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Cardiac involvement in Fabry disease: Recent advances, unresolved issues, and unmet needs

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Fabry disease is an X-linked lysosomal storage disorder caused by deficient activity of the enzyme α-galactosidase A, leading to the accumulation of globotriaosylceramide in various tissues, including the heart. Cardiac involvement is a prominent feature and a major cause of morbidity and mortality in Fabry disease, manifesting as left ventricular hypertrophy, myocardial ischaemia, heart failure, and arrhythmias. Secondary mechanisms, triggered by lysosomal storage, contribute to myocardial damage, in particular, myocardial inflammation. Early cardiac involvement can be subtle, but with disease progression, it becomes a major determinant of morbidity and mortality. Recent progresses in diagnostic techniques, such as advanced cardiac magnetic resonance imaging with T1 and T2 mapping, have improved early detection of Fabry-related cardiac disease. Enzyme replacement therapy and newer treatments like chaperone therapy have shown potential in managing cardiac manifestations when initiated early, while the progression of cardiac involvement may be difficult to halt in patients diagnosed late in the disease course. Gene therapy and substrate reduction therapy are emerging treatment modalities that hold promise but require further clinical evaluation. The limited efficacy of available therapies and the variability of cardiac response to treatment represent main unresolved issues, together with challenges in monitoring disease progression, and the need for additional therapeutic strategies targeting secondary mechanisms. Unmet needs in clinical practice include the identification of disease-specific and cardiac-specific biomarkers for early detection, staging, and monitoring cardiac damage. Similarly, strategies for prognostic stratification and better prevention of cardiovascular complications are essential to improve the care of these patients.

Fabry disease

Fabry disease (FD) is an X-linked genetic metabolic disorder caused by pathogenic variants in the *GLA* gene leading to lysosomal storage of glycosphingolipids in many cellular lines.[1] The primary pathogenetic mechanism underlying FD physiopathology is the absence or reduced activity of the enzyme alpha-galactosidase A (α-Gal A).[1] Deficient enzymatic activity leads to lysosomal storage of globotriaosylceramide (Gb3), globotriaosylsphingosine (lyso-Gb3), and other glycosphingolipids.[2] Since lysosomal function is central in cellular homeostasis, FD can determine a wide range of systemic alterations. Organs presenting low cellular turnover are mainly affected, and their involvement represents a major prognostic factor in FD patients.[1-3] Disease severity is strictly related to the degree of residual enzymatic activity leading to a significant phenotypic heterogeneity. Many nonsense, missense, and truncating GLA variants have been identified[3] leading to absent or nearly absent enzymatic

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activity in male patients, causing a classical phenotype with childhood onset and severe cardiac, renal, vascular, and central nervous system involvement in adulthood.[1,3] Patients with genetic variants associated with moderate residual α-Gal A activity (such as N215S in the Caucasian population or IVS4+919G>A in Taiwan)[3] develop the disease later in life (late-onset phenotype) often with a milder phenotype characterized by prevalent or isolated cardiac involvement.[1] In females, lyonization and skewed X-chromosome inactivation determine a wide heterogeneity in α-Gal A activity and consequent cellular storage/dysfunction.[2,3] Therefore, females often present variable systemic involvement with atypical features leading to significant diagnostic delay.

Pathophysiology of cardiac involvement

Cardiac involvement is a major prognostic determinant and a major cause of morbidity.

Fabry disease has been classically described as a storage cardiomyopathy, but the physiopathology of cardiac damage appears now more complex and sustained by multiple mechanisms. Lysosomal sphingolipid storage occurs in all cardiac lines, including myocytes, fibroblasts, conduction tissue, and endothelial, smooth muscular, and endocardial cells.[2] Ditaranto *et al.* recently compared cardiac magnetic resonance (CMR) and endomyocardial biopsy findings showing that myocyte size increases with storage and that histological changes precede *in vivo* imaging changes: myocyte hypertrophy before detectable left ventricular hypertrophy (LVH), storage before detectable T1 lowering, and fibrosis before detectable late gadolinium enhancement (LGE). In particular, the authors demonstrated that T1 starts to lower and LVH develops when vacuolated myocyte area exceeds respectively 10% and 20% of total area.[4]

