CARDIOLOGY Rounds®

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Fabry's Cardiomyopathy: Diagnosis, Pathophysiology and the Role of Enzyme Replacement Therapy

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Fabry disease is an X-linked abnormality of glycosphingolipid metabolism that results in systemic deposition of sphingolipid, especially in the vascular endothelium and myocardium, which leads to left ventricular hypertrophy (LVH), endothelial dysfunction, and valvular disease. Both males and females are affected with the disorder, but females have a delayed presentation. Fabry disease is an important cause of undiagnosed ventricular hypertrophy in the absence of systemic hypertension and aortic stenosis. These patients present with heart failure, arrhythmias, and valvular heart disease. The development of LVH and adverse ventricular remodeling heralds a poor prognosis. The diagnosis is established by measuring plasma α-galactosidase activity and confirmed by genetic analysis. Genetic counseling is available. In patients with Fabry's cardiomyopathy, enzyme replacement therapy (ERT) significantly slows the progression of LVH without significant effects on endothelial dysfunction. This issue of *Cardiology Rounds* reviews the diagnosis, pathophysiology, cardiovascular (CV) symptoms, and treatment of Fabry disease.

Fabry disease (FD or Fabry-Anderson disease) is a life-threatening lysosomal storage disorder due to an X-linked inborn metabolic defect of the lysosomal enzyme, α-galactosidase A (α-Gal A). This deficiency leads to the progressive accumulation of the glycosphingolipid, globotriaosylceramide (Gb3), within vulnerable cells, tissues, and organs, including those of the cardiovascular system,[1-3] and results in endothelial dysfunction, ventricular hypertrophy, and valvular heart disease.[2-4] Two variants of FD exist: the classic variant, which is early-onset and presents with angiokeratomas and painful peripheral neuropathy; and the late variant, which is characterized by the development of end-organ damage, including renal, cardiac, and cerebrovascular disease. Although FD has been considered an orphan disease with an estimated prevalence of ~1 in 50,000 males, recent data suggest that the true incidence of α-Gal A deficiency is 1 in ~3,100, with an 11:1 ratio of patients with the late-onset phenotype variant compared with the classic phenotype. This suggests that the late-onset phenotype of FD may be underdiagnosed among males with cardiac, cerebrovascular, and/or renal disease.[5] Hemozygous male patients have a marked reduction in detectable α-Gal A activity, while affected heterozygous females tend to have a higher level of enzyme activity. Hence, in comparison to men, affected women tend to develop symptoms later and survive for at least 10-15 years longer.

Diagnosis

In patients who present with undiagnosed LVH, there are several distinct diagnoses that may contribute to the disease, including athlete's heart, hypertrophic cardiomyopathy, Fabry's cardiomyopathy, and glycogen-storage disease (Pompe disease) (Figure 1). LVH is

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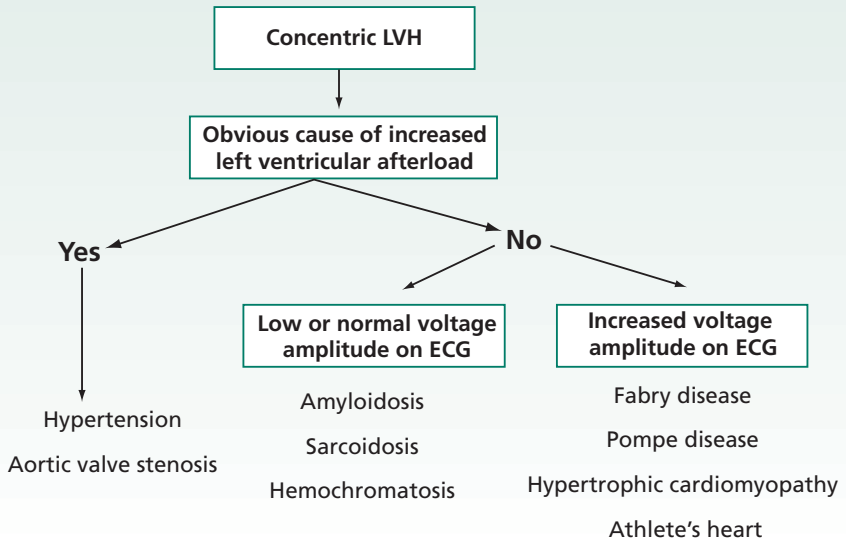
Figure 1: Diagnostic approach to a patient with undiagnosed left ventricular hypertrophy (LVH)



the common manifestation of late-onset FD. The diagnosis is based on history, physical examination, and a 12-lead electrocardiogram (ECG). Renal function assessments, based on serum creatinine and estimated glomerular filtration rate (GFR) and screening for proteinuria are also useful. A transthoracic echocardiogram defines the degree and extent of LVH, associated valvular lesions, and allows for follow-up assessment. Cardiac magnetic resonance imaging (MRI) has recently been shown to add important diagnostic information, such as presence of late enhancement in the inferolateral wall which, by itself, is a marker of poor prognosis.[6,7]

