Cardiac abnormalities in Anderson-Fabry disease and Fabry’s cardiomyopathy

RP MORRISSEY, KJ PHILIP, ER SCHWARZ

Summary

Fabry’s disease is an X-linked lysosomal storage disease most often associated with renal dysfunction and death due to renal failure in patients’ fourth and fifth decades of life. However, cardiac manifestations including arrhythmias, angina and heart failure are common and probably under-recognised. Furthermore, Fabry’s disease is now recognised as also affecting female carriers, who manifest signs later than males. A variant of Fabry’s has been identified that only affects cardiac tissue, which presents as an unexplained hypertrophy of the left ventricle in middle-aged patients, possibly with women more affected than men.

Given that epidemiological studies report a prevalence of Fabry’s cardiomyopathy among middle-aged patients with cardiac hypertrophy to be anywhere from one to 12%, it is reasonable to screen these patients for alpha-galactosidase A deficiency. Although mortality data is lacking from randomised, controlled trials of galactosidase replacement therapy, there are some reports of improvement in cardiac endpoints. Therefore patients with known Fabry’s disease should be screened early for cardiac involvement, as treatment benefit may not be seen once cardiac fibrosis has developed.

Keywords: Fabry’s, Anderson-Fabry, left ventricular hypertrophy, restrictive cardiomyopathy, tissue Doppler imaging, cardiac MRI (CMR), late/delayed gadolinium enhancement

Fabry’s disease is one of roughly 40 lysosomal storage disorders that result in the accumulation of glycoproteins. Also called Anderson-Fabry disease, Fabry’s is caused by mutations in the GLA gene, which encodes alpha-galactosidase A, resulting in accumulation of glycosphingolipids, specifically globotriaosylceramide, within the lysosomes.1 This accumulation leads to cellular dysfunction, particularly in the endothelium, resulting in hypo-perfusion of tissues and further inflammation. The most frequently involved organs include the kidneys, heart, peripheral nerves and skin.2 Although an X-linked condition, heterozygous females as well as hemizygous males can be affected.

Anderson-Fabry disease, or angiokeratoma corporis diffusum, was independently described by Johann Fabry in Germany and William Anderson in England in 1898 in separate dermatology journals.3,4 However, it was not until 1963 when it was classified as a storage disorder,5 and 1967 when the enzymatic defect was identified.6 More recently, an atypical variant of Fabry’s, which presents as cardiac hypertrophy in middle-aged adults has been identified.7

The incidence of Fabry’s disease is estimated to be 1:55 000 male births,8 however, due to the constellation of presenting symptoms as well as some mutations allowing limited alpha-galactosidase A activity, the actual incidence of Fabry’s, including atypical, sub-clinical or late-variant phenotypes is likely to be much higher, even as high as 1:3 100 male births.6

Manifestations of Fabry’s disease are directly related to accumulated glycosphingolipids in tissues. Clinical symptoms usually present in childhood with painful neuropathy of the hands and feet, nausea and abdominal pain.9 Angiokeratomas, collections of enlarged cutaneous capillaries, specifically of the trunk, increase in number and size with age. Proteinuria and eventual renal failure result from the accumulation of glycosphingolipids in the tubular epithelial, glomerular and endothelial cells, resulting in both focal and diffuse glomerulosclerosis and microvascular dysfunction. Males progress to renal failure by their fourth decade and females by their fifth decade if untreated.9

Transient ischaemic attacks and strokes are 12 times more common than the general population in males between the ages of 25 and 44.10 Other neurological symptoms include decreased hearing, anhydrosis, abnormal peripheral sensation, e.g. temperature, pin-prick, and the neuropathic pain previously mentioned. Corneal opacities can also develop, although these usually do not affect vision. As will be discussed subsequently, manifestations of cardiac involvement include palpitations, dyspnoea or angina, usually secondary to an arrhythmia or myocardial hypertrophy.

Female ‘carriers’ or heterozygotes can also be affected and more often have cardiac manifestations.11 Signs of organ dysfunction due to glycosphingolipid accumulation also present later in women, with neurological features presenting at a mean age of 16 years and cardiac and renal involvement manifesting at mean ages of 33 and 37, respectively.11 The mechanism by which women are affected by this X-linked condition is most often attributed to X-inactivation; however, this has been called into question.12,13

One group reports the median cumulative age of death as

Review Article
being 50 years in males and 70 in females, although another series reports mean ages of 45 and 55 years, respectively. It has been generally stated in the literature that, at least prior to enzyme replacement therapy, men died from the consequences of renal failure, and women succumbed to cardiac complications.

Cardiac involvement

Fabry’s patients with cardiac involvement may present with dyspnoea, palpitations, syncope or angina, depending on the cardiac tissue involved. Classic Fabry’s is associated with cardiac manifestations including arrhythmias, valvular abnormalities and cardiomyopathy; however, the cardiac variant of Fabry’s presents later in life as left ventricular hypertrophy (LVH) with residual alpha-galactosidase A activity. Sixty per cent of Fabry’s patients have some cardiac manifestation, usually arrhythmias.