Over time, progressive glycosphingolipid storage activates secondary pathways of damage, including programmed cell death, mitochondrial dysfunction, and inflammation.[1,2] Progressive myocardial damage results in worsening diastolic function and in advanced stages systolic left ventricular dysfunction with development of end-stage heart failure in most severe cases.[5] Myocardial ischaemia determined by microvascular dysfunction causes chronic and acute coronary syndromes further contributing to cardiac function deterioration.[1,2] Atrial fibrillation and ventricular arrhythmias in FD are likely determined by a complex interplay between hypertrophy, fibrosis, inflammation, and ischaemia.[2] The accumulation of glycosphingolipids in the atria and conduction tissue could explain the presence of shortened PR interval in early phases and development of atrioventricular block and life-threatening arrhythmias in advanced disease.[2] Moreover, a storage-induced dysregulation of structure and function of cardiac ion channels, demonstrated by studies on pluripotent stem cells derived from FD subjects, can further contribute to electrocardiogram (ECG) abnormalities and arrhythmia propensity.[2] Lysosome dysfunction also leads to impaired endocytosis and autophagy with consequent mitochondrial dysfunction and cellular energetic depletion.[6] Moreover, glycolipid storage can provoke direct oxidative damage on myofibrillar elements, deoxyribonucleic acid, and mitochondria.[6] These deranged metabolic pathways can therefore determine apoptotic and necrotic processes leading to cellular death and fibrosis formation.[6] Lysosomal storage also impairs the endoplasmic reticulum function with subsequent enhanced oxidative stress and unfolded protein response, an established trigger of inflammation.[6] Indeed, Gb3 and lyso-Gb3 accumulation may induce chronic inflammatory pathways, together with oxidative stress and impaired autophagy.[6] Exposure of neo-antigens, unfolded protein response and direct glycolipids, can trigger natural killer T cell activation through the toll-like receptor 4 and transforming growth factor beta pathways.[6] These mechanisms could significantly modulate the extracellular space and increase fibrosis formation, thereby contributing to long-term adverse remodelling.

The diagnosis of Fabry cardiomyopathy

Clinical manifestations

Male FD patients with a classic phenotype have a childhood onset of the disease presenting systemic manifestations related to peripheral nervous system (neuropathic pain, hypohidrosis, hearing loss, dizziness) and dermatological (angiokeratomas), ophthalmological (cornea verticillata, retinal vasculopathy), and gastrointestinal involvement. During the second to third decades, kidney (proteinuria, albuminuria, renal failure), cerebrovascular, pulmonary, and musculoskeletal manifestations become also evident.[3] These extracardiac features may help to identify undiagnosed FD patients and help in the differential diagnosis with other hypertrophic phenotypes.[3]

Cardiac involvement may manifest with different symptoms, ranging from fatigue, dyspnoea, chest pain, and palpitations.[1,2] Impaired diastolic dysfunction usually occurs in patients with LVH, causing heart failure with preserved ejection fraction that in advanced stages may progressively evolve to overt systolic dysfunction.[5] Angina is a common clinical manifestation of Fabry cardiomyopathy, and episodes of myocardial infarctions without significant epicardial coronary lesions have been described.[1,2]

Atrial fibrillation onset often represents an index of significant underlying cardiac substrate and can worsen symptomatic status and prognosis in terms of haemodynamic derangement and increased thromboembolic risk.[1,2] Sustained and non-sustained ventricular tachycardia and high-degree atrioventricular block can complicate the clinical course of the disease and identify a high-risk subgroup of patients requiring implantation of cardioverter defibrillators in primary or secondary prevention.[1,2]

Electrocardiogram and echocardiography

Reduced P wave duration and shortened PR intervals are early ECG findings, while in more advanced stages, progressive atrial remodelling and atrioventricular conduction delays are common.[1,2,7] Specific ECG alterations (such as prolonged peak R wave interval and reduced QRS spatial velocity) can significantly precede LVH development.[1] Increased QRS voltages are usually associated with LVH appearance together with ST segment alterations and presence of negative T waves[1,2]

in inferolateral leads reflecting posterolateral segments fibrosis.[1,2]

The cardiological instrumental 'red flags' of FD range from conventional echocardiography to advanced multimodality imaging. Left ventricular hypertrophy is considered the hallmark of cardiac involvement in FD. The most common phenotypic presentation is concentric hypertrophy, although eccentric and apical forms have also been reported.[2] Increasing evidence challenges the hypertrophy-centric paradigm of cardiac involvement in FD, particularly in females, suggesting a prevalence of cardiac damage without LVH higher than previously recognized. In fact, recent evidence emphasizes an early and prolonged pre-hypertrophic phase of cardiac disease. Focusing on early markers of cardiac involvement, diastolic left ventricular dysfunction and the impairment of longitudinal systolic function are early features of cardiac involvement and represent the substrate for the onset of clinical symptoms.[1,2,5] Moreover, emerging echocardiographic tools, such as deformation imaging of the left ventricle and left atrium (LA), may not only allow a timely diagnosis but possibly contribute to differentiate FD cardiomyopathy from other causes of LVH. The LA speckle-tracking analysis has demonstrated early-stage atrial myopathy in FD, with reductions in LA reservoir, conduit, and booster functions, independently from LVH or LA enlargement.[8] Initial stages of cardiac involvement are also characterized by reduced longitudinal strain, primarily affecting the latero-basal wall, with progressive decline in radial strain paralleling the development of LVH.[2]