The diagnostic tests available for Fabry disease are:

- plasma and/or urinary globotriaosylceramide levels
- plasma α-galactosidase activity (<1.2 nmol/hr/mL is diagnostic)
- tissue biopsy (skin, kidney, and/or heart) with histological examination for glycosphingolipid deposition
- mutation analysis for confirmation of diagnosis, genetic counseling, and family screening.

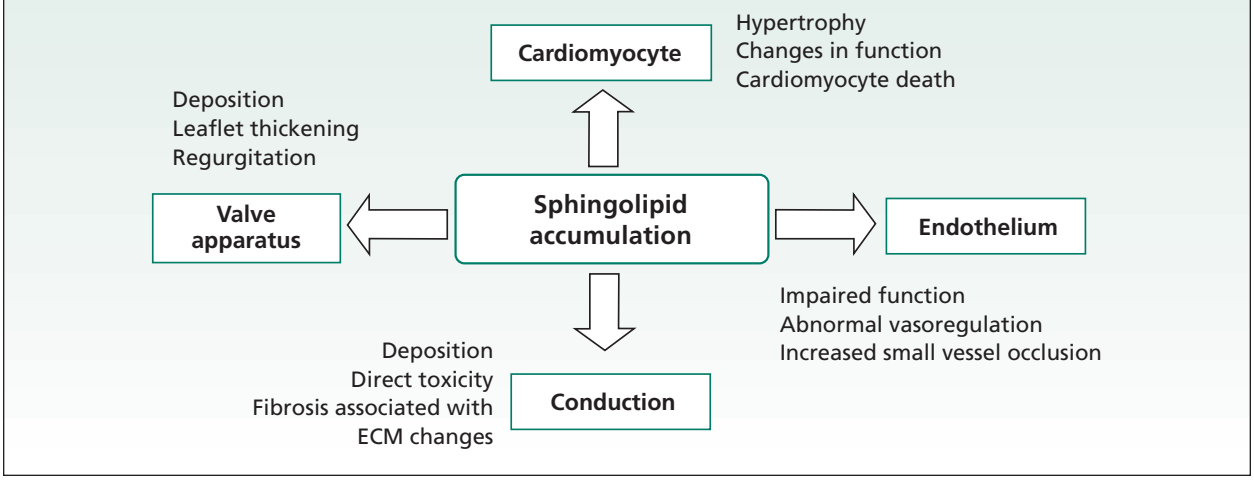
Pathophysiology of Fabry's cardiomyopathy

The accumulation of glycosphingolipid occurs in the lysosomes of cardiac tissues, including the myocardium, endocardium (endothelium), and conduction system, where it is responsible for multiple CV manifestations of Fabry disease (Figure 2).[4,8] Emerging evidence suggests that there may be considerable extralysosomal accumulation of globotriaosylceramide.[2,3,9] Two key pathophysiological events relate to the direct injury resulting from stored glycosphingolipid accumulation and to the energy-depletion hypothesis, which asserts that there are secondary effects of glycosphingolipid on cardiac metabolism.[2,3] The heart is often enlarged with biventricular hypertrophy and the cut surface of the heart usually has a pale yellowish appearance. Histological examination frequently reveals widespread involvement not only of the myocardium, but also the endocardium, conducting tissues, and cardiac valves, particularly the mitral valve.[1-3] LVH and right ventricular hypertrophy are observed and the cardiomyocytes have a vacuolated appearance due to lysosomal inclusions. In vascular structures (including the endothelium), there is a variable degree of interstitial fibrosis in the absence of myofibrillar disarray.[2,4] Although the absolute amount of globotriaosylceramide within cardiomyocytes is low, the heart contains the highest levels of glycosphingolipid compared with other organs such as the liver, skin, and kidney.[2,4] Transmission electron microscopy reveals perinuclear vacuoles consisting of single membrane-bound vesicles that contain concentric, lamellar, electron-dense deposits in endothelial cells, vascular smooth muscle cells, and cardiomyocytes.[4,10,11] The major clinical manifestations result from the accumulation of glycosphingolipid substrate in endothelial cells, eventually leading to the occlusion of small arterioles.[9,12]