As in other organ tissues, cardiac dysfunction is due to glycosphingolipid accumulation in the myocytes and conduction tissue, but probably more importantly with respect to the cardiomyopathy is myocyte hypertrophy and fibrosis as glycosphingolipid deposition accounts for less than 3% of the total myocardial mass. Hypertrophic myocytes contain vacuoles laden with sphingolipids, resulting in eventual fibrosis. The extent of myocyte hypertrophy and the accumulation of glycosphingolipid-laden vacuoles correlates with the extent of LV wall thickening on imaging. Similar cell degeneration occurs in valvular as well as conduction tissue.

Cardiomyopathy

Although the hallmark of cardiac involvement in Fabry’s disease (classical or the cardiac variant) is LVH, Fabry’s cardiomyopathy is a restrictive cardiomyopathy, as it results from the accumulation of glycosphingolipids, whereas hypertrophic cardiomyopathy, i.e. non-physiological hypertrophy, is due to abnormal contractile proteins. However, the hallmark of restrictive cardiomyopathy is impaired ventricular filling, and in one series of 30 patients, no patient had severe diastolic dysfunction consistent with a restrictive pattern. Mild to moderate diastolic dysfunction is often present. Furthermore, most restrictive cardiomyopathies do not have LVH.

Amyloidosis can present with hypertrophy but it can easily be distinguished from Fabry’s in that the voltage is decreased on ECG. Also unlike other infiltrative cardiomyopathies, in Fabry’s only 1% of the myocardium contains the infiltrative material (glycosphingolipids). Therefore, as with other cardiomyopathies secondary to glycogen or lysosomal storage disorders, Fabry’s cardiomyopathy could be considered a ‘pseudo’-hypertrophic cardiomyopathy in that myocyte hypertrophy and fibrosis play a more prominent role than restrictive physiology in contributing to the heart failure.

In the cardiac variant of Fabry’s disease, patients have some alpha-galactosidase A activity and present later in life, often with only cardiac manifestations, although proteinuria can also be present. The cardiac variant, first described in 1990, may be due to alternative splicing in the alpha-galactosidase A gene, and in the first published case series, five of seven patients had no mutations in the coding regions despite very low levels of mRNA. The aetiology of the cardio-tropism of the cardiac variant of Fabry’s has not been elucidated.

Both the classical and cardiac variant of Fabry’s can cause global LVH or an asymmetrical septal hypertrophy similar to hypertrophic obstructive cardiomyopathy. However, systolic function is usually preserved, although there is a trend towards increased LV end-diastolic volume. Diastolic dysfunction is often present, but usually only moderate at worst and without a restrictive filling pattern. In heterozygous women with Fabry’s (mean age 40 years), 12.7% had concentric remodelling, 52.7% had concentric LV hypertrophy; and 10.9% had eccentric LVH by echocardiogram. Similar percentages were seen in hemizygous men, with 37% having concentric hypertrophy, and 37 and 10% having asymmetric septal hypertrophy.

Hypertrophy is present in 51 to 55% of males with a median age of 43 to 45 years, versus 33 to 38% of females with a median age of 55 years. Gender, age and renal function are directly and independently related to the presence of LVH, but not to blood pressure, i.e. LVH is the direct result of myocardial infiltration and not from primary hypertension or secondary to renal dysfunction. The prevalence of LVH has also been shown to be logarithmically related to alpha-galactosidase A activity. In a relatively large case series of 1 448 Fabry’s patients, 11% of men and 6% of women had congestive heart failure (CHF) symptoms and 35% had evidence of cardiac hypertrophy. However, the mean ejection fraction (EF) was preserved (63.1 ± 9.1%).

In a case-control series using echocardiography, tissue Doppler imaging (TDI) and cardiac MRI (CMR) to characterise Fabry’s cardiomyopathy, a distinct pattern of progression was seen in genetically- or biopsy-proven cases of Fabry’s disease. No patient had late gadolinium enhancement (LGE) (indicative of fibrosis, as will be discussed later) without LVH. Women younger than 20 years had no evidence of hypertrophy, normal radial and longitudinal function on TDI and no LGE. Women without LVH had reduced longitudinal function isolated to the lateral wall of the LV. Women with LVH had reduced longitudinal and radial function; women with LVH and LGE had severely reduced longitudinal and radial function.

Males without LVH had reduced longitudinal function in the lateral wall and septum, whereas males with LVH but without LGE also had reduced radial function. Males with LVH and LGE had severe longitudinal and radial dysfunction. In general, global LV function was not impaired. Similarly, another series found no evidence of either LVH or LV remodelling by echocardiogram in patients younger than 30 years old. Therefore, functional abnormalities arise before hypertrophy, and fibrosis visible on CMR only occurs after hypertrophy. These changes take time to develop as the glycosphingolipids accumulate.

The disproportionate amount of fibrosis in the lateral wall may be due to increased wall stress or a relatively oxygen-deficient environment. Lastly, there is no evidence of RV regional functional abnormalities or late-enhancement, possibly due to decreased work load of the right heart or that enhancement is more difficult to detect in the RV due to its smaller size and fewer myocytes.

