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EDITORIALS

Fabry disease – A challenge for diagnosis and treatment

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Fabry disease is a genetically inherited lysosomal storage disease, characterised by intracellular and plasmatic accumulation of glycosphingolipids, especially globotriaosylceramide (GL-3) as a result of a deficiency of alfa A glactosidase enzyme in lysosomes. Fabry was the first to describe it in 1898, but there is data suggesting that Hebra, a famous Austrian dermatologist, had described Fabry skin lesions before.

The gene responsible is located on the X chromosome, so it has an X linked recessive transmision (table 1), all males in a family developing the disease. Its particularity is represented by the fact that carrier females may develop different degrees of disease manifestations. Obviously a percentage of carrier females dose never develop the disease. Incidence among men was reported as much as 1:40000, while there is no official data about its incidence in females. In general population there it has been reported to develop as frequent as 1:117000.

Normally, alfa galactosidase A is involved in lipid particles metabolism, especially GL3, turning them into smaller particles which are released in the plasma, in order to be eliminated or to be used in other substances structure. If there is an enzymatic deficiency, an abnormal accumulation of these lipids occurs in the plasma and different cells, affecting their structure and function. Endotelial vascular cells, renal tissue, cardiac tissue and nervous structures are the most to be affected.

Phenotipically, two forms of disease have been described: typical or classic variant, the most frequent one and the atypical variant (cardiac or renal variant) with late onset and often underdiagnosed (TABLE 2).

Gene Symbol	Chromosomial locus	Protein
GLA	Xq22	Alpha-galactosidase A

TABLE 1. Fabry disease genetics

Disease variant	Classic variant	Renal variant	Cardiac variant
Onset age (years)	4-8	>25	>40
Life expectancy (years)	41	>60	>60
Angiokeratoma	++	-	-
Acroparesthesia	++	+/-	-
Hypohidrosis/anhidrosis	++	+/-	-
Corneal involvement	+	-	-
Cardiac involvement	+	+/-	+
Neurological involveme nt	+	-	-
Renal involvement	+	+	+/-
Enzyme activity	<1%	>1%	>1%

TABLE 2. Clinical Features related to phenotype (Mehta et al 2004, Eng et al 2007)

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Pain (acroparesthesia) is a very common symptom, often the first to develop and it may have several characteristics. These pain episodes are described as burning, tingling, and numbness and are thought to be related to the involvement of the vascular supply and small fibers of the peripheral nervous system. Pain, especially in the hands and feet, may occur daily and may vary in severity. These episodes may occur in both sexes and may begin as early as age of 2 years. Pain may be triggered by a body temperature increase due to exercise, fever, emotional stress, or environmental temperature changes. Extreme pain attacks, referred to as Fabry pain crises, usually affect male patients and are described as severe episodes that last several hours to days. These episodes may be accompanied by low-grade fever, body pains, and fatigue.

Because of lipid deposits in the sudoripary glands and in their nervous structures, anhidrosis or hypohidrosis occur, this anomaly resulting in high fever episodes and maladaptation to temperature variations. 12% of the carrier females and 6.4% of males may present with hyperhidrosis.

Dermal manifestations of Fabry disease include cutaneous vascular lesions (angiokeratomas Figure 1). Weakening of the capillary wall and vascular ectasia within the epidermis and dermis causes angiokeratomas. They usually manifest at age 5-13 years and initially appear as small, slightly raised, purplish-red, nonblanching angiectases. The number and size of these lesions progressively increase with age. They often appear on the thies, hips buttocks, back, penis and scrotum and have symmetrical bilateral disposition. Corneal manifestations are reported in more than 70-90% of patients. In vivo confocal microscopy demonstrated structural alterations throughout the entire ocular surface epithelia.

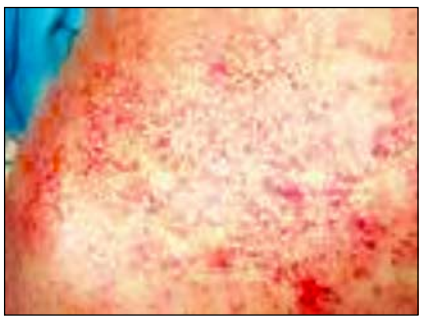

FIGURE 1. Figure 1. Angiokeratoma corporis diffusum (free download from www.lysomed.be/.../fabry/lyso_pt_fa_body_fr.asp)