Cardiovascular manifestations of Fabry disease

Although the clinical manifestations may be heterogeneous, in its classic form, Fabry disease is slowly progressive. Cardiac involvement is frequent and may be variable; however, FD is an important cause of heart disease with LVH and a restrictive filling pattern. The

Figure 2: Spectrum of cardiac disease in patients with Fabry disease



ECM = extracellular matrix

involvement of different parts of the heart results in different alterations in the CV system and, overall, patients develop progressive hypertrophic infiltrative cardiomyopathy, arrhythmias, conduction abnormalities, coronary heart disease, and/or valvular abnormalities (Figure 2).[1-3] The presence of interstitial fibrosis and the thinning of the inferolateral wall are associated with older age, more advanced hypertrophy, and a poor prognosis.[2,6,7] The predominant cardiac symptoms include exercise intolerance, angina, palpitations, and syncope. Involvement of the myocardium leads to progressive hypertrophy in all chambers, with increasing wall thickness and progressive deterioration in systolic and diastolic function.[2,3,9] Left ventricular systolic function as measured by conventional testing is seldom decreased in patients with Fabry disease. However, studies using tissue Doppler imaging by strain-rate imaging may document a substantial decrease in contractile performance that occurs earlier in the longitudinal than in the radial dimension.[1,3,13] Patients with FD have very abnormal coronary microvascular function with impaired coronary flow reserve.[14]

Cardiac involvement may be the only symptom in some hemozygous males and up to 5% of males and 12% of females with late-onset hypertrophic cardiomyopathy may have the cardiac variant of Fabry disease.[15-17] Differentiation from hypertrophic cardiomyopathy is important, since enzyme replacement therapy for Fabry disease is safe and effective.[3,18] Diastolic dysfunction is a common feature of Fabry disease. In contrast to genuine restrictive cardiomyopathies, a restrictive physiology is rarely found but, if found, it is most often in the advanced stages of the disease and associated with significant fibrosis.[2,3,11] The syndrome of LVH, interstitial fibrosis, and metabolic vasculopathy leads to diastolic dysfunction with an increased susceptibility to diastolic heart failure. If the endocardium is affected, there is progressive alteration of the mitral and aortic valves (thickening of the leaflets) with the development of mitral valve prolapse and mild mitral regurgitation.[2,3] When the endothelium of the coronary arteries is involved, progressive coronary artery disease develops (and myocardial ischemia) without luminal stenosis of the epicardial coronaries.[2,3,9,14] Direct involvement of the conduction tissues and autonomic nervous system can lead to conduction disturbances and bradyarrhythmias, while ventricular hypertrophy and fibrosis can increase the susceptibility to ventricular tachyarrhythmias.[2,19]

Enzyme replacement therapy for Fabry's cardiomyopathy

The advent of enzyme replacement therapy (ERT) for lysosomal storage disorders, including FD, has revolutionized our understanding of these diseases, while providing seminal benefits to patients. ERT has been shown to slow the progression of kidney disease and improve neuropathic pain in patients with FD.[20,21] Halting the progression of end-organ disease, including the cardiac manifestations, and improving clinical symptoms is the aim of ERT in Fabry disease.[3,9,18,20]

Currently, the two formulations of intravenous enzyme therapy available are agalsidase alpha and agalsidase beta.[3] In phase III/IV double-blinded studies, it has been demonstrated that there is a reduction in left ventricular mass within 6 months of starting ERT.[3] These findings are supported by open-label observations in both male and female Fabry patients.[3,22,23] Long-term follow-up studies have revealed a persistent reduction in left ventricular mass that is associated with

improvements in systolic function.[3] The clinical improvements in systolic and diastolic function following ERT correlate with the reduction in ventricular mass and the normalization of the PR interval, which may ultimately reduce clinical events.[24,25] Late enhancement (as determined by cardiac MRI) is a marker in 30%-50% of patients with FD and LVH and is associated with a lack of regression in ventricular hypertrophy, suggesting that an early therapeutic window for ERT may exist in patients with early FD.[1,26]

Although ERT has been shown to remove globotriaosylceramide from endothelial cells in different organs, including the heart,[20,27] it is questionable whether the removal of endothelial deposits from coronary arteries will improve coronary function. Indeed, recent findings demonstrated that the coronary flow reserve was depressed in patients with FD and was unaffected by ERT.[14] Further work is necessary to determine whether treatment at an earlier stage in the course of the disease may improve coronary microvascular function in patients with FD. An alternative therapeutic strategy is infusion of galactose (a competitive inhibitor of α-Gal A), which allows the stabilization of residual enzyme activity.[9] In patients with Fabry's cardiomyopathy, management should also include the treatment of associated problems, as in patients with other types of heart disease.[3] Early use of angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blockers together with device therapy (eg, pacemakers and automated implanted defibrillators) are routine therapies for these patients based on well-established indications. In addition, traditional CV risk factors, including renal disease in patients with Fabry disease, should be ascertained and managed aggressively.

