Current status of cardiac manifestations in Fabry disease and their treatment

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Abstract

In the present paper, we discuss cardiac symptoms in Fabry patients, the main imaging and laboratory methods to diagnose myocardial involvement in this disease. In the second part, we present the main treatment options in Fabry patients, including enzyme replacement therapy, substrate reduction treatment, chaperone therapy, gene treatment.

Keywords: Fabry disease, enzyme replacement therapy, chaperone treatment, substrate reduction therapy, gene treatment

Main cardiac symptoms in Fabry patients are represented by: dyspnea or other signs of heart failure, angina and chest pains, palpitations (arrhythmia), syncope. An often documented imaging finding in Fabry patients is the presence of left ventricular hypertrophy. This hypertrophy correlates with the incidence of cardiac symptoms. The more severe the hypertrophy, the more severe are the associated symptoms. Left ventricular hypertrophy is more prevalent in men compared to women, and its prevalence increases with age in both sexes. Left ventricular hypertrophy may be accentuated by the presence of chronic kidney disease and arterial hypertension [1].

Coronary heart disease is frequently encountered in Fabry patients, as these patients are predisposed to early atherosclerosis. Angina pectoris may be secondary to endothelial dysfunction and small vessel disease, but also to a high oxigen demand as a consequence of left ventricular hypertrophy.

Palpitations are a frequent finding in Fabry individuals. The incidence of arrhythmias correlates with the presence of left ventricular hypertrophy and of myocardial fibrosis. The occurence of myocardial fibrosis predisposes to lethal arrhytmias , and is also associated with a reduced efficacy of enzyme replacement treatment. Arrhythmias may generate, in less severe cases, syncopes, but also, in more severe cases, cerebral strokes [1].

Valve disease may be present in quite a small percentage of Fabry patients, being secondary to endocardial cerebroside infiltration, but also to fibrosis.

Cardiac involvement may represent a cause of death in Fabry patients. Mortality may also be enhanced in Fabry patients' affected relatives.

Some imaging methods may be of help in diagnosing cardiac involvement in Fabry patients. The ECG may document left ventricular hypertrophy with negative T waves in precordial leads. In earlier stages, a short PR segment may be present whereas in more advanced stages, sino-atrial and atrio-ventricular blocks may arise. ST segment and T waves changes may be secondary to hypertrophy in the early stages, but secondary to fibrosis in advanced stages. Advanced AV blocks necessitating cardiostimulation may occur in advanced cases with heart fibrosis (late diagnosis), or in patients with no enzyme replacement or late enzyme replacement therapy.

Cardiac ultrasound represents a screening method for documenting Fabry cardiomyopathy. Left ventricular hypertrophy may be concentric, but also

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apical, or septal hypertrophy may be present. Associated papillary muscle hypertrophy, but no outflow tract obstruction may be present. In time the infero-posterior left ventricular wall may get fibrosed, thinned and hipokinetic. Already in earlier phases of disease, tissue doppler myocardial imaging may show pathological strain in the postero-basal left ventricular segments. Besides left ventricular hypertrophy, an enlarged left atrium may be present. In not very advanced disease stages, left ventricular diastolic performance may be altered (a finding more early detected at tissue doppler imaging), whereas in advanced stages, the left ventricular ejection fraction may be depressed (secondary to fibrosis). Mitral and aortic valve thickening with or without regurgitation, and also ascending aorta dilation may be present. Changes in the diameter of the vertebral arteries and increased stiffness of large and medium arteries were also reported [2].

Magnetic resonance imaging diagnose more accurately the size and localization of left ventricualar hypertrophy. Gadolinium MRI reveals left ventricular posterolateral wall fibrosis. Papillary muscle hypertrophy may be present at MRI even in early stages of disease. Also, apical hypertrophy may be better quatified at MRI. MRI can also better appreciate involvement of the right ventricular free wall [2].

Some studies evaluate PET/MRI for detection of cardiac impairment in Fabry patients and they documented that hybrid PET/MR imaging can appreciate early cardiac injury in these patients [3].

Laboratory tests are useful for diagnosing associated diseases, and for evaluating organ injuries (kidney failure). Indices of inflammation are associated with disease severity. Plasma NT-proBNP levels correlate with left ventricular hypertrophy and fibrosis, left ventricular diastolic failure. In advanced disease, serum troponin levels are high. Efficient enzyme replacement may lower serum globotriaosylceramide (GB3) levels. Severe Fabry disease may be accompanied by high serum troponin levels [2].

Electrophysiological cardiac mapping may prove useful in Fabry patients presenting different atrial and ventricular arrhythmias.