Coronary artery disease/angina

Patients with Fabry’s have been documented as having an increased risk for coronary artery disease (CAD). However, in case-control series and cross-sectional studies, there is no evidence of increased admissions for myocardial infarctions,
need for revascularisation procedures, or CAD by myocardial perfusion scan. However, there is a higher frequency of angina compared to case-matched controls and it is more common in patients with LVH. Angina is present in 13 to 20% of patients, and equal among men and women.

This is not to say that patient’s with Fabry’s are not more susceptible to thrombotic or embolic phenomena. In one series of Japanese patients there was a high incidence of thrombotic events (9/65 with strokes). Despite a lack of significant coronary artery disease on angiograms, in one series, diffuse hypo-echogenic plaques were more common in Fabry’s patients compared to age-matched controls by intravascular ultrasound.

It has also been shown that coronary flow is reduced in patients with Fabry’s despite normal peripheral endothelial function. However, patients with hypertrophic cardiomyopathy also have slow coronary flow compared to controls. Therefore the exact aetiology of angina in patients with Fabry’s is still open to debate.

### Arrhythmias

Patients with Fabry’s are more prone to both atrial and ventricular arrhythmias due to glycosphingolipid deposition and fibrosis as well as atrial dilatation and relative ischaemia secondary to LVH. However, in one series, both systolic and diastolic blood pressures were normal, implying that atrial arrhythmias, in particular atrial fibrillation, were not secondary to long-standing hypertension or renal disease but to Fabry’s. Interestingly, in this series arrhythmias were 1.5 times more likely in males (although other cardiac events were similar), possibly due to more advanced cardiomyopathy and renal dysfunction in hemizygotes versus heterozygotes.

The most common ECG finding is voltage criteria for LVH, although various degrees of block as well as PR-interval shortening have also been described. Atrial arrhythmias, e.g. atrial fibrillation are more common than ventricular arrhythmias. In a case series of 78 patients over 10 years, 13% had paroxysmal atrial fibrillation (which was four times that of the general population for age) and 8% had non-sustained ventricular tachycardia (VT); all patients with VT had LVH. Predictors for atrial fibrillation were age, left atrial size, LV wall thickness, LV mass index (VT); all patients with VT had LVH. Predictors for atrial fibrillation were age, left atrial size, LV wall thickness, LV mass index and angina. Permanent pacemakers were implanted in 10.6% of patients for complete heart block or symptomatic bradycardia.

An international series of 714 patients also found that the incidence of arrhythmias was increased in patients with LVH. Corresponding to observational reports that women die from ventricular fibrillation at a younger age than men, the incidence of ventricular fibrillation was 1.5 times more likely in women compared to men.

### Valvular disease

Mitral and aortic valve abnormalities were present in 57 and 47% of one series (where LVH was present in 61%), although no severe regurgitation was noted. Another larger series documents mitral valve regurgitation in 32% of patients. In a series of 111 patients, there were no cases of severe valvular disease, including nine patients with end-stage disease. The most common valvular abnormality was mild mitral regurgitation (n = 57). The incidence of Fabry’s patients undergoing valve replacement surgery is low. Therefore valves are not the most significantly affected tissue of the heart in patients with Fabry’s and do not cause much burden.

### Evaluating for cardiac involvement

In a retrospective cohort analysis of patients with amyloidosis,Fabry’s, hypertrophic obstructive cardiomyopathy and hypertensive heart disease patients, no single clinical characteristic, ECG finding or echocardiographic feature could differentiate between the various causes of LV hypertrophy, including echogenicity, valvular abnormalities, renal dysfunction and diastolic dysfunction. However, painful neuropathy, anhydrosis, lack of hypertension and presence of Sokolow-Lyon criteria for LVH on ECG were significant for Fabry’s disease by univariate analysis. Furthermore, if none of hypertension, orthostasis, pericardial effusion or a papillary muscle anomaly was present, the sensitivity and specificity for Fabry’s disease was 92 and 87%, respectively.

### Echocardiography

As previously described, the echocardiogram shows varying degrees of hypertrophy and usually a preserved systolic function, with LVH more often seen in older individuals. Diastolic dysfunction, sometimes displaying a restrictive pattern, can be present, but peak E velocity, peak A velocity and deceleration time of the mitral valve are most often normal, and diastolic dysfunction is usually not present in the absence of LVH.

Furthermore, diastolic dysfunction does not distinguish Fabry’s cardiomyopathy from hypertrophic obstructive cardiomyopathy. As previously discussed, valvular abnormalities, most often mitral and aortic, are not associated with severe regurgitation.

A case-control series of 40 consecutive patients showed that 82.5% of Fabry’s patients – 94% of Fabry’s patients with LVH – had a ‘binary appearance’ of the endocardial border, which was not present in any matched hypertrophic cardiomyopathy patient, hypertensive or otherwise, representing a sensitivity and specificity of 94 and 100%, respectively, for detecting Fabry’s cardiomyopathy. Furthermore, pathological examination of the ‘binary’ areas revealed endocardium and myocardium laden with glycosphingolipids, separated by a subendocardial ‘empty space’.