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance provides detailed insights into myocardial tissue characterization and reveals distinct patterns according to the pathophysiological stages of FD. An initial 'accumulation phase' is associated with low native T1 values before LVH or LGE onset. Reduced native T1 values have emerged as early markers of intracellular Gb3 accumulation, preceding LVH. However, a recent histological study demonstrated that when T1 mapping values start to decrease, more than 45% of cardiomyocytes present cytoplasm vacuoles occupying more than 10% of the cytoplasm,[5] thus questioning the role of T1 mapping as early marker of cardiac involvement. Myocardial injury then evolves through development of myocardial oedema and inflammation, reflected by high T2 level and LGE in the basal inferolateral wall and low native T1 values in the remote myocardium (septum), with or without LVH.[2] In the advanced 'fibrosis and functional impairment phase,' patients present LVH, pseudonormalization of T1 values matching LGE areas.[1,2] Late gadolinium enhancement in FD usually initially affects the basal lateral wall with a midwall distribution that can progress to transmural involvement, associated with wall thinning. Cardiovascular magnetic resonance plays a central role also in risk stratification by identifying high-risk features, such as pronounced LVH, diffuse LGE, and T1 mapping dispersion, all associated with adverse clinical outcomes.[1,9] Cardiovascular magnetic resonance feature tracking analysis can detect impaired left atrial total and conduit strain values even in patients without LVH[10] (*Figure 1*). Furthermore, recent studies have identified a loss of the base-to-apex circumferential strain gradient as an early and independent marker of cardiac involvement beyond T1 mapping values.[11]

Treatment of Fabry disease cardiomyopathy

Optimal management of FD requires a multidisciplinary approach involving different cardiological and non-cardiological specialties, as well as nephrologists, geneticists, and specialized nursing care and psychological. Treatment of FD cardiomyopathy relies on both FD-specific therapies and conventional pharmacological and non-pharmacological treatments. Specific therapies include enzyme replacement therapy (ERT) and oral chaperone therapy, while emerging therapeutic strategies are under development. Regarding conventional cardiological treatment, specific recommendations have been provided in a recent consensus document.[12]

Enzyme replacement therapy

The advent of ERT has markedly changed the natural history of FD, demonstrating efficacy in reducing Gb3 accumulation and improving cardiac, renal, and neurological outcomes. Enzyme replacement therapy is administered intravenously every 2 weeks. An expert consensus document recommends the early initiation of ERT to achieve better outcomes starting in classic males during childhood regardless of symptoms and in late-onset males-classic/late-onset females at the first signs of organ involvement.[12] The administration of recombinant proteins used in ERT can elicit humoral immune responses, typically leading to the formation of anti-drug antibodies (ADAs) within 3–6 months of treatment initiation. Regular monitoring of anti-ERT antibodies is crucial, especially in cases of suboptimal clinical response. If adverse reactions or poor clinical responses occur, switching between the two ERT formulations remains a viable option. Long-term follow-up and registry data indicate that ERT may slow the progression of LVH and reduce the incidence of cardiovascular events.[12] Despite these findings, there is no evidence showing that this treatment can prevent myocardial fibrosis. Moreover, ERT appears less effective in reducing disease progression in advanced stages of FD, particularly in the presence of significant myocardial fibrosis.[2,6]

Chaperone therapy

Migalastat is an orally administered small-molecule chaperone that stabilizes specific mutant forms of α-Gal A, facilitating proper protein folding and lysosomal trafficking. Migalastat is suitable for patients with amenable GLA variants, which account for approximately 30–50% of FD-related mutations, predominantly missense mutations. The approved dosage is 123 mg, taken orally every other day at the same time of the day. Phase III clinical trials and clinical studies demonstrated stabilization of renal function and reduction of indexed left ventricular mass assessed by echocardiography.[2,12] A recent CMR-based study[13] after 18 months of migalastat treatment failed to show a significant left ventricular mass reduction while suggesting a potential disease stabilization based on the increase of septal T1 mapping values associated with improved functional capacity at cardiopulmonary exercise test. However, real-world data