Fabry-related cardiovascular disease is a key cause of premature death.Polymorphism of the cardiac manifestations is well kown, as is the fact that it has a clinical expression starting with the third decade of life. Early signs of cardiac involvement include interventricular septal and left ventricular hypertrophy (fig.2) associated with mitral regurgitation. Rythm or conduction disturbances are also present. Damage to the coronary vascular bed may lead to angina pectoris, variant angina, and myocardial infarction. Echocardiography is the key of early cardiac involvement. Cardiac variants are the most widely recognized and studied in this case the disease is limited to the heart and does not damage the vascular endotheliumIn 2003 a clinical study reviewed the functional and anatomical cardiac manifestations in 20 hemizygous male patients with Fabry disease. Left ventricular hypertrophy and/or concentric remodeling were found in 60% of cases; structural changes in mitral and aortic valves in 25% and 10%, respectively; and short PR interval in 40%.

Renal involvement is an important feature and is the most important cause of premature death in classic Fabry disease. It is the result of progressive accumulation of GL-3 in the renal endothelium and other kidney cells. Microalbuminuria, proteinuria, and isosthenuria may develop in adolescence and early adulthood. Progressive kidney disease is determined by the progression of proteinuria, an increase in serum creatinine levels, and by the reduction of the glomerular filtration rate (GFR) during the third decade of life leading to end stage renal disease Branton et al. (2002) reviewed the medical records of 105 male patients with Fabry disease. Fifty percent of patients developed proteinuria by age 35 years and chronic renal insufficiency by age 42. Detectable residual alpha-galactosidase A activity was associated with a slower progression of Fabry renal disease, and with lower scores for renal histologic damage and renal content of globotriaosylceramide. Conservative mutations in the GLA gene were also associated with a slower progression in Fabry renal disease

Neurological manifestations are various. Patients may present with transient ischemic attacks, vascular thromboses, seizures, or hemorrhagic or ischemic stroke. The mean age at onset of symptomatic cerebrovascular disease

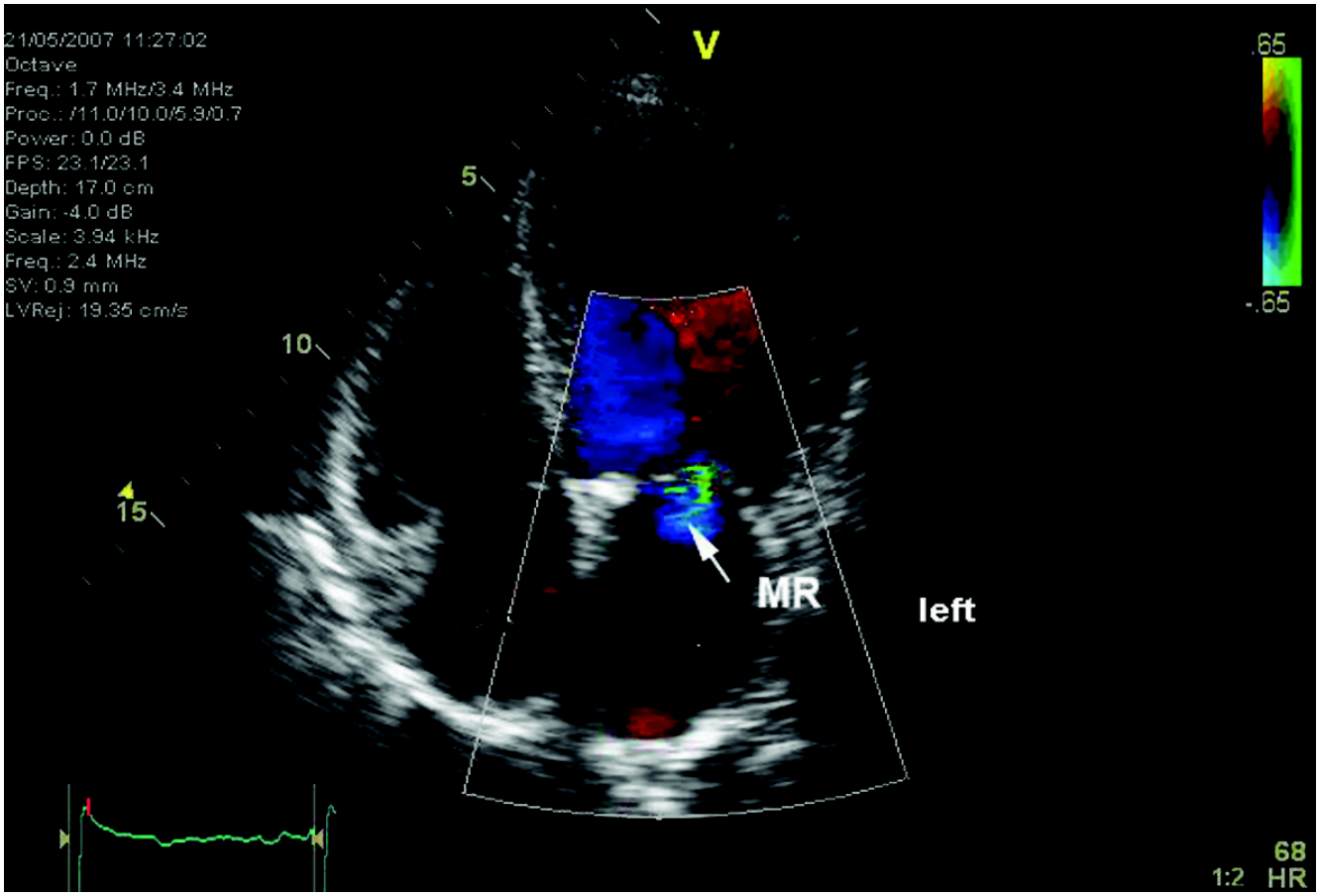

FIGURE 2. An apical four-chamber view shows mild left ventricular hypertrophy and mild right ventricular hypertrophy. Color Doppler mapping showing mild mitral regurgitation due to the valvular changes associated with Fabry disease (modified after Linhart A. The heart in Fabry disease. In: Mehta A, et al (eds). Fabry disease: perspectives from five years of FOS, 2006)

was 38.4 and 40.3 years in the men and women, respectively Paroxysmal attacks of severe rotational vertigo, sensorineural hearing loss, peripheral neuropathy are also described.

Gastrointestinal symptoms may include: postprandial bloating, abdominal cramping and pain, early satiety, diarrhea/constipation, nausea, vomiting. Obstructive and constrictive lung diseases have both been documented in a subgroup of patients, often presenting as wheezing, dyspnea, or bronchitis. Priapism has been associated with Fabry disease.

Clinical manifestations in female carriers vary because of random X-chromosome inactivation. Most of female carriers remain asymptomatic throughout life, but some develop clinical symptoms as variable and severe as those of affected males

Demonstration of alpha-galactosidase A deficiency in leukocytes or plasma is the definitive method for the diagnosis of affected hemizygous males. In classic variant enzyme activity decrease under 1%, while in atypical variants it is mentained above 1%. This testing is not useful in females where DNA isolated from blood or biopsy specimens can be used for analysis of the a-Gal A gene sequence to identify the disease-causing mutation. DNA testing is the preferred method for identifying and confirming the carrier status of females in whom enzyme activity is within or near the reference range. After certitude diagnosis, several organ related test are recommended in order to asses the magnitude of disease damages and the life expectancy.

For a long time this disease treatment was a symptomatic one, but now enzyme replacement treatment with human recombinant enzyme is approved in 27 contries. Fabrazyme® and Replagal TM were investigated in several clinical trials including phase IV studies, and as a result they are approved both by EMEA and

FDA. It is pointed out that enzyme replacement therapy may reduce the risk of death, myocardial infarction, cerebrovascular disease, end stage renal disease by 53%, in patient cautiously selected. Results are better if treatment is initiated earlier. The most serious and most common adverse reactions reported with Fabrazyme are infusion reactions. Serious, frequently occurring related adverse reactions are: chills, pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face edema, rash, and somnolence. Most patients develop IgG antibodies to Fabrazyme. A few patients developed IgE or skin test reactivity specific to Fabrazyme, and the physician should test for IgE patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti- Fabrazyme IgE. A judicious analysis of potential risks associated with enzyme replacement treatment is recommended. Gene therapy with bicistronic retroviral vector that engineers expression of both the therapeutic GLA gene and the human IL2R-alpha chain gene represent an encouraging perspective for Fabry disease treatment.

Adjunctive treatment plays an important role: analgetics, use of angiotensin-converting enzyme (ACE) inhibitors and/or blockers in patients with proteinuria, control of hypertension, hypolipemiant medication, prophylaxis with antiplatelet or anticoagulant medication, permanent cardiac pacing, coronary revascularisation dyalisis, kidney transplant, hearing aids.

To conclude with, Fabry disease is still a challenge, new perspectives for diagnosis and treatment being studied. Prognosis for patients with Fabry disease has improved with the more widespread use of advanced medical techniques.

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