Update on Coronary Involvement in Fabry Disease

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Abstract
Fabry disease is a multisystemic disorder with consequent morbidity and mortality at an early age in patients of both genders. Although renal failure has been previously described as the cause of death with the highest prevalence, recent studies, based on the analysis of the population recorded in the Fabry Registry, reported that 40% of deaths had a cardiovascular origin. Data from the same registry emphasize the high risk for these patients suffering cardiovascular events—particularly acute myocardial infarction—and to the fact that this risk is higher for those patients who need dialysis. Microvascular dysfunction is a constant in patients with Fabry disease, which affects young patients, independently from other cardiac involvement manifestations—such as left ventricular hypertrophy—and from the patient's gender.

Introduction

Fabry disease (FD) is an X-linked genetic disorder caused by the deficiency of the lysosomal α-galactosidase A enzyme (αGal-A), which is responsible for the glycosphingolipids degradation, with their subsequent and progressive accumulation, particularly globotriaosylceramide (GL-3), in various tissues.

More than 50% of patients with FD present cardiovascular involvement, the main sign of which is left ventricular hypertrophy (LVH) simulating a hypertrophic cardiomyopathy.[1,2] The GL-3 intracellular accumulation has been described in cardiomyocytes, conduction system, heart valves, and vascular endothelium.[3,4]

Myointimal Compromise

Left ventricular hypertrophy is progressive and increases with age in both genders.[1,5] Frequently, patients present symptoms such as dyspnea on exertion, heart palpitations, and angina. These cardiological symptoms are more frequent among men, and frequency increases with age as the disease progresses.[6]

Fabry disease has historically been accepted as an endothelial pathology, and its physiopathology was based on glycosphingolipids deposit, with the resulting increase in the volume of endothelial cells and later occlusion of the arterial lumen. However, there has been a recent change in the pathophysiological concept of this disease. There are several studies that have proven an increase in the intima–media thickness (IMT) of the carotid and radial arteries and a possible prothrombotic state of patients with FD.[7,8]

Barbey et al carried out a carotid echo Doppler evaluation of 53 patients with FD, observing an IMT increase at that level, compared with a healthy control group.[8] Later, the authors were able to observe a proliferation of cardiomyocytes and cultured vascular smooth muscle cells (VSMCs) when put in contact with the patients' plasma. Their conclusion was that there should be a growth-promoting factor in the patients' plasma. Among the trophic postulated factors, there is a GL-3 metabolite known as lyso-GL3, which has proved to promote VSMC proliferation and hypertrophy.[9,10]

Another metabolite that has been shown to stimulate differentiation and proliferation of VSMC is sphingosine-1-phosphate (S1P).[11] Brakch et al have recently studied

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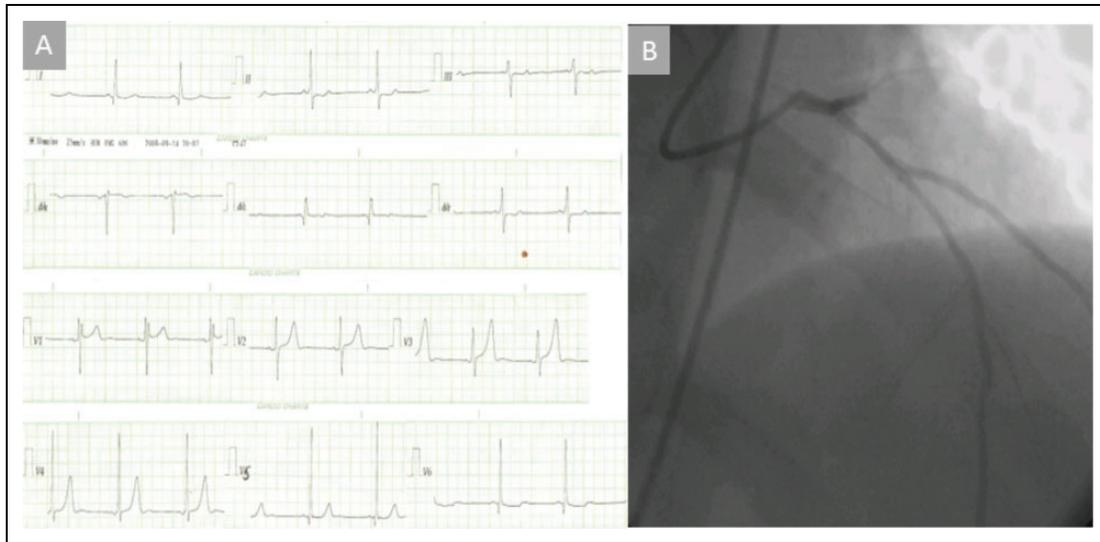Email: gustavo.h.cabrera@hotmail.com

Figure 1. Electrocardiogram and cinecoronariography of a 44-year-old man with classic phenotype. He presented acute subendocardial myocardial infarction. A, Electrocardiogram showing depressed unevenness of inferolateral ST segment. B, Cinecoronariography showing occlusion of the circumflex artery.