However, relying on the ‘binary sign’ has been challenged recently by Kounas et al., where they found the sensitivity and specificity of the binary appearance on echocardiogram to differentiate Fabry’s from hypertrophic obstructive cardiomyopathy to be 35 and 79%, respectively. Furthermore, only 3.5% of patients with LVH wall thickness less than 15 mm had a binary sign, albeit the number of subjects examined was small. A recent small, blinded study reported that a binary appearance of the endocardium on echocardiography has a sensitivity of only 15.4%, but a specificity of 73.3%.

### Tissue Doppler imaging (TDI)

Although two-dimensional echocardiogram cannot be used to screen patients with Fabry’s disease for signs of cardiac involvement before the development of LVH, the addition of TDI may be reliable in detecting sub-clinical involvement. In a case-control series of 20 patients with Fabry’s (half with LVH) and 10 control patients, those with Fabry’s showed reduced contraction and relaxation even before the development of LVH. Lateral or septal systolic velocities (Sa) < 10 cm/s or early diastolic velocities (Ea) < 10 cm/s each showed a sensitivity and specificity of 100% in mutation-positive patients without LVH.
A recent larger study confirmed the usefulness of TDI in detecting sub-clinical cardiac involvement, showing significantly lower Ea velocities (lateral 12.00 ± 3.34 cm/s, septal 5.52 ± 2.12 cm/s), although Sa velocities did not differ between Fabry’s patients and controls. Late diastolic velocities (Aa) and isovolumetric contraction times (IVCT) were also significantly lower in Fabry’s patients without LVH compared to controls. Isovolumic relaxation times (IVRT) were significantly longer in all Fabry’s patients compared to controls. IVCT ≤ 105 ms was the best predictor for sub-clinical involvement with a sensitivity of 100% and specificity of 91%. An Ea velocity of < 15.5 cm/s had a sensitivity of 44.4% and specificity of 93.2% while IVRT > 60 ms had a sensitivity and specificity of 27.8 and 96.6%, respectively, for detecting pre-clinical cardiac involvement in Fabry’s patients.42

Therefore TDI may be a valuable and inexpensive modality for detecting cardiac involvement in hemizygous men and heterozygous or ‘carrier’ females.29

Cardiac MRI
Cardiac MRI (CMR) has firmly established its usefulness in the evaluation of left ventricular dysfunction and cardiomyopathy, specifically in the absence of coronary artery disease on angiogram, i.e. non-ischaemic cardiomyopathy.31 CMR is non-invasive and can be used to not only assess cardiac function, but also for tissue abnormalities such as fibrosis, infiltration and inflammation.

With respect to Fabry’s cardiomyopathy, most commonly seen on CMR is regional or global myocardial hypertrophy; however, one potential distinguishing feature of cardiac hypertrophy due to Fabry’s disease is late enhancement of gadolinium, also called delayed contrast enhancement. Gadolinium enhancement occurs when chelated gadolinium stays in the intercellular space; in conditions causing fibrosis, the intercellular space is increased and distribution is slower.31 Areas of late gadolinium enhancement (LGE) in Fabry’s cardiomyopathy correspond histologically to collagen, but unlike post myocardial infarction scarring, the collagen is not in disarray.31 The scarring in Fabry’s is not as well defined as fibrosis seen post myocardial infarction (MI), with LGE being able to differentiate between the two.31

Although LGE is not a specific finding with regard to restrictive or hypertrophic cardiomyopathies and can be seen in any aetiology of LVH,29 fibrosis may be more focal than other forms of cardiomyopathy (e.g. versus global sub-endocardial involvement in amyloidosis) and various cardiomyopathies may have different tissue predilections (e.g. papillary muscle in cardiac sarcoidosis).31 Although reports are not always consistent for various cardiomyopathies27 and more work needs to be done to evaluate the utility of LGE in differentiating different cardiomyopathies,31 for reasons which have not been completely elucidated, the earliest evidence of LGE in Fabry’s disease is the basal infero-lateral wall (also known as the postero-lateral wall).40,44-50

A recent study comparing patients with symmetric hyper trophy cardiomyopathy and Fabry’s cardiomyopathy found late gadolinium enhancement of the infero-lateral basal or mid-basal segments sparing the sub-endocardium to be specific for Fabry’s.37 However, LGE is only present in severe stages of Fabry’s cardiomyopathy, reflecting the extensive fibrosis due to glycosphingolipid accumulation,42,46 and LGE has been shown to correlate with a poorer prognosis in non-ischaemic cardiomyopathy.34

Another potential method for screening patients with Fabry’s disease for early cardiac involvement or differentiating physiological LVH from Fabry’s cardiomyopathy using CMR is T2 relaxation time, which has been shown to be prolonged in Fabry’s patients with and without increased myocardial wall thickness.59

ECG
ECG findings are non-specific but may show manifestations of conduction tissue infiltration, such as PR prolongation,39 varying degrees of heart block, sinus bradydysrhythmias, sick sinus syndrome, and atrial or ventricular arrhythmias.39 Myocardial infiltration may present as evidence of atrial enlargement or LVH.

