiography identified LVH in only 65% of patients (16.86 ± 2.74 mm), suggesting that echocardiography may underestimate the severity of LVH in AFD patients (P=0.001). Moreover, all patients exhibited characteristic CMR findings of cardiac involvement in AFD, including decreased T1 values (95% of patients) and late gadolinium enhancement (LGE) associated with myocardial fibrosis (55% of patients).

Conclusion: This study demonstrated that CMR is a valuable tool for detecting and assessing cardiac involvement in AFD patients, providing characteristic CMR findings, including LVH, decreased T1 values, and LGE associated with myocardial fibrosis. Moreover, this study highlighted the diagnostic superiority of CMR over echocardiography in assessing LVH in AFD patients.

1. Introduction

Anderson-Fabry disease (AFD) is a rare X-linked inherited lysosomal storage disorder caused by GLA gene mutations, resulting in decreased or absent activity of the enzyme α-galactosidase A (α-Gal A) and abnormal accumulation of the metabolic substrate globotriaosylceramide (Gb3) and its deacylated form, globotriaosylphosphoglycerol (Lyso-Gb3)[1]. Cardiac involvement is the primary cause of reduced life expectancy in AFD patients[2], mainly manifested as decreased cardiac function, left ventricular hypertrophy (LVH) and myocardial fibrosis [3]. Early diagnosis and specific treatment, such as enzyme replacement therapy (ERT) and chaperone therapy, are critical for delaying disease progression and improving patient outcomes [4]. Although echocardiography is the first-line screening and diagnostic modality for AFD [5], it has limitations in assessing patients' cardiac involvement comprehensively [6]. Advanced cardiac magnetic resonance (CMR) techniques, such as T1 Mapping and gadolinium-enhanced CMR, offer more accurate measurements of myocardial thickness and mass than echocardiography [7, 8], and have also been used to evaluate cardiomyocyte injury. Decreased T1 values and late gadolinium enhancement (LGE) are characteristic CMR findings in cardiac lesions of AFD [9]. In this cross-sectional study, clinical data of 20 patients from nine families with AFD were collected in order to evaluate the value and advantages of advanced CMR technologies in assessing cardiac function, cardiac structure, and cardiomyocyte injury.

2. Materials and methods

Population: In this cross-sectional study, patients diagnosed with AFD in the Department of Nephrology of Zhongda Hospital Southeast University were enrolled from January 2022 to March 2023. The diagnostic process was in accordance with the expert consensus for diagnosis and treatment of Fabry disease in China (2021)[10]. Patients’ clinical characteristics were recorded, including 24-hour urinary protein quantity, glomerular filtration rate, serum creatinine, brain natriuretic peptide (BNP), cardiac troponin I (Tnl), D-Dimer, electrocardiogram, 24 hours dynamic electrocardiogram, cranial magnetic resonance imaging, pulmonary function, vision and hearing examination, etc. Additionally, cardiac imaging findings, including echocardiography and CMR, were collected. This study was performed in compliance with the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the Ethics Review Committee of Zhongda Hospital Southeast University (2023ZDSYLL054-P01). Informed consent was obtained from all patients who participated in this study.

Echocardiography: Echocardiography and CMR are two widely used imaging techniques to evaluate cardiac structure and function. In this study, echocardiography was performed using a GE Vivid E9 Ultrasound Machine. Two observers with more than five years of work experience assessed chamber size, ventricular wall movement, diastolic function, and valvular function of patients with AFD. Left ventricular ejection fraction (LVEF) was automatically calculated by the commercially available post-processing software. LVEF < 50% was used as the diagnostic criterion for reduced ejection fraction [11]. LVH was defined as maximal end-diastolic wall thickness ≥13mm in any region of the left ventricle [12].