17 patients with FD comparing them with a control group of 17 people. The plasma levels they found were significantly higher in S1P in patients with FD. At the same time, they found a positive correlation between S1P levels, carotid IMT, and the left ventricular mass index in patients of both genders.[12] There is another possible hypertrophy mediator, endothelin-1,[13] which has been reported to appear in high levels in plasma.

Pathophysiology of Coronary Angina

The myocardial ischemia caused by the endothelial accumulation of GL-3 is an issue that should be considered, since between 13% and 30% of patients of both genders refer angina. Based on the reports and necropsies of coronary event cases, it has been suggested that coronary disease and acute myocardial infarction (AMI) occur more frequently in association with FD than in the general population and at an earlier age.

Schiffmann et al, documented the presence of a significant compromise of epicardial arteries in a patient after a massive infarction.[14] It is worth mentioning that though the patient was 47 years old at the time of the coronary event, he already presented an advanced multisystemic involvement.

In 2008, Kovarnic et al, published coronary findings in 9 patients with FD (5 women) who had undergone intravascular ultrasound (IVUS) compared with 10 control patients. The IVUS showed that the lesions inpatients with FD were more diffuse and hypoechogenic, suggesting that the plates were more lipidic because of the presence of glycosphingolipid deposits in the smooth muscle and endothelial cells.[15]

Analyzing AMI prevalence in large groups of patients enrolled in international records, it was possible to observe that in a 2.869 (49% male) patient population belonging to the International Fabry Registry, 6% of men and 4% of women presented major cardiac events including AMI, their average age being 45 and 54 years, respectively.[16]

In our cohort of 105 patients with FD from Argentina, 6 (5.7%) presented acute coronary syndrome (ACS). Three were men and only 1 of them presented AMI previous to the FD diagnosis (Figure 1). From those 6 patients, 2 presented coronary obstructions that required myocardial revascularization, and none of these patients had coronary risk factors; the coronary arteries were angiographically normal in the remaining 4 patients. All of these patients presented LVH in the echocardiogram (Figure 2). There was electrocardiographic alteration like ST depression or T-wave inversion compatible with myocardial ischemia in all the events with normal previous electrocardiograms. All these events where considered as unstable angina. Unfortunately, only 2 patients with ACS had cardiac troponin I (cTNI) done, and in both patients, it was increased (Figure 3).

Coronary Reserve in FD

It is important to point out that it was originally thought that patients with FD presented higher atherosclerotic coronary disease. In the bibliography and in our cohort, though, there have been cases described of patients of both genders with angina, and even electrocardiographic alterations, compatible with myocardial ischemia but not with obstruction of epicardial coronary arteries, which suggests a microvascular origin.

