Fabry disease - Update 2021

Compiled by Dr. Andrés R. Pérez Riera

Fabry disease (FD) is an X-linked progressive multisystemic genetic sphingolipidoses caused by deficient activity of lysosomal α-galactosidase A.

Men aged>30 years and women aged>40 years most often present with unexplained left ventricular hypertrophy (LVH), usually concentric and non-obstructive, but sometimes mimicking sarcomere hypertrophic cardiomyopathy (HCM), particularly when isolated, as in the cardiac or late-onset variant of the disease.

In HCM cohorts, up to 1% of patients have been diagnosed with FD. Frequent cardiac arrhythmias including chronotropic incompetence, severe conduction disturbances and others, heart failure and sudden death, and cardiovascular complications are currently the leading cause of death at a mean age of 55 years in men and 66 years in women.

Complementary to screening for extracardiac manifestations, the initial cardiac evaluation should include Holter recordings, echocardiography and late gadolinium and T1 mapping Cardiovascular magnetic resonance imaging (MRI).

Abnormalities of a non-**hypertrophied inferolateral wall at the base of the left ventricle** (thinning, decreased strain, midwall fibrosis) and low native T1 signal on MRI are evocative. MRI, native T1 is low in FD because of sphingolipid accumulation.

Myocyte storage starts in childhood and accumulates faster in men before triggering two processes: a sex-independent scar/inflammation regional response (LGE) and, in men, apparent myocyte hypertrophy diluting the T1 lowering of sphingolipid[6].

Aggressive cardiac management may include the control of cardiovascular risk factors, anticoagulation, permanent cardiac pacing and/or an implantable cardioverter defibrillator device, while antiarrhythmics and β-blockers should be used with caution.

Specific therapy should be initiated at the earliest stage, when the first structural or functional cardiac abnormalities are detected, and should include enzyme replacement therapy (available since 2001) or chaperone therapy (available since 2016) (the use of which is limited to patients with Fabry disease and an amenable α-galactosidase A [GLA] gene mutation) [1].

Cardiologists can play a critical role in the early detection of FD

- LVH is prevalent in Fabry
- ECG abnormalities in combination with other signs and symptoms could indicate FD
- ECG abnormalities in FD include[2-5]:

· -Voltage criteria and repolarization changes related to LVH and/or remodeling
· - ST segment depression
· - T-wave inversions
· - The presence of LVH was associated with a significantly higher frequency of cardiac symptoms, arrythmias, and valvular disease[2]
· - Short PR interval (< 120 ms) due to a short P wave
· -Enlarged QRS complex
· - Prolonged QTc intervals

Other signs and symptoms[4]

· Acroparesthesia
· Heat/cold, exercise intolerance
· GI distress
· Hypohidrosis
· Corneal whorling: IT is a telltale sign of this rare, debilitating and eventually fatal lysosomal storage disorder, Fabry disease causes lipids to accumulate in the various organs of the body.
· Corneal opacities — grey, brown, or yellowish streaks that appear on the cornea, the clear outer layer that covers the lens of the eye. Sometimes, they first appear as a haze or fog over the cornea, becoming more streak-like with time.
· Angiokeratoma
· Progressive renal disease
· Early ischemic stroke

References

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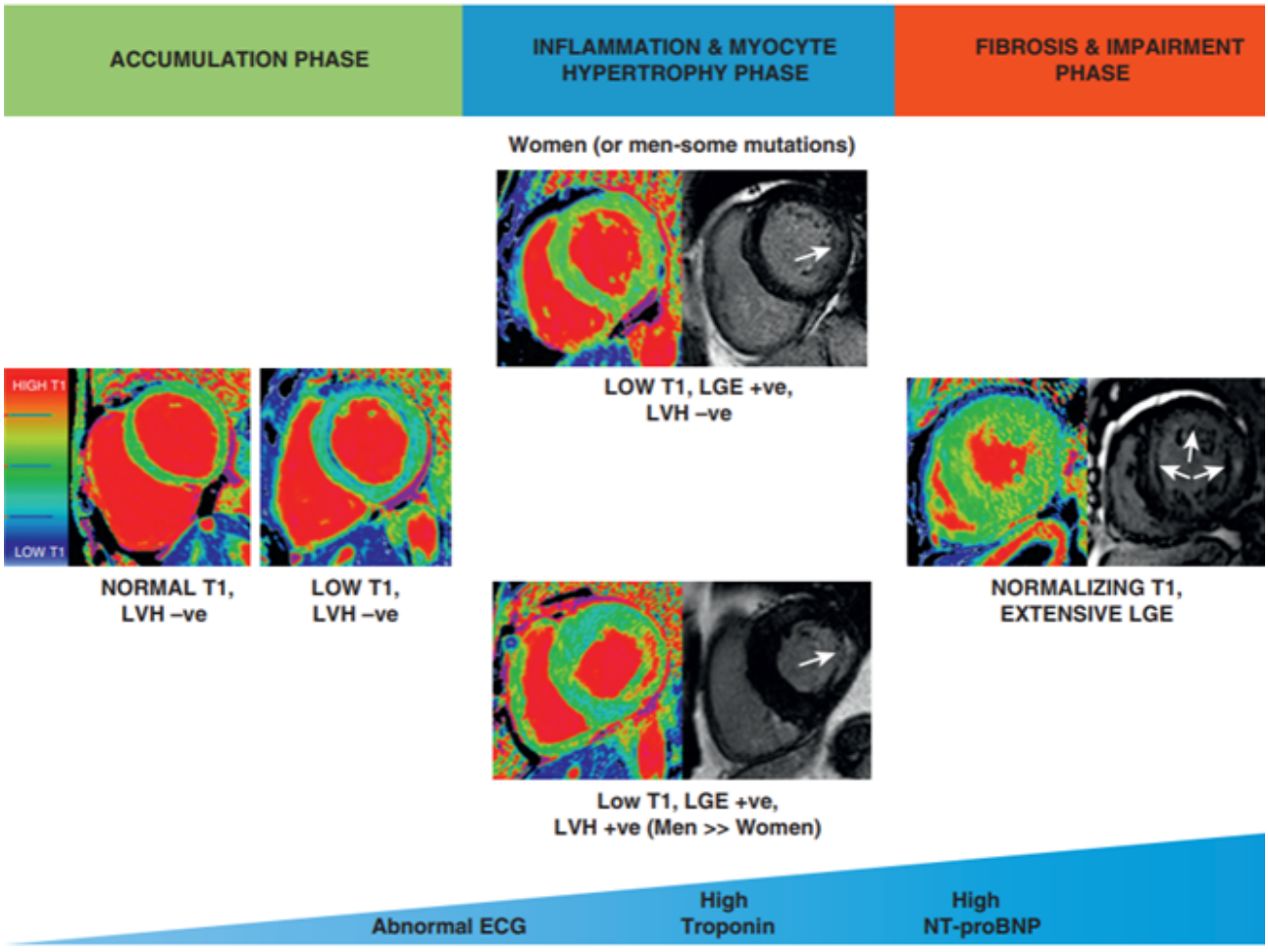
Proposed Myocardial Phenotype Evolution in Fabry Disease[6].



The disease developmental model consists of an accumulation phase (silent myocyte storage and greater T1 lowering), a myocyte hypertrophy and inflammation phase, and a fibrosis and impairment (late) phase. Arrows refer to the area of LGE.