Screening patients with LVH for Fabry’s disease
Of patients with late-onset cardiac hypertrophy, the prevalence of Fabry’s disease has been reported to be as high as 6% in men (mean age 53 years)44 and 12% in women (mean age 50 years).44 A recent study from Spain showed the incidence to be 1% by genotyping (mean age 58 years) (0.9% in men and 1.1% in women), although low alpha-galactosidase activity was present in 3%.59 Strong consideration should be made to check alpha-galactosidase A activity in middle-aged patients with hypertrophy in the absence of long-standing hypertension.

Treatment
Enzyme replacement therapy (ERT) for the treatment of Fabry’s disease was first performed in the 1970s,46 however, open-label phase 2 trials were not performed until the 2000s.47 ERT using recombinant human alpha-galactocidase A (generic names agalsidase alpha and agalsidase beta) was approved for use in Europe in 2001 and in the United States in 2003.44

Initial randomised controlled trials (RCT) showed that 69% of the treatment group was free of renal microvascular endothelial deposits of globotriaosylceramide (primary endpoint) versus no change in the placebo group after 20 weeks (p < 0.001). There was also a statistically significant difference in endothelial deposits in the heart (p < 0.001).48

Although there did not appear to be a difference in quality of life as assessed by the SF-36,44 another RCT showed a statistically significant decrease in pain severity and improvement in quality of life (primary outcome). This study also showed improvement in renal architectural distortion (mesangial diameter (p = 0.01) and increase in creatinine clearance (p = 0.02).49

In a more recent, larger RCT, 42% of placebo patients versus 27% of treated patients had clinical events (defined as renal, cardiac or cerebrovascular event or death); the time to first clinical event adjusted for baseline proteinuria favoured agalsidase beta but included the null (hazard ratio 0.47, CI: 0.21–1.03; p < 0.06). Time to first cardiac event (arrhythmia, angina or MI) was not affected. Although overall the results were less than overwhelming, treatment effect was greater in patients with preserved renal function.44 There are no data currently regarding ERT and affect on mortality.

Cardiomyopathy
Observational studies have been performed which specifically analyse cardiac endpoints in Fabry’s patients on ERT. Several studies have documented statistically significant improvement
in LVH by echocardiography\(^{11, 16}\) and CMR\(^{67, 68}\). Hughes et al. also document a 20% reduction in myocardial Gb, content by cardiac biopsy at six months of therapy, versus a 10% increase in patients receiving placebo.\(^{44}\) At least one study has documented an improvement in diastolic dysfunction (29% decrease of E/Ea; \(p < 0.002\)), although there was no improvement in LVH or renal function.\(^{46}\) However, at two years, one study has shown no statistically significant changes on ECG, stress echocardiography or CMR, although one-year follow-up data did look promising.\(^{70}\)

Although improvement in symptoms of CHF and angina have been reported as improved with therapy,\(^{71}\) this remains open to question.\(^{72}\) The lack of efficacy may be due to the degree of fibrosis. As hypothesised previously,\(^{44}\) a recent case-control study found a statistically significant reduction in LVH (\(p < 0.001\)), improved myocardial function by TDI (\(p = 0.045\)) and improved exercise capacity (\(p = 0.014\)) in patients with no fibrosis by late gadolinium enhancement at three years. However, in patients with mild or severe fibrosis, there was only minimal improvement in LVH and no improvement in LV function or exercise capacity.\(^{73}\)

**Angina and arrhythmias**

Interestingly, in one series, conduction and valvular abnormalities were more common in patients receiving treatment, most likely reflecting the biases of observational studies.\(^{74}\) Overall, there is little data on the incidence/prevalence of arrhythmias with and without treatment, however one author reports on the lengthening of an ‘abbreviated PR interval’ in one patient.\(^{72}\) Coronary microvascular dysfunction does not appear to improve on therapy,\(^{75, 76}\) nor does angina improve despite improvement in LVH,\(^{73, 77}\) however, this may be confounded by the degree of cardiac involvement (see above). Regardless, this does imply that angina may be more related to microvascular dysfunction than to hypertrophy and supply–demand mismatch of oxygenation.

**Conventional therapy**

Fabry’s patients with obstructive coronary artery disease should be managed as any other patient, including treatment with aspirin, lipid-lowering therapy, anti-anginals, beta-blockers, etc, and revascularisation should be according to the standard of care.\(^{75}\) However, special considerations with regard to coronary artery bypass grafting may be warranted. One case report has suggested that at least in untreated Fabry’s patients, vein grafts may be better conduit vessels than the left internal mammary artery due to an increased amount of sphingolipid infiltration, thus making arterial conduits more susceptible to premature failure.\(^{78}\)

Significant valvular dysfunction should be managed per the current guidelines,\(^{72}\) and case reports of both aortic\(^{79}\) and mitral\(^{80}\) valve replacements have been documented. Pacemaker for symptomatic bradycardia, heart block, etc. should be implanted according to current device guidelines.\(^{81}\)

Medical therapy for Fabry’s patients with systolic dysfunction should include: angiotensin-converting enzyme inhibitor (ACEI) or aldosterone receptor blocker (ARB), beta-blocker, hydralazine plus nitrate in patients of African descent after maximal titration of ACEI or ARB, and diuretics for volume management. Furthermore, ICD and biventricular pacing should also be considered after maximal medical therapy as per guidelines.\(^{82}\) Diastolic dysfunction should be treated with diuretics for systolic management, although there is some retrospective data that statins may improve mortality.\(^{83}\)

Symptomatic Fabry’s cardiomyopathy mimicking hypertrophic obstructive cardiomyopathy may benefit from septal alcohol ablation.\(^{84}\) Fabry’s patients with end-stage heart failure on maximal medical therapy should also be considered for transplant regardless of the aetiology.\(^{35}\) Interestingly, the transplanted organ would also produce alpha-galactosidase A, possibly protecting from future cardiac abnormalities due to glycosphingolipid accumulation.