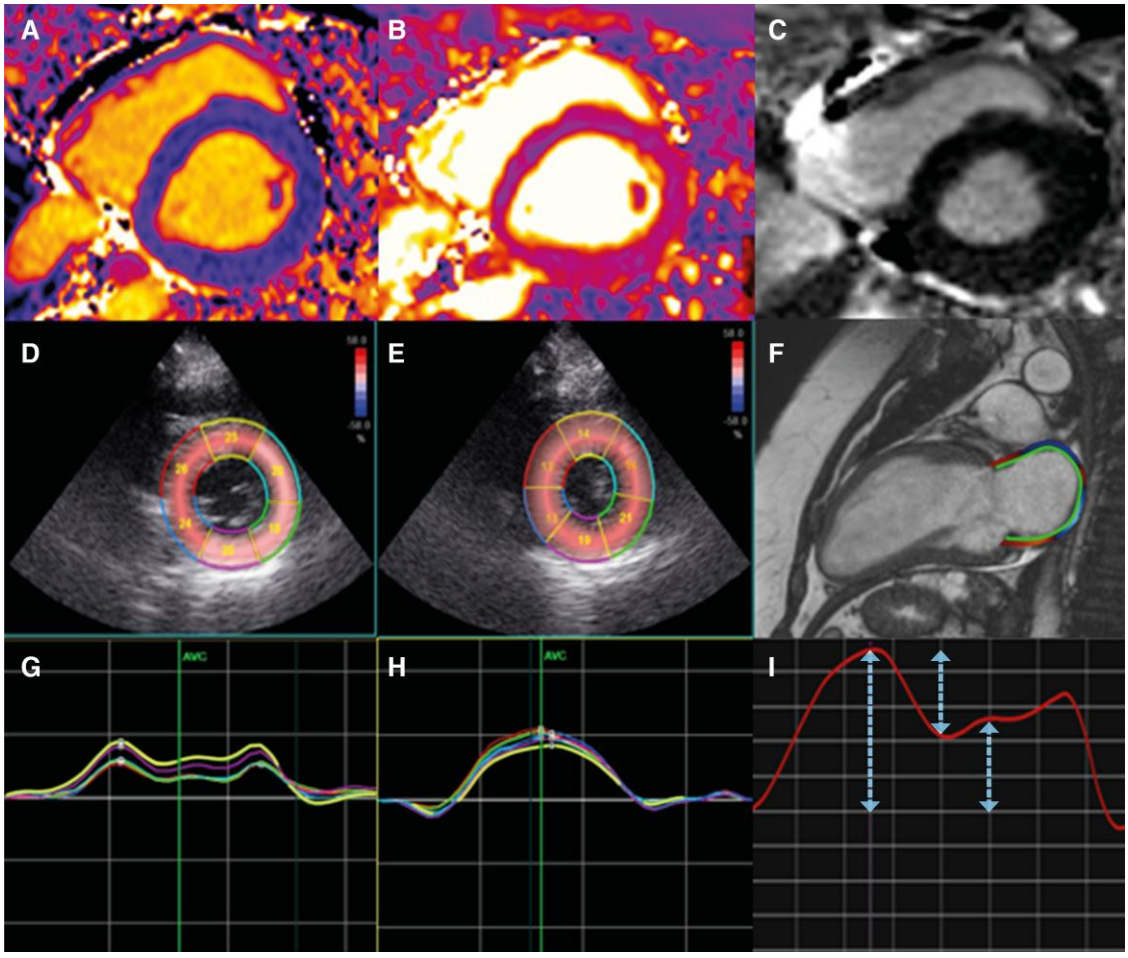

Figure 1 An illustrative case of advanced imaging assessment in a 21-year-old female patient in the pre-hypertrophic stage of Fabry disease. Basal left ventricular short-axis Shortened MOdified Look-Locker Inversion recovery (ShMOLLI) and inversion recovery-prepared T1-weighted gradient echo sequences reveal initially reduced T1 mapping values (*A*), approximately 930 ms (normal range: 1050–950 ms), with no evidence of oedema on T2 mapping (*B*) nor late gadolinium enhancement (*C*). Left ventricular short-axis echocardiographic views highlighting the loss of radial strain gradient between the basal (*D*) and apical segments (*E*), with (*G*) demonstrating lower strain curves in the inner half layer of the six basal left ventricular myocardial segments (16%), compared with (*H*) the higher/normal radial strain values in the six apical segments (21.5%). At cardiac magnetic resonance, a two-chamber balanced steady-state free precession image (*F*) shows a normal atrial volume (29 mL/m^2), despite a marked reduction across all phases of left atrial strain (reservoir, conduit, and booster function) (*G-I*), providing valuable insight into the underlying left atrial myopathy.