Endomyocardial biopsy represents an invasive method for making a positive diagnosis or to exclude cardiac Fabry involvement. For example, in a patient with severe left ventricular hypertrophy with the presence of serum enzyme and reduced serum GB3 levels, the biopsy may be of help in making or excluding the diagnosis of Fabry disease [2].

Enzyme replacement therapy is of major importance in treating Fabry patients with cardiac symptoms or organ involvement. Main drugs are agalsidase beta and agalsidase alpha. If early treated, left ventricular hypertrophy can be forestalled, or if mild, it may regress. Enzyme replacement treatment may also improve myocardium contractility [4] (Spinelli, Clin. Genetics, 2004). An early enzyme replacement treatment (before the appearance of myocardial fibrosis) may prevent malignant ventricular arrhytmias. Studies have documented reduced GB3 myocardial deposits with enzyme replacement treatment. If fibrosis is already present , enzyme replacement treatment may not remove it [5]. With enzyme replacement, serum cerebroside levels significantly decreased, a fact more obvious in younger individuals.

Enzyme replacement (ER) treatment should be initiated in male children, even younger than 18 years, if Fabry disease, with all its clinical manifestations, was diagnosed. In male adolescents and adults with Fabry disease, ER therapy is mandatory. In female Fabry patients presenting clinical symptoms (neurologic, renal, cardiac, general), ER therapy must be initiated. Therapy should be initiated also in asymptomatic females, but with disease involvement in different organs. In asymptomatic females with no documented organ involvement, ER therapy may be withheld, but they should be followed-up [6]. New enzyme replacement therapy drugs are actually in advanced clinical human studies. One of them involves the pegunigalsidase alpha, which is similar to alpha galactosidase A [7].

Associated treatment remains important In preventing or treating cardiovascular involvement in Fabry patients. Angiotensine converting enzyme inhibitors or receptor blockers may be of benefit in Fabry patients. Beta blockers may be associated with adverse secondary effects. As amiodarone may inhibit intracellular galactosidase activity, this drug should be avoided in these patients. If symptomatic AV block occurs, cardiologists may consider permanent pacemakers, whereas in cases of atrial fibrilation, amiodarone may incur secondary effects. If malignant ventricular arrhythmias are present, a cardioverter-defibrillator may be an option. Antiagregant drugs are used for stroke prevention, whereas oral and new oral anticoagulants are mandatory in persistent atrial fibrillation [8].

Chaperone therapy represents a therapeutic option in lisosomal storage diseases, in the near future. Chaperones are molecules that stick to the involved enzyme, helping its folding, its functioning in the lysosome. In Fabry disease different chaperones are tested, chaperones that inhibit the activity of alpha-galactosidase. An iminosugar, 1-deoxygalactonojirimycin, very active in vitro, augments alpha galactosidase activity in Fabry disease individuals. This chaperone ligates to the enzyme and ameliorates its stability and lysosomal activity. It may also prevent a rapid enzyme metabolization. *In vitro* cell cultures studies documented that compouns like ambroxol, pioglitazone may augment lysosomal activity of alpha galactosidase, in Fabry disease [9].

Another treatment option in Fabry patients is the enzyme substrate reduction. Its principle consists in reducing the production of glucosphingolipids by blocking the enzyme glucosylceramide synthetase. As such we will

have less GB3 deposits in different organs in Fabry patients. At present, Fabry patients are treated with a galactose preparation of N-butyl-deoxynojirimycin (lucerastat) associated with enzyme replacement and results are promising [9]. It was doccumented (in mice), that in Fabry disease, an enzyme inhibitor (eliglustat tartrate) reduces ceramide deposits in different organs and tissues. In Fabry patients, in which a-galactosidase activity is still present, the enzyme inhibitor may be sufficient in order to reduce cerebroside accumulation in tissues, but in patients which lack completely alpha-galactosidase activity, the inhibitor has to be associated with alpha-galactosidase enzyme replacement [10].

Gene therapy, is evaluated in Fabry disease. Two methods of gene delivery are employed: viral and nonviral. The viral method utilizes oncoretro- or lentinoviruses, the lacking gene beiing introduced into the virus. Two techniques of viral gene therapy are actually in use: ex vivo gene therapy, and in vivo gene therapy. In ex vivo gene therapy, a lentivirus is used as a vector to introduce the alpha galactosidase gene into hematopoietic stem cells, cells that are later infused in autologous recipients [11]. In vivo gene therapy, consists in delivering the adenovirus asociated gene by iv route to the liver. Subsequently the liver secretes alpha-galactosidase , in therapeutic levels, followed by a significant decrease in globotriaosylceramides deposited in different organs [12].

Nonviral gene therapy uses biosynthetic systemic mRNA treatment. mRNA encoding alpha- galactosidase was injected In Fabry mice. As a consequence a high alpha galactosidase serum activity, with reduced (GB3) deposits in all tissues, were documented [13].

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