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Short Commentary

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Fabry disease: What we should know?

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Abstract

Fabry disease is a X-linked recessive transmission with mainly involvement of the heart, kidney and brain. Males are affected and females can show the same symptoms but with more slowly progression. Acroparesthesia and Fabry crisis are the first symptoms in the affected patients. As soon as we suspect of Fabry disease, we can do dried blood spot for screening. In the female if the test is negative and the suspicious is high, molecular study is the choice test. Enzyme replace therapy in the earlier stages will improve the prognosis.

Clinical presentation

Fabry disease, is a X-linked sphingolipidosis, caused by incapacity to produce an enzyme call alfa-galactosidase or alfa-GAL and is associated with severe multiorgan dysfunction. The incidence is 1 in 40,000 to 1 in 60,000 live births for males. Females are symptomatic in many cases. Without this enzyme, globotriaosilceramide or GL-3, keep in the cells. The result is the accumulation of this material in the blood vessels, affecting the brain, heart and kidneys. In the childhood the presentation may be subtle and confuse with growth pain or even juvenile rheumatoid arthritis. The symptoms starts between 6 and 9 years of age. Pain is the first symptom and also the most common. Appear when the temperature change, the patient is exposed to high temperatures, fever or excessive hot weather, stress and tiredness. Most patients showed 2 types of pain: Acroparesthesia and "Fabry crisis".

Acroparesthesia - The pain is in the hands and feet. Is like a burn that can affect the patient daily or not.

Fabry crisis - Epidoses of intensive pain, like burn, initially in the hands and later in the feet and later in other parts of the body. Can take minutes or weeks. Other symptoms included: Hypohidrosis/anidrosis: frequent fever, excess heat with exercises and hot weather intolerance, angiokeratoma: cutaneous eruption purple-red color- are found from the umbilical region to the knees and sometimes only in the elbows or knees, buttocks and scrotum in 80% of patients, cornea verticillata: same as the bycicle wheal (dont affect the vision), epigastric pain, diarrhea and nausea after meal, renal failure because of excessive proteinuria in urine with progressive renal involvement which may result in end- stage renal disease, cardiomegaly, defect of the heart valves, arrythmias, ascending aortic dilatation, coronary artery disease, conduction abnormalities and heart insufficiency, dizziness, vertigo, hearing loss, headache, stroke episode and depression. All these symptoms can present in males but also in females, in this case with later onset and slower progression [1-6].

Typical case presentation:

- 31 years old male, with:
- Anhidrosis since 9 years of age, even after vigorous physical exercise associated with xerostomy.
- Past history revealed hands pain at 3 years of age that was diagnosed as juvenile rheumatoid arthritis. He has also purpuric macules and the biopsy revealed angiokeratoma.
- Abdomen CT scan showed hepatic and left renal cyst.
- The blood spot test confirmed low enzyme activity of α-Galactosidase A: 0.13 (N: >1.8 uM/hr).
- The molecular study confirmed GLA gene hemizygous mutation in exon 7 [7].

Metabolic derangement: The primary defect is a deficiency of the lysosomal enzyme α-galactosidase A, which releases galactose from ceramide trihexoside (globotriasylceramide, Gb3) and related glycosphingolipids (especially galabiosylceramide, Gb2), due to mutations of the GLA gene.

The accumulation of Gb3 cause infarction and ischemia in the kidney, heart and brain.

Genetics: Fabry disease has an X-linked recessive transmission. The risk is 50% for the next pregnancy.

More than 600 mutations are so far been described in the literature. The mutation N215S is associated with heart problems. De novo mutations are rare in this disease.

Diagnostic tests: When we have a suspicious case in a affected male or female we can do the screening diagnosis using the dried blood spot (DBS) In the early stage in boys and girls if they have two or more manifestations, we need to do the DBS. When the patient is an adult only one or more manifestation is enough for doing the screening test (Figure 1). Females may have normal or low activity and DBS can be normal. Molecular analysis is the test of choice [1,2,6]. Urinary Gb3 is a good biomarker to monitor the treatment .

Treatment and prognosis: Renal, heart and vascular complications can cause reduce of life expectancy and for this reason enzyme replace therapy (ERT) is important to invert this prognosis when the diagnosis is made in the earlier stage of the disease. Two essentially similar products, agalsidase alpha and agalsidase beta, exist. There is increasing evidence that ERT can halt disease progression. The dose is 1 mg/Kg, every 2 weeks. The initial dose is better not to be more than 0,25 mg/min (15 mg/h), and can be increase in future perfusions. Current research using oral therapy with migalastat hydrochloride is in phase III clinical trial [1].

Consensus criteria for initiation of ERT: The group agreed that a differentiation should be made between male and female patients, and between patients with classical and non-classical Fabry disease.

The division of females into classical and non-classical FD is based on the presence or absence of clustered angiokeratoma, cornea verticillata, or a very high Gb3 level.

For males with classical FD, consensus was achieved that treatment with ERT may be considered in patients of 16 years or older even if they have no symptoms or clinical signs of organ involvement.

The diagnosis of classical FD in these patients is based on the presence of a GLA mutation, absent or very low residual enzyme activity, and the presence of at least one of the following: angiokeratoma, cornea verticillata, or a very high Gb3 level.

Classically affected males and females and males with non-classical FD should be treated as soon as there are early signs of organ involvement (kidney, heart and/or CNS signs) consistent with FD and not fully explained by other pathology. Treatment may be considered in females with non-classical FD and early clinical signs consistent with FD.