CMR: All participants underwent CMR at MAGNETOM Vida 3.0T(Siemens Healthineers, Germany). Images were acquired in 6-mm short-axis and long-axis slices (two-chamber, three-chamber, four-chamber view) with Fast Low Angle Shot (FLASH) sequence. T1 mapping was performed on four-chamber and the second, fifth, eighth layer planes of short-axis. The contrast medium for enhanced scanning was intravenous administration of 0.15 mmol/kg ProHance® (Gadoteridol) Injection. Before and six to ten minutes after contrast administration, T1 mapping was performed using the modified Look-Locker inversion recovery (MOLLI) sequence. LGE sequences were performed 10-15 minutes aftercontrast administration, 10 consecutive short-axis slices were collected with phase-sensitive inversion recovery gradient-recalled echo sequence, with an inversion time individually determined to null the myocardial signal. The LVEF was automatically calculated by the commercially available post-processing software. LVEF < 50% was used as the diagnostic criterion for reduced ejection fraction. The end-diastolic left ventricular wall thickness (LVWT) and left ventricular mass index (LVMI) were obtained. LVWT≥13mm was used as the diagnostic criterion for LVH. Two experienced observers with over 11 years of CMR experience...
Statistical Analysis: Statistical analysis was performed using SPSS software, version 25.0. The normal distribution of variables was tested by Kolmogorov-Smirnov test. Continuous variables subject to normal distribution were quoted as the mean ± standard deviation (SD), and categorical variables were quoted as the frequency (percentage). Paired T-test was used to compare the two groups of measurement data with normal distribution and homogeneity of variance obtained from the same patient using different imaging techniques. Rank sum test was used if the measurement data were not subject to the normal distribution. $P < 0.05$ was defined as significant.

3. Results

3.1 Patient characteristics

In this study, 20 patients (11 males and 9 females) with a mean age of diagnosis of $44.35 \pm 13.41$ years were examined. The mean age of diagnosis for males was $35.09 \pm 9.32$ years, while that for females was $55.67 \pm 7.50$ years, indicating that females may have a higher likelihood of delayed diagnosis. All patients had GLA gene mutations with or without decreased $\alpha$-Gal A activity and increased Lyso-GL-3 levels (Table 1). Using the revised criteria of the American College of Medical Genetics (ACMG), all of the patients were classified as having a variant of pathogenic, likely pathogenic, or variants of unclear significance (VUS), indicating that variants in these patients had high pathogenicity and 17 patients received ERT eventually. The 20 patients included in this study were from nine families with a family history of AFD (Fig. 1). Of note, the F8 family exhibited a typical aggregation of AFD, with five patients included in this study.

<table>
<thead>
<tr>
<th>Patient/family</th>
<th>Sex</th>
<th>Age(yrs)</th>
<th>GLA variants</th>
<th>ACMG</th>
<th>$\alpha$-Gal A</th>
<th>Lyso-GL-3(ng/ml)</th>
<th>frequency of ERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1f</td>
<td>female</td>
<td>49</td>
<td>c.548-1G &gt; T</td>
<td>VUS</td>
<td>-</td>
<td>5.4</td>
<td>31</td>
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<td>c.548-1G &gt; T</td>
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<tr>
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<td>10.68</td>
<td>0</td>
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<tr>
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<td>c.641C &gt; A</td>
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<td>84</td>
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<td>30</td>
<td>c.617T&gt;C</td>
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<td>4.57$\mu$mol/L/h</td>
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<td>31</td>
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<tr>
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<td>c.91C &gt; A</td>
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<td>21</td>
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<td>c.92C &gt; A</td>
<td>VUS</td>
<td>1.43$\mu$mol/L/h</td>
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<td>13</td>
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<td>c.92C &gt; A</td>
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<td>12</td>
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<tr>
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<td>c.263A &gt; G</td>
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<td>30.79</td>
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<td>4.82</td>
<td>0</td>
</tr>
<tr>
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<td>57</td>
<td>c.902G &gt; A</td>
<td>pathogenic</td>
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<td>3.90</td>
<td>2</td>
</tr>
<tr>
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<td>3.09</td>
<td>14</td>
</tr>
<tr>
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<td>c.902G &gt; A</td>
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<td>0.43$\mu$mol/L/h</td>
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</tr>
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<td>c.974G&gt;A</td>
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<td>0.31$\mu$mol/L/h</td>
<td>32.5</td>
<td>13</td>
</tr>
<tr>
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<td>c.974G&gt;A</td>
<td>pathogenic</td>
<td>3.17$\mu$mol/L/h</td>
<td>4.56</td>
<td>0</td>
</tr>
</tbody>
</table>

3.2 Clinical manifestations

The patients in our study presented with varying degrees of renal and extrarenal organ injury that showed familial aggregation. The frequency of organ damage in male and female is similar, but the onset age of female is significantly later than that of male (Fig. 2). The primary manifestation of renal injury was proteinuria, with 70.0% of patients exhibiting this symptom. The mean 24-hour urinary protein for all patients was $1.14 \pm 1.56$ g/24 h, with 15.0% of patients showing massive proteinuria. Haematuria was observed in 45.0% of patients, while chronic renal dysfunction was seen in 65.0% of patients, with one patient developing end-stage renal disease and requiring hemodialysis treatment. Among the extrarenal organs, the heart was the
most vulnerable (90.0%), followed by cerebral vessels (55.0%) and the lungs (55.0%). Seven patients (35.0%) displayed typical skin lesions characterized by angiokeratomas located on the trunk and inner thighs. Peripheral nerve injury was observed in seven patients (35.0%) as long-term neuropathic pain in the hands and feet with or without hypohidrosis, and only one patient (5.0%) showed nocturnal hyperhidrosis. Typical corneal opacity was found in 2 patients (10.0%). One patient (5.0%) experienced gastrointestinal symptoms characterized by diarrhea. No patients displayed hearing impairment in this study.