This finding would be in agreement with what was observed in other cardiomyopathies and even in patients with LVH secondary to pressure overload, where it is frequent to find ischemia secondary to coronary reserve (CR) reduction, due to the coronary microvascular involvement, though the mechanisms involved turned out to be different.
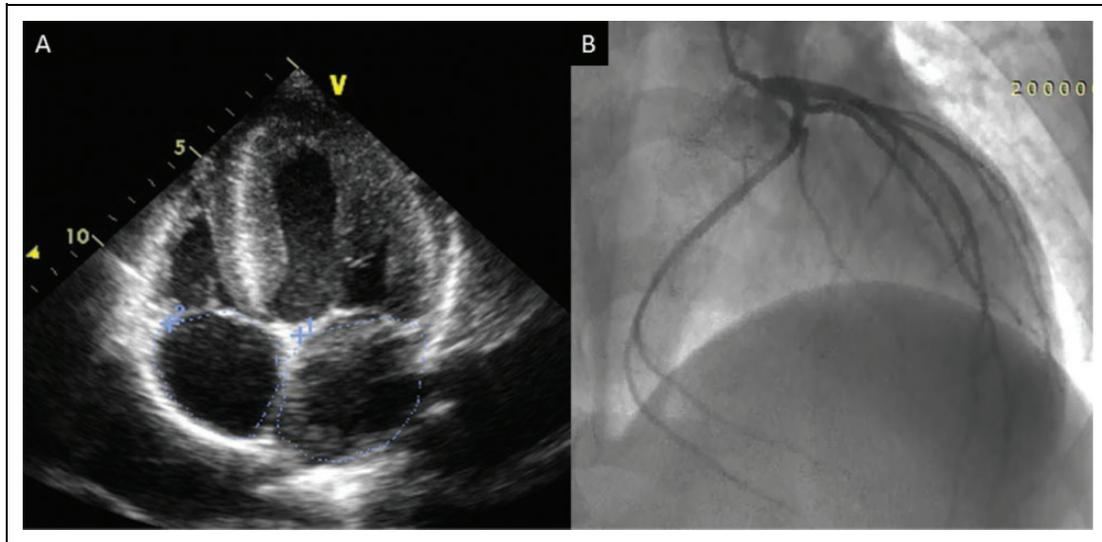
Figure 2. Echocardiogram and cinecoronariography of a 37-year-old man with classic phenotype and stage 5 chronic renal failure. The patient presented acute coronary syndrome with ultrasensitive troponin increase. A, Echocardiogram of severe concentric hypertrophy. B, Coronary arteries with no obstructions in cinecoronariography.
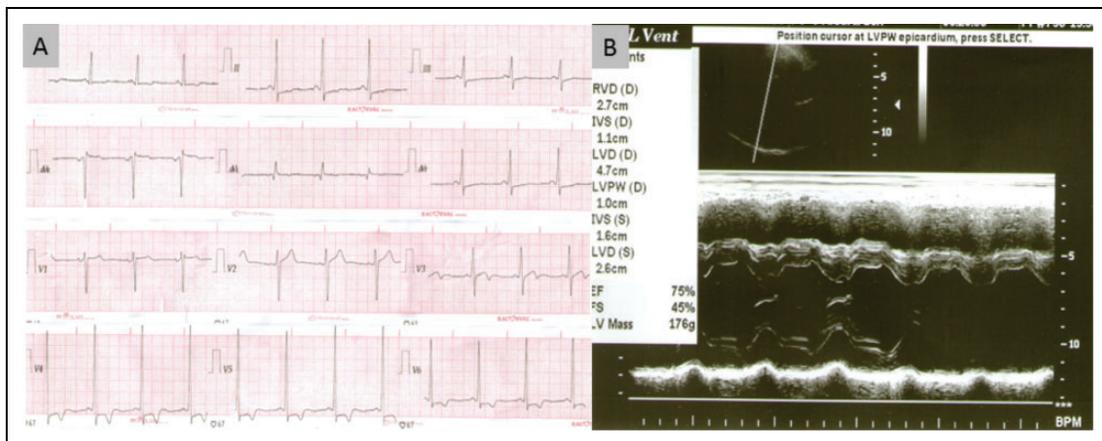

Figure 3. A, Electrocardiogram of a 52-year-old woman with FD with classic phenotype and acute coronary syndrome with ultrasensitive troponin increase. Criteria compatible with left ventricular hypertrophy and clearly altered ventricular repolarization can be observed. B, Echocardiogram showed mild ventricular hypertrophy.

In normal conditions, coronary flow is determined by the gradient between the aortic diastolic and the right atrial pressure, which is opposed by the intramyocardial compressive resistance and the resistance of the coronary tree, defined by the muscle tone of the self-regulating arterioles. When myocardial oxygen demand increases, the coronary bed can dilate 4 to 6 times, increasing the blood flow. This self-regulation phenomenon is known as CR. In 2006, Elliot et al evaluated the coronary microvascular function measuring the coronary resting flow and after the hyperemia induced through 140 mg/kg/min intravenous adenosine.[17] Concerning the control group (24 healthy patients), the 10 male patients with FD presented LVH, a lower baseline myocardial flow, and no increase after the adenosine administration. This response was interpreted as the absence of CR flow due to microvascular involvement. It is important to notice that these patients did not present obstructions in the coronary angiography,

In 2008, a histopathological study of 13 patients (5 women) with FD diagnosis and angina was published.[18] All patients were studied with the positron emission tomography (PET) stress test and cinecoronariography. They were compared with 25 patients with FD and no angina and with 20 patients with mitral valve stenosis and normal function of the left ventricle. Patients with FD and angina had LVH and presented myocardial perfusion defects compared with the other groups. The epicardial arteries were free of obstructions in all patients, but the patients with FD (with and without angina) presented slow coronary flow.