raised concerns about the lack of efficacy with some variants showing significant discrepancy between *in vitro* and *in vivo* amenability.[14]

Novel therapies

Novel ERTs, like pegunigalsidase alfa, have been engineered to minimize ADA formation and improve the bio-distribution, thus extending the bioavailability.[2,6] Substrate-reducing agents, such as ibiglustat (Venglustat) and lucerastat, are orally administered iminosugars that are genotype independent and directly inhibit glycosphingolipid synthesis. They are currently under investigation as single therapy or possible synergistic coadministration with ERT. In both treatments, promising initial results from Phase 2 and 3 of clinical trials demonstrated a significant reduction of plasma Lyso-Gb3.

Gene therapy using either viral or non-viral vectors offers the possibility of introducing corrected version of the *GLA* gene. Initial clinical trials (Phase I/II) have applied *ex vivo* approach showing promising preclinical results in increasing α-Gal A activity leading to a reduction of plasmatic Lyso-Gb3. However, challenges remain regarding adequate tissue uptake and immune responses against the newly expressed enzyme in patients with null α-Gal A activity. mRNA therapies are also in experimental stages, encapsulated with nanoparticles targeting hepatocytes to produce and secrete endogenous α-Gal A. This approach avoids insertional mutagenesis and aims to produce glycosylation profiles that do not trigger immune responses.[2,6]

Unsolved issues and unmet cardiological needs

Despite advances in understanding disease pathophysiology and in diagnosing and treating FD, several cardiological issues remain unsolved, and many clinical needs are unmet.

Concerning the diagnostic approach, awareness among cardiologists is not yet diffuse and screening programmes

appear limited by the high rate of detection of variants associated with late-onset phenotype, with no immediate therapeutic impact but with relevant social and economic implications. In addition, specific laboratory or imaging biomarkers that can easily detect early cardiac involvement are still lacking. Indeed, currently used biomarkers, such as plasma Lyso-Gb3, do not specifically correlate with cardiac pathology.

From a therapeutic perspective, the efficacy of currently available treatments on cardiac disease progression remains unclear. While data suggest that FD-specific therapies may stop or slow cardiac damage if administered very early in life, their impact on disease progression and long-term cardiac outcomes of established FD cardiomyopathy appear very limited. In addition, the clinical significance of ADAs and possible strategies to minimize their effect remain to be clarified. On the other hand, behind the issues regarding *in vivo* amenability,[14] the potential of chaperone therapy to revert cardiac storage seems limited as well.

While in other myocardial disorders like cardiac amyloidosis, efforts have been made not only to arrest the pathological process but also to revert the myocardial damage in FD, the focus has been almost exclusively remained on strategies to restore enzymatic activity. Therefore, while gene therapy appears promising, novel approaches aiming to clear myocardial tissue deserve further research and development. Similarly, the identification of secondary therapeutic targets beyond halting storage appears crucial to prevent cardiac damage. Inflammation and mitochondrial dysfunction appear at the present time, the most suitable candidates for adjunctive therapies.[6,15]

The development of newer therapies requires also validated tools to assess their efficacy on cardiac damage. We learnt from previous studies that cardiac damage may progress slowly compared with the resolution of current imaging techniques, claiming for the development of more accurate biomarkers or imaging techniques to monitor disease progression or regression. Staging and prognostic stratification of cardiac damage represent additional unsolved issues in FD. The recently proposed echocardiographic staging provides a good prognostic stratification[5] but remains unclear whether it can be used to monitor disease evolution. In the future, the integration of clinical data with patient-reported outcome measures and data deriving from implantable and wearable devices will further improve follow-up and disease monitoring. This approach, requiring the management of large amounts of data, will likely be facilitated by artificial intelligence–based systems. This patient empowerment can be supported by a close integration of referral centres in research networks and with patients' advocacy groups.

Conclusions

Several cardiological challenges remain unsolved in FD. Improved tools for early diagnosis, more effective therapies targeting cardiac complications, and the development of heart-specific biomarkers and prognostic stratification tools are crucial unmet needs. The integration of new therapies such as gene therapy, precision medicine approaches, and interdisciplinary care will be essential to improving quality of life and prognosis of FD patients. Whenever diagnosis is uncertain or management present complexities, patients should be referred to a specialized FD centre.

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Data availability

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