3.3 Cardiac involvement

This study evaluated the cardiac involvement of AFD patients using laboratory and imaging examinations. Out of the 20 patients, three (15.0%) showed increased TnI levels (TnI > 0.04 ng/mL), nine (45.0%) showed increased BNP levels (BNP > 100 pg/mL), and one (5.0%) showed increased D-Dimer levels (D-Dimer > 500µg/L). Cardiac dysfunction was observed in six patients (30.0%), of which three were classified as NYHA Class III and three as NYHA Class II. Electrocardiogram results revealed sinus rhythm in all patients, with seven patients (35.0%) showing left ventricular high voltage and three (15.0%) showing combined right ventricular high voltage. 24 hours dynamic electrocardiogram showed that six patients (30.0%) had arrhythmia, of which three patients (15.0%) had premature atrial beats and one patient (5.0%) had premature ventricular beats.

Echocardiography was used to assess cardiac function and cardiac structure, while CMR could assess cardiac function, measure myocardial thickness and mass, and detect cardiomyocyte lesions (Table 2). Echocardiography showed that although only one of these patients was diagnosed with reduced ejection fraction, 18 patients (90.0%) had varying degrees of valve dysfunction, including mitral regurgitation in 12 patients (60.0%), tricuspid regurgitation in 15 patients (75.0%), and aortic valve dysfunction in five patients (25.0%). 13 patients (65.0%, 16.86 ± 2.74mm) met the criteria for echocardiographic diagnosis of left ventricular hypertrophy, seven of whom (35.0%) accompanied by left atrial enlargement.
Table 2
Characteristic echocardiography and CMR findings of cardiac involvement in AFD patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Echocardiography</th>
<th>CMR</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td>LVEF (%)</td>
<td>Valvular function</td>
</tr>
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<td>F1f</td>
<td>female</td>
<td>49</td>
<td>59</td>
<td>aortic valve calcification</td>
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<tr>
<td>F1m</td>
<td>male</td>
<td>32</td>
<td>66</td>
<td>mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td>F2m</td>
<td>male</td>
<td>36</td>
<td>76</td>
<td>pulmonary valve, mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td>F3m</td>
<td>male</td>
<td>32</td>
<td>72</td>
<td>pulmonary valve, tricuspid regurgitation</td>
</tr>
<tr>
<td>F3f</td>
<td>female</td>
<td>57</td>
<td>71</td>
<td>pulmonary valve, mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td>F4m</td>
<td>male</td>
<td>30</td>
<td>73</td>
<td>pulmonary valve, mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td>F5m</td>
<td>male</td>
<td>32</td>
<td>70</td>
<td>mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td>F5f1</td>
<td>female</td>
<td>58</td>
<td>69</td>
<td>mitral regurgitation</td>
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<tr>
<td>F5f2</td>
<td>female</td>
<td>59</td>
<td>65</td>
<td>aortic valve, mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td>F6m1</td>
<td>male</td>
<td>28</td>
<td>59</td>
<td>aortic valve and tricuspid regurgitation</td>
</tr>
<tr>
<td>F6f</td>
<td>female</td>
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<td>66</td>
<td>mitral and tricuspid regurgitation</td>
</tr>
<tr>
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<td>52</td>
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<td>tricuspid regurgitation</td>
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<td>F8f1</td>
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<td>73</td>
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</tr>
<tr>
<td>F8f2</td>
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<td>66</td>
<td>normal</td>
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<tr>
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<td>mitral regurgitation</td>
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<tr>
<td>F9f</td>
<td>female</td>
<td>44</td>
<td>78</td>
<td>normal</td>
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</table>