The myocardial biopsy of the patients with angina showed lumen narrowing in most of the intramyocardial arteries due to

hypertrophy, proliferation of VSMC and endothelial cells, and glycosphingolipid deposits. In the areas where the severely narrowed arteries were located, the myocardium had been replaced by fibrosis. In patients with FD and no angina, this structural compromise of the arteries was mild. It should be pointed out that no correlation was found between this arterial damage and age, or gender, or LVH degree. The authors conclude that angina and perfusion defects are due to the progressive engagement of the intramural arteries, with the subsequent increase in coronary resistance and in the hypertrophied myocardium oxygen demand.

Patients with FD (both genders) and LVH, even if their epicardial coronary arteries are unobstructed, may present myocardial ischemia and angina and even AMI. However, Tomberli et al demonstrated that the microvascular coronary involvement could be present even without LVH, suggesting that it could be an early damage of the disease.[19] The population included in this study consisted of 30 patients with FD-confirmed diagnosis, where 12 (40%) of them were male. The analysis of the mutations showed that 10 were related to the disease classic phenotype, whereas the remaining (p.Asn215-Ser) were associated with a milder form of the disease of later onset (fourth to fifth decade). This form is characterized by the absence of the classical signs and symptoms and by prevalent cardiac involvement in the absence of endothelial GL-3 deposits. Sixty seven percent (10 men and 10 women) of patients presented LVH in echocardiograms, and the average age was 51 years (range 23-75 years). The microvascular function was evaluated with PET/dipyridamole and compared with a control group of 24 healthy patients, comparable in terms of gender and age (13 men, age: 46 ± 16 years). There was a very low coronary response to dipyridamole in all patients with FD compared with the control group. Average levels were below 1.25 mL/min/g, indicating a severe coronary microvascular dysfunction (CMD). This was observed even in patients with FD and without LVH.

Moreover, there was a clear regional heterogeneity of the myocardial flow with hypoperfusion prevailing in the apical region. Coronary microvascular dysfunction was more severe in male patients, but it was present in both genders. This presence was independent from the existence of LVH and from the treatment with the recombinant human enzyme.

The hypothesis put forth by the authors states that the microvascular dysfunction includes pathophysiological mechanisms mediated by the LVH (reduced capillary density, extravascular compression forces) and others that affect microvasculature directly (endothelial dysfunction due to GL-3 deposits, nitric oxide deregulation, or microvascular remodeling). Therefore, LVH would not be casual and would contribute to the dysfunction, since the microvascular compromise is present even in patients with no hypertrophy.

Cardiac Troponin I

Cardiac troponin I is a laboratory parameter well known to reflect acute and chronic cardiac muscular damage. Previous studies have demonstrated that an increase in cTNI occurs in a substantial proportion of patients with FD and that cTNI elevation correlates with fibrosis masses by late gadolinium enhancement (LGE) on cardiac magnetic resonance (MR) images.[20]

Myocardial fibrosis is a key feature of FD-related cardiomyopathy. Fibrosis and LGE are more focal than in other forms of cardiomyopathy, sparing the subendocardium. This fibrosis was initially thought to result from tissue ischemia secondary to endothelial accumulation of glycosphingolipids in the microvasculature. Recently Nappi et al published in 2015 their experience using simultaneous PET/MR imaging on 13 patients with confirmed FD (8 males). They showed that with this technique, it was possible to differentiate mature fibrosis or scar from fibrosis associated with active inflammation. It is noteworthy that all patients with active inflammation also had elevated cTNI values. These findings support the role of focal inflammatory processes triggered by cardiomyocyte GL-3 storage for the pathogenesis of interstitial myocardial fibrosis in patients with FD.[21]

Conclusion

The presence of myocardial ischemia in patients with FD should not be discarded, even in the absence of lesions in the epicardial coronary arteries. Microvascular dysfunction is a constant in patients with FD, which affects young patients, independently from other cardiac involvement manifestations such as LVH and from the patient's gender. These findings suggest that the reduction in maximum coronary flow might precede the development of LVH and even that chronic ischemia could generate the fibrosis found in these patients. They even make it evident that CMD is also present in patients of a milder FD phenotype, who carry the p.Ans215Ser mutation.

The pathophysiological mechanism of myocardial fibrosis is still unclear. It seems that there are 2 possible explanations, one is the presence of myocardial ischemia due to CMD and the second is the role of focal inflammatory processes triggered by cardiomyocyte GL-3 storage.