Conclusions

Fabry disease is caused by an inborn, X-linked, metabolic defect of the lysosomal enzyme, α-Gal A, that results in abnormal lysosomal storage. Accumulated glycolipid deposition in endothelium and vessel walls leads to vasculopathy, endothelial dysfunction, ventricular hypertrophy, and valvular heart disease. The classic variant has an early onset, while the late variant is associated with end-organ damage and CVD. Recent data suggest the prevalence is 1 in ~3,100. Both males and females are affected; however, women have a delayed presentation. Patients with late-variant Fabry disease present with heart failure, arrhythmias, and valvular heart disease. LVH and adverse ventricular remodeling indicates a poor prognosis. A significant number of patients are misdiagnosed as having hypertrophic cardiomyopathy. While measurement of plasma α-galactosidase is diagnostic, genetic analysis provides diagnostic confirmation. Genetic counseling is available. In patients with Fabry's cardiomyopathy, enzyme replacement therapy slows the progression of LVH, but does not have a significant effect on endothelial dysfunction. The early recognition and diagnosis of Fabry disease is crucial and provides an opportunity to reduce the CV burden from this disease.

With the initiation of the Canadian Fabry Disease Initiative (CFDI), all patients in Canada with Fabry disease will be able to receive ERT (see below for locations and contact numbers).

Official Regional Centres: Canadian Fabry Disease Initiative (CFDI)

Ontario: Dr. Joe Clarke – Hospital for Sick Children/ University Health Network: Phone: 416-813-5335

Quebec: Dr. Daniel Bichet – Hospital du Sacre-Coeur de Montreal: Phone: 514-338-2486

Atlantic: Dr. Michael West – QEII Health Science Centre Halifax. Phone: 902-473-4023

Alberta, Manitoba, Saskatchewan: Dr. Robin Casey – Alberta Children's Hospital. Phone: 403-943-7211

British Columbia: Dr. Sandra Sirrs – Vancouver General Hospital. Phone: 604-875-4111, ext 66901

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Dr. R. Iwanochko *is the Medical Director of the Robert J. Burns Nuclear Cardiology Laboratory, Cardiac Ambulatory Care, University Health Network*

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Abstracts of Interest

Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A.

ELLIOTT PM, KINDLER H, SHAH JS, SACHDEV B, RIMOLDI OE, THAMAN R, TOME MT, MCKENNA WJ, LEE P, CAMICI PG. LONDON, UK

OBJECTIVE: To measure coronary flow reserve (CFR), an index of microvascular function, in Anderson-Fabry disease (AFD) at baseline and after enzyme replacement therapy (ERT).

METHODS AND RESULTS: Mean (SD) myocardial blood flow (MBF) at rest and during hyperaemia (adenosine 140 microg/kg/min) was measured in 10 male, non-smoking patients (53.8 (10.9) years, cholesterol 5.5 (1.3) mmol/l) and in 24 age matched male, non-smoking controls (52.0 (7.6) years, cholesterol 4.5 (0.6) mmol/l) by positron emission tomography (PET). Resting and hyperaemic MBF and CFR (hyperaemic/resting MBF) were reduced in patients compared with controls (0.99 (0.17) v 1.17 (0.25) ml/g/min, $p<0.05$; 1.37 (0.32) v 3.44 (0.78) ml/g/min, $p<0.0001$; and 1.41 (0.39) v 3.03 (0.85), $p<0.0001$, respectively). This coronary microvascular dysfunction was independent of cholesterol concentrations. PET was repeated in five patients after 10.1 (2.3) months of ERT; resting and hyperaemic MBF and CFR were unchanged after ERT (0.99 (0.16) v 0.99 (0.16) ml/g/min; 1.56 (0.29) v 1.71 (0.3) ml/g/min; and 1.6 (0.37) v 1.74 (0.28), respectively; all not significant).

CONCLUSIONS: The results of the present study show that patients with AFD have very abnormal coronary microvascular function. These preliminary data suggest that ERT has no effect on coronary microvascular dysfunction. Further work is necessary to determine whether treatment at an earlier stage in the course of the disease may improve coronary microvascular function in patients with AFD.

Heart 2006 Mar; 92(3):357-60.

Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy

BEER M, WEIDEMANN F, BREUNIG F, ET AL, WURZBERG, GERMANY

The present study evaluated the evolution of cardiac morphology, function, and late enhancement as a noninvasive marker of myocardial fibrosis, and their inter-relation during enzyme replacement therapy in patients with Fabry's disease using magnetic resonance imaging and color Doppler myocardial imaging. Late enhancement, which was present in up to 50% of patients, was associated with increased left ventricular mass, the failure of a significant regression of hypertrophy during enzyme replacement therapy, and worse segmental myocardial function. Late enhancement may predict the effect of enzyme replacement therapy on left ventricular mass and cardiac function.

Am J Cardiol 2006;97(10):1515-8.

Agalsidase-beta therapy for advanced Fabry disease: a randomized trial

BANIKAZEMI M, BULTAS J, WALDEK S, ET AL, FABRY DISEASE CLINICAL TRIAL STUDY GROUP. NEW YORK, NEW YORK.

BACKGROUND: Fabry disease (alpha-galactosidase A deficiency) is a rare, X-linked lysosomal storage disorder that can cause early death from renal, cardiac, and cerebrovascular involvement.

OBJECTIVE: To see whether agalsidase beta delays the onset of a composite clinical outcome of renal, cardiovascular, and cerebrovascular events and death in patients with advanced Fabry disease.

DESIGN: Randomized (2:1 treatment-to-placebo randomization), double-blind, placebo-controlled trial.

SETTING: 41 referral centers in 9 countries.

PATIENTS: 82 adults with mild to moderate kidney disease; 74 of whom were protocol-adherent.

INTERVENTION: Intravenous infusion of agalsidase beta (1 mg per kg of body weight) or placebo every 2 weeks for up to 35 months (median, 18.5 months).

MEASUREMENTS: The primary end point was the time to first clinical event (renal, cardiac, or cerebrovascular event or death). Six patients withdrew before reaching an end point: 3 to receive commercial therapy and 3 due to positive or inconclusive serum IgE or skin test results. Three patients assigned to agalsidase beta elected to transition to open-label treatment before reaching an end point.

RESULTS: Thirteen (42%) of the 31 patients in the placebo group and 14 (27%) of the 51 patients in the agalsidase-beta group experienced clinical events. Primary intention-to-treat analysis that adjusted for an imbalance in baseline proteinuria showed that, compared with placebo, agalsidase beta delayed the time to first clinical event (hazard ratio, 0.47 [95% CI, 0.21 to 1.03]; P = 0.06). Secondary analyses of protocol-adherent patients showed similar results (hazard ratio, 0.39 [CI, 0.16 to 0.93]; P = 0.034). Ancillary subgroup analyses found larger treatment effects in patients with baseline estimated glomerular filtration rates greater than 55 mL/min per 1.73 m^2 (hazard ratio, 0.19 [CI, 0.05 to 0.82]; P=0.025) compared with 55 mL/min per 1.73 m^2 or less (hazard ratio, 0.85 [CI, 0.32 to 2.3]; P= 0.75) (formal test for interaction, P=0.09). Most treatment-related adverse events were mild or moderate infusion-associated reactions, reported by 55% of patients in the agalsidase-beta group and 23% of patients in the placebo group.

LIMITATIONS: The study sample was small. Only one third of the patients experienced clinical events, and some patients withdrew before experiencing any event.

CONCLUSIONS: Agalsidase-beta therapy slowed progression to the composite clinical outcome of renal, cardiac, and cerebrovascular complications and death compared with placebo in patients with advanced Fabry disease. Therapeutic intervention before irreversible organ damage may provide greater clinical benefit.

Ann Intern Med 2007;146(2):77-86.

Upcoming meetings

20-21 April 2007
12th Annual Atlantic Canada Cardiovascular Conference
Dalhousie, Nova Scotia
Contact: Renée Downs
Tel.: 902-494-1560
Email: renee.downs@dal.ca

5-9 May 2007
American Association for Thoracic Surgery (AATS)
87th Annual Meeting
Washington, DC
Contact: Tel.: 978-927-8330
Fax: 978-524-8890

24-27 June 2007
European Heart Rhythm Association (EHRA)
EUROSPACE Congress
Lisbon, Portugal
Contact: http://www.escardio.org/bodies/associations/EHRA/

1-5th September 2007
European Society of Cardiology
Annual Meeting
Vienna, Austria
Contact: www.escardio.org

20-24 October 2007
Canadian Cardiovascular Society
CCC 2007
Quebec City, Quebec
Contact: www.cardiocongress.org

4-7 November 2007
American Heart Association
Scientific Sessions 2007
Orlando, Florida
Contact: http://scientificsessions.americanheart.org

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