Characteristic CMR findings of cardiac involvement in AFD were found in all of the patients (Table 2, Fig. 3, Fig. 4). Compared with echocardiography, CMR was more sensitive in detecting reduced ejection fraction, as it was observed in three patients (15.0%) using CMR but only one patient using echocardiography. In this study, 17 patients (85.0%, 18.41 ± 4.56 mm) met the criteria for CMR diagnosis of left ventricular hypertrophy due to AFD, and one of whom (5.0%) with right ventricular hypertrophy. Figure 3A were the end-diastolic frames from cine in AFD patient (F1f), indicating left ventricular hypertrophy, especially myocardium of interventricular septum (LVWT = 19 mm). When measuring myocardial thickness, CMR would yield a greater value than echocardiography (P = 0.001), where the difference was considered statistically significant, suggesting that echocardiography underestimates the severity of cardiac hypertrophy. The cardiomyocyte injury in AFD could be observed by T1 Mapping and gadolinium-enhanced cardiac magnetic resonance (Fig. 3B, C), including decreased T1 values and LGE. In this study, 19 patients (95.0%, 1108.45 ± 53.24 ms) showed decreased T1 values and LGE region, the T1 values of the patients decreased, with a minimum value of 1100 ms. Interestingly, in the non-LGE region, the T1 values of the patients increase to 1500-1600 ms. Figure 3C showed the presence of LGE in AFD patient (F1f), in which decreased subendocardial perfusion and LGE were observed in the apical segment, decreased myocardial perfusion and LGE in the basal inferolateral region. The LVMi (103.41 ± 61.74 g/m2) of patients in this study was associated with left ventricular hypertrophy (Fig. 4). Patients with LGE tended to have greater myocardial thickness and LVMi. Based on
the research results, the researchers recommended that all AFD patients in this study start ERT. However, three patients did not receive ERT due to economic reasons, and only 17 patients started ERT.

4. Discussion

AFD is a serious condition that can result in a poor prognosis if left undiagnosed and untreated. It is crucial for clinicians to be aware of AFD and its clinical manifestations to enable earlier identification and diagnosis. The clinical manifestations of AFD are highly heterogeneous, including angiokeratomas, neuropathic pain of the hands and feet, corneal opacities, and proteinuria [13, 14]. As the disease progresses, it can lead to end organ damages such as renal, cardiac, and cerebrovascular, which can impair quality of life and reduce life expectancy. The present study aimed to describe the organ involvement in 20 patients with AFD and compared the effectiveness of echocardiography with advanced CMR technologies (T1 Mapping and gadolinium-enhanced cardiac magnetic resonance) in evaluating cardiac function, structure, and cardiomyocyte lesions. The results of this study are intended to help clinicians recognize red flags for AFD and determine the optimal time to initiate ERT.

Abnormal deposition of Gb3 in lysosomes, leading to the increased sphingolipid deposition followed by chronic inflammation hypertrophy, and fibrosis is the major pathological feature of cardiac lesions of AFD[15]. Patients with AFD frequently die as a result of cardiovascular complications, which must be differentiated from other causes of left ventricular hypertrophy [16, 17]. In this study, all 20 patients developed cardiac lesions including arrhythmia, left ventricular hypertrophy, cardiac dysfunction, etc. The incidence of cardiac involvement was found to be higher compared with the previous study, where only 43% of patients showed cardiac involvement [18], which may be because the inclusion of patients with advanced-stage renal injury. Most of AFD patients have various cardiac arrhythmias, including bradyarrhythmia, conduction block and ventricular high voltage [19]. In this study, six patients (30.0%) had arrhythmia.

The acquisition of cardiac geometry and hemodynamics through the emission and reception of ultrasound waves is the primary function of echocardiography. This non-invasive imaging modality is widely used in the assessment and monitoring of patients with Anderson-Fabry disease AFD. Classic cardiac involvement in AFD can present LVH and systolic or diastolic dysfunction with preserved ejection fraction, which cannot be attributed to pressure overload [20]. Previous studies have reported a lower detection rate of left ventricular hypertrophy in AFD patients diagnosed by echocardiography, at 44% [21]. In contrast, our study has demonstrated a higher detection rate. This disparity may be due to the fact that our echocardiography observers were aware of the clinical diagnosis of the patients.

CMR has emerged as the gold standard for assessing cardiac function due to its higher spatial resolution and greater precision in measuring myocardial thickness and mass [22]. In addition to its ability to accurately measure cardiac structure, CMR can also be used to characterize myocardial function and detect pathological conditions such as cardiomyocyte injury [23]. T1 Mapping is a novel CMR technique that represents allows early identification of deposition of sphingolipids in myocardial by collecting different recovery times of myocardial longitudinal magnetization vector and then calculating T1 values. T1 value is determined by the tissue composition. Cardiomyopathy of AFD is characterized by decreased T1 values after abnormal deposition of sphingolipids in cardiomyocytes [24]. Another novel CMR technique is gadolinium-enhanced cardiac magnetic resonance, which can detect areas of fibrosis by comparing gadolinium concentrations in different regions of the myocardium after gadolinium contrast injection. This technique is a significant modality to detect myocardial fibrosis in AFD [25].

In this study, characteristic CMR findings of cardiac involvement in AFD were observed, including decreased T1 values and LGE, which have high reproducibility and can significantly distinguish AFD from other myocardial hypertrophic diseases [26, 27]. CMR also revealed that most patients had varying degrees of LVH [28], with maximal left ventricular wall thickness measured by CMR significantly higher than that measured by echocardiography. This suggests that echocardiography may underestimate the severity of myocardial hypertrophy. Additionally, CMR had a higher detect rate for decreased ejection fraction than echocardiography, indicating that CMR is more accurate and comprehensive in observing cardiac structure and assessing cardiac function [29]. By using T1 Mapping and gadolinium-enhanced cardiac magnetic resonance, decreased T1 values and LGE were detected in all patients, with 95.0% of patients (19 patients) showing decreased T1 values and 55.0% of patients (11 patients) showing LGE. In one patient, LGE was observed even though the T1 value did not decrease, indicating that the patient’s disease had progressed to the late stage with both sphingolipid deposition and fibrosis. Therefore, pseudo normalization of T1 value may indicate that the patient has more severe myocardial injury.

ERT and chaperone therapy are specific treatments for AFD, which can improve clinical symptoms while delaying disease progression. ERT, in particular, is shown to significantly delay the onset of renal dysfunction, proteinuria, and/or cardiac fibrosis by replenishing the patients with missing agalsidase [30]. A meta-analysis has reported favorable outcomes of ERT treatment on reducing left ventricular hypertrophy and LVMi in patients. However, it is essential to perform early comprehensive evaluation of patients to determine the need for ERT and initiate it as soon as possible for those with organ involvement [31]. In this study, CMR was performed on all the patients, and it was found that even patients with mild clinical manifestations had decreased T1 values with or without LGE, indicating the presence of myocardial lesions. These characteristic CMR findings provide evidence to initiate ERT treatment and can be used to evaluate treatment efficacy.

In conclusion, cardiac is the main target organ involved in AFD. CMR has been found to be more sensitive than echocardiography in detecting characteristic cardiac abnormalities in AFD patients. Therefore, we recommend the use of CMR with T1 Mapping and gadolinium-enhanced cardiac magnetic resonance for the clinical diagnosis and treatment of AFD. However, it should be noted that this study has certain limitations, including its small sample size and limited clinical phenotype, as the study population was solely drawn from the nephrology department. Therefore, a multidisciplinary approach involving the fields of nephrology, cardiology, neurology, dermatology, and other related disciplines may be necessary to achieve a comprehensive diagnosis and treatment of AFD.
Declarations

Contributions
B.W., X.Z. and A.Z. designed this study, J.Y., Z.W., Z.L., Y.Y., X.S., J.C., W.Y. S.Z. analyzed the data, J.Y. drafted and edited the manuscript.

Data availability statement
Data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available due to privacy or ethical restrictions.

Conflict of Interest
All the authors declared no competing interests.

Funding
This study was supported by grants from the National Natural Science Foundation of China\'No.82070735\to Prof. Bin Wang.

References


**Figures**

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**Figure 1**

The family tree of AFD family. The proband is denoted with an arrow. Squares indicate male patients and circles indicate female patients.
The frequency of organ damage in AFD patients. The abscissa is the injured organ; The ordinate is the average age of onset; The bubble width is the frequency of organ damage. Orange bubbles represent female patients, and blue bubbles represent male patients.

CMR of patients with AFD. A: End-diastolic frames from cine in AFD patient (F1f): The myocardium is extensively thickened, the ventricular septal myocardium is significantly thickened, and the thickest myocardium is 19mm; B: T1Mapping(3.0T) in AFD patient (F1f): T1 values was uneven; the T1 value in the corresponding area of LGE was increased, the T1 value of non LGE zone is about 1100-1200ms; C: Gadolinium-enhanced cardiac magnetic resonance (10-15min) in AFD patient (F1f): Decreased subendocardial perfusion and LGE (indicated by the red arrow) were observed in the apical segment.
Figure 4

Characteristic CMR findings of cardiac involvement in AFD patients. The abscissa is the LVWT (mm) of each patient; The ordinate is the minimum T1 value (ms) of each patient; The bubble width is the LVMI of each patient. The red bubble represents that the patient has LGE, the blue bubble represents that the patient has no LGE. The red line is the critical line for the diagnosis of left ventricular hypertrophy (LVWT≥13mm), and the blue rectangle is the normal T1 value (1200–1300ms) in this center.