Patients with FD present a coronary compromise, which could dramatically influence the natural history of the disease. The presence of CMD could be the predictor of a patient bad evolution. Its presence could influence the clinical approach to the patient and also influence the decisions made regarding this challenging disease.

References

1. Linhart A, Kampmann C, Zamorano JL, et al; European FOS Investigators. Cardiac manifestations of Anderson-Fabry disease:

results from the international Fabry outcome survey. *Eur Heart J*. 2007;28(10):1228-1235.

2. Weidemann F, Breunig F, Beer M, et al. The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. *Eur Heart J*. 2005;26(12):1221-1227.

3. Eng CM, Guffon N, Wilcox WR, et al; International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human alphagalactosidase. A replacement therapy in Fabry's disease. *N Engl J Med*. 2001;345(1):9-16.

4. Seydelmann N, Wanner C, Stork S, Ertl G, Weidemann F. Fabry disease and the heart. *Best Pract Res Clin Endocrinol Metab*. 2015;29(2):195-204.

5. Germain DP, Weidemann F, Abiose A, et al; On Behalf of the Fabry Registry. Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry registry. *Genet Med*. 2013;15(12):958-965.

6. Boutouyrie P, Laurent S, Laloux B, Lidove O, Grunfeld JP, Germain DP. Arterial remodelling in Fabry disease. *Acta Paediatr Suppl*. 2002;91(439): 62-66.

7. Kalliokoski RJ, Kalliokoski KK, Penttinen M, et al. Structural and functional changes in peripheral vasculature of Fabry patients. *J Inherit Metab Dis*. 2006;29(5):660-666.

8. Barbey F, Brakch N, Linhart A, et al. Increased carotid intima-media thickness in the absence of atherosclerotic plaques in an adult population with Fabry disease. *Acta Paediatr Suppl*. 2006; 95(451):63-68.

9. Aerts JM, Groener JE, Kuiper S, et al. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. *Proc Natl Acad Sci U S A*. 2008;105(8):2812-2817.

10. Rombach SM, Dekker N, Bouwman MG, et al. Plasma globotriaosylsphingosine: diagnostic value and relation to clinical manifestations of Fabry disease. *Biochim Biophys Acta*. 2010;1802(9): 741-748.

11. Lockman K, Hinson JS, Medlin MD, Morris D, Taylor JM, Mack CP. Sphingosine 1-phosphate stimulates smooth muscle cell differentiation and proliferation by activating separate serum response factor co-factors. *J Biol Chem*. 2004;279(41): 42422-42430.

12. Brakch N, Dormond O, Bekri S, et al. Evidence for a role of sphingosine-1 phosphate in cardiovascular remodelling in Fabry disease. *Eur Heart J*. 2010;31(1):67-76.

13. Linhart A, Palecek T, Bultas J: Endothelin-1 is associated with advanced clinical symptoms and end-organ involvement in patients with Fabry's disease. *Eur Heart J*. 2001;21:492.

14. Schiffmann R, Rapkiewicz A, Abu-Asab M, et al. Pathological findings in a patient with Fabry disease who died after 2.5 years of enzyme replacement. *Virchows Arch*. 2006;448(6):337-343.

15. Kovarnik T, Mintz GS, Karetova D, et al. Intravascular ultrasound assessment of coronary artery involvement in Fabry disease. *J Inherit Metab Dis*. 2008;31(6):753-760.

16. Patel MR, Cecchi F, Cizmarik M, et al. Cardiovascular events in patients with Fabry disease natural history data from the Fabry registry. *J Am Coll Cardiol*. 2011;57(9):1093-1099.

17. 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(3):357-360.

18. Chimenti C, Morgante E, Tanzilli G, et al. Angina in Fabry disease reflects coronary small vessel disease. *Circ Heart Fail*. 2008; 1(3):161-169.

19. Tomberli B, Cecchi F, Sciagra R, et al. Coronary microvascular dysfunction is an early feature of cardiac involvement in patients with Anderson-Fabry disease. *Eur J Heart Fail*. 2013;15(12): 1363-1373.

20. Feustel A, Hahn A, Schneider C, et al. Continuous cardiac troponin I release in Fabry disease. *PLoS One*. 2014;9(3): e91757.

21. Nappi C, Altiero M, Imbriaco M, et al. First experience of simultaneous PET/MRI for the early detection of cardiac involvement in patients with Anderson-Fabry disease. *Eur J Nucl Med Mol Imaging*. 2015;42(7):1025-1031.