Based on limited data from small studies, it appears that treatment should be initiated early, ideally before the development of fibrosis (late enhancement on CMR).\(^{10}\) However, ERT does not replace conventional medical therapy for arrhythmias, angina and heart failure.

**Conclusion**

Although Fabry’s disease in the general population is rare, it may be relatively common in patient’s presenting with late cardiac hypertrophy. Cardiac involvement in both the classical and cardiac variant, Fabry’s disease is characterised by arrhythmias and LV hypertrophy. The hypertrophy in Fabry’s cardiomyopathy can potentially be distinguished from other aetiologies by TDI when isovolumic contraction time is ≤ 105 ms and Ea is < 10 cm/s, and by expert interpretation of late gadolinium enhancement and prolonged T2 relaxation time on cardiac MRI. TDI may also be able to detect cardiac involvement before the development of hypertrophy.

Treatment with enzyme replacement therapy may decrease the frequency of cardiac events, decrease hypertrophy, and, if started early before the development of fibrosis, may improve cardiac function and prevent deterioration in functional capacity. Middle-aged patients presenting with hypertrophy, particularly in the absence of other common aetiologies, should be evaluated for alpha-galactosidase deficiency.

**References**

1. Phillips JA, Kniffin CL, Kelly J, et al. #301500 Fabry Disease. OMIM. Available at: http://www.ncbi.nlm.nih.gov/entrez/dispomim. cg?disp=301500. Accessed on: February 19, 2009.
2. Zarate YA, Hopkin RJ. Fabry’s disease. Lancet 2008; 372: 1427–1435.
3. Anderson W. A case of ‘angeokeratoma’. Br J Dermatol 1898; 10: 113–117.
4. Fabry J. Ein Beitrag zur Kenntnis der Purpura haemorrhagica nodularis (Purpura papulosa haemorrhagica Hbren). Arch Dermatol Syph 1898; 43: 187–200.
5. Sweely CC, Klionsky B. Fabry’s disease: classification as a sphingolipidosis and partial characterization of a novel glycolipid. J Biol Chem 1963; 238: 3148–3150.
6. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry’s disease. Ceramidetrihexosidase deficiency. N Engl J Med 1967; 276: 1163–1167.
7. Nakao S, Takekata T, Mueda M, et al. An atypical variant of Fabry’s disease in men with left ventricular hypertrophy. New Eng J Med 1995; 333: 288–293.
8. Spada M, Pagliardini S, Yasuda M, et al. High incidence of later-onset Fabry disease revealed by newborn screening. Am J Hum Genet 2006; 79: 31–40.
9. Schiffmann R, Warnock DG, Banikzemi M, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebral vascular events before enzyme replacement therapy. Nephrol Dial Transplant 2009. Available at: http://ndt.oxfordjournals.org/cgi/content/full/gfp031v2. Last accessed on April 14, 2009.
10. Vedder AC, Linthorst GE, van Bremen MJ, et al. The Dutch Fabry cohort: diversity of clinical manifestations and Gb3 levels. J Inherit Metab Dis 2007; 30: 68–78.

11. Deegan PB, Baehner AF, Barba Romero MA, Hughes DA, Kampmann C, Beck M. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet 2006; 43: 347–352.

12. Wang RV, Leis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med 2007; 9: 34–45.

13. Cox GF. Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. Prog Pediatr Cardiol 2007; 24: 15–25.

14. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 2001; 38: 750–760.

15. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet 2001; 38: 769–775.

16. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004; 34: 236–242.

17. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 2003; 138: 338–346.

18. Kampmann C, Linhart A, Baehner F, et al. Onset and progression of the Anderson-Fabry disease related cardiomyopathy. Int J Cardiol 2008; 130: 367–373.

19. Pieron M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. Circulation 2003; 107: 1978–1984.

20. Hughes SE, McKenna WJ. New insights into the pathology of inherited cardiomyopathy. Heart 2005; 91: 257–264.

21. Stoffelberger C, Finsterer J. Extracardiac medical and neuromuscular complications in restrictive cardiomyopathy. Clin Cardiol 2007; 30: 375–380.

22. Wood MJ, Piccard MH. Utility of echocardiography in the evaluation of individuals with cardiomyopathy. Heart 2004; 90: 707–712.

23. Linhart A, Palecek T, Bultas J, et al. New insights in cardiac structural changes in patients with Fabry’s disease. Am J Heart 2000; 139: 1101–1108.

24. Linhart A, Lubanda JC, Palecek T, et al. Cardiac manifestations in Fabry disease. J Inherit Metab Dis 2001; 24: 75–83.

25. Elleder M, Bradová V, Smíd F, et al. Cardiocyte storage and hypertrophy as a sole manifestation of Fabry disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. Virchows Arch A Pathol Anat Histopathol 1990; 417: 449–455.

26. Ogawa K, Sugamata K, Furamoto N, et al. Restricted accumulation of globotriaosylceramide in the hearts of atypical cases of Fabry’s disease. Hum Pathol 1990; 21: 1067–1073.

27. Ishii S, Nakao S, Minamikawa-Tachino R, Desnich RJ, Fan QJ. Alternative splicing in the alpha-galactosidase A gene: increased exon inclusion results in the Fabry cardiac phenotype. Am J Hum Genet 2002; 70: 994–1002.

28. Sadick N, Thomas L. Cardiovascular manifestations in Fabry disease: a clinical and echocardiographic study. Heart Lung Circ 2007; 16: 200–206.

29. Shah JS, Lee P, Hughes D, et al. The natural history of left ventricular systolic function in Anderson-Fabry disease. Heart 2005; 91: 533–534.

30. Kampmann C, Baehner F, Whybra C, et al. Cardiac manifestations of Anderson-Fabry disease in heterozygous females. J Am Coll Cardiol 2002; 40: 1668–1674.

31. Linhart A, Kampmann C, Zamorano JL, et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J 2007; 28: 1228–1235.

32. Ponderels LJ, Strotmann J. Congestive heart failure in Fabry cardiomyopathy: Natural history experience in an international cohort of 1,448 patients. J Heart Lung Transplant 2006; 25: 570.

33. Weidemann F, Breunig F, Beer M, et al. The variation of morphologic and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. Eur Heart J 2005; 26: 1221–1227.

34. Utsumi K, Ueda K, Watanabe M, et al. Thrombosis in Japanese patients with Fabry disease. J Neurol Sci 2009. Available at: http://www.jnsjournal.com/article/S0022-510X(09)00413-4/abstract. Last accessed on April 15, 2009.

35. Kovarnik T, Mintz GS, Karetova D, et al. Intravascular ultrasound assessment of coronary artery involvement in Fabry disease. J Inherit Metab Dis 2008; 31: 753–760.

36. Kalliokoski RJ, Kalliokoski KK, Sundell J, et al. Impaired myocardial perfusion reserve but preserved peripheral endothelial function in patients with Fabry disease. J Inherit Metab Dis 2005; 28: 563–573.

37. Cortigiani L, Rigo F, Gherardi S, Galdieri M, Sicari R, Picano E. Prognostic implications of coronary flow reserve on left anterior descending coronary artery in hypertrophic cardiomyopathy. Am J Cardiol 2008; 102: 1718–1723.

38. Roud shepherd CP, Foerster JM, Bing OH. The abbreviated PR interval of Fabry’s disease. N Engl J Med 1973; 289: 357–358.

39. Shah JS, Hughes DA, Sackewitz B, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. Am J Cardiol 2005; 96: 842–846.

40. Weidemann F, Strotmann JM, Niemann M, et al. Heart Valve Involvement in Fabry Cardiomyopathy. Ultrasound Med Biol 2008. Available at: http://www.elsevier.com/locate/iumb. Last accessed on April 14, 2009.

41. Hoigne P, Attenhofer Jost CH, Duru F, et al. Simple criteria for differentiation of Fabry disease from amyloid heart disease and other causes of left ventricular hypertrophy. Int J Cardiol 2006; 111: 413–422.

42. Toro R, Perez-Isa L, Doxastakis G, et al. Clinical usefulness of tissue Doppler imaging in predicting preclinical Fabry cardiomyopathy. Int J Cardiol 2009; 132: 38–44.

43. Pieron M, Chimenti C, De Cobelli F, et al. Fabry’s disease cardiomyopathy: echocardiographic detection of endomyocardial glycosphingolipid compartmentalization. J Am Coll Cardiol 2006; 47: 1663–1671.

44. Kouns S, Demetreescu C, Pantazis AA, et al. The binary endocardial appearance is a poor discriminator of Anderson-Fabry disease from familial hypertrophic cardiomyopathy. J Am Coll Cardiol 2008; 51: 2058–2061.

45. Koskenvuo JW, Englihm E, Kantola IM, et al. Echocardiography in Fabry disease: diagnostic value of endocardial border binary appearance. Clin Physiol Funct Imaging 2009; 29: 177–180.

46. Pieron M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. Circulation 2003; 107: 1978–1984.

47. German T, van Rossum AC. The use of cardiac magnetic resonance imaging to determine the aetiology of left ventricular disease and cardiomyopathy. Heart 2008; 94: 510–518.

48. Moon JC, Sachdev B, Elkington AG, et al. Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium. Eur Heart J 2003; 24: 2151–2155.

49. Moon JC, Reed E, Sheppard MN, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2004; 43: 2260–2264.

50. Rudolph A, Abdel-Aty H, Bohil S, et al. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. J Am Coll Cardiol 2009; 53: 284–291.

51. Silva C, Moon JC, Elkington AG, John AS, Mohiaddin RH, Pennell DJ. Myocardial late gadolinium enhancement in specific cardiomyopathies by cardiovascular magnetic resonance: a preliminary experience. J Cardiovasc Mag (Hagerstown) 2007; 8: 1076–1079.

52. Bohil S, Wasmuth R, Abdel-Aty H, et al. Delayed enhancement cardiovascular magnetic resonance imaging reveals typical patterns of myocardial injury in patients with various forms of non-ischemic heart disease. Int J Cardiovasc Imaging 2008; 24: 597–607.

53. Mahrohldt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-
ischaemic cardiomyopathies. Eur Heart J 2005; 26: 1461–1474.

54. Marcus CB, Nijveldt R, Beek AM, Van Rossum AC. Delayed contrast enhancement magnetic resonance imaging for the assessment of cardiac disease. Heart Lung Circ 2007; 16: 70–78.

55. Naguse SF, Mahmariain JJ. Noninvasive cardiac imaging in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2006; 48: 2410–2422.

56. Sekizawa K, Mahnholdt H, Vogelsberg H. Cardiac magnetic resonance in myocardial disease. Heart 2007; 93: 1520–1527.

57. De Cobelli F, Espósito A, Belloni E, et al. Delayed-enhanced cardiac MRI for differentiation of Fabry's disease from symmetric hypertrophic cardiomyopathy. Am J Roentgenol 2009; 192: W97–102.

58. Wu KC, Weiss RG, Thiemann DR, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol 2008; 51: 2414–2421.

59. Imbriaco M, Spinelli L, Cuocolo A, et al. MRI characterization of myocardial tissue in patients with Fabry's disease. Am J Roentgenol 2007; 188: 850–853.

60. Sachdev B, Takenaka T, Terguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002; 105: 1407–1411.

61. Chimienti C, Pieroni M, Morgante E, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. Circulation 2004; 110: 1047–1053.

62. Monserrat L, Gimeno-Blanes JR, Marín F, et al. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2007; 50: 2399–2403.

63. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A—replacement therapy in Fabry's disease. N Engl J Med 2001; 345: 9–16.

64. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med 2007; 146: 77–86.

65. Schifflmann R, Kopp JB, Austin HA 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. J Am Med Assoc 2001; 285: 2743–2749.

66. Spinelli L, Pissani A, Sabbatini M, et al. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. Clin Genet 2004; 66: 158–165.

67. Beer M, Weidemann F, Breunig F, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. Am J Cardiol 2006; 97: 1515–1518.

68. Hughes DA, Elliott PM, Shah J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart 2008; 94: 153–158.

69. Kovacevic-Preradovic T, Zuber M, Jost CH, et al. Anderson-Fabry disease: long-term echocardiographic follow-up under enzyme replacement therapy. Eur J Echocardiogr 2008; 9: 729–735.

70. Koskenuo JW, Hartiala JJ, Nuutila P, et al. Twenty-four-month agalsidase A replacement therapy in Fabry disease has only minimal effects on symptoms and cardiovascular parameters. J Inherit Metab Dis 2008; 31: 432–441.

71. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation 2009; 119: 524–529.

72. Waldek S. PR interval and the response to enzyme-replacement therapy for Fabry's disease. N Engl J Med 2003; 348: 1186–1187.

73. Chimienti C, Morgante E, Tanzilli G, et al. Angina in Fabry disease reflects coronary small vessel disease. Circ Heart Fail 2008; 1: 161–169.

74. Elliott PM, Kindler H, Shah JS, et al. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. Heart 2006; 92: 357–360.

75. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Sperutz JA. 2009 Appropriateness criteria for coronary revascularization. J Am Coll Cardiol 2009; 53: 530–553.

76. Chimienti C, Morgante E, Critelli G, Russo MA, Frustaci A. Coronary artery bypass grafting for Fabry's disease: veins more suitable than arteries? Pathol Pract 2007; 38: 1864–1867.

77. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol 2008; 52(13): e1–142.

78. Choi S, Seo H, Park M, et al. Fabry disease with aortic regurgitation. Ann Thorac Surg 2009; 87: 625–628.

79. Miyata M, Sato T, Iwai-Takano M, Suzuki H, Ishibashi T, Takeishi Y. Mitral valve replacement due to mitral valve regurgitation in patient with Fabry disease. J Card Fail 2008; 14: S151.

80. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol 2008; 51: e1–62.

81. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the diagnosis and management of heart failure in adults. J Am Coll Cardiol 2009; 53: e1–e90.

82. Fukutsa H, Little WC. Observational studies of statins in heart failure with preserved systolic function. Heart Fail Clin 2008; 4: 209–216.

83. Magee S, Linhart A, Bultas J, et al. Fabry disease: percutaneous transluminal septal myocardial ablation markedly improved symptomatic left ventricular hypertrophy and outflow tract obstruction in a clinically affected male. Echocardiography 2005; 22: 333–339.

84. Karras A, De Lente Decker P, Delahousse M, et al. Combined heart and kidney transplantation in a patient with Fabry disease in the enzyme replacement therapy era. Am J Transplant 2008; 8: 1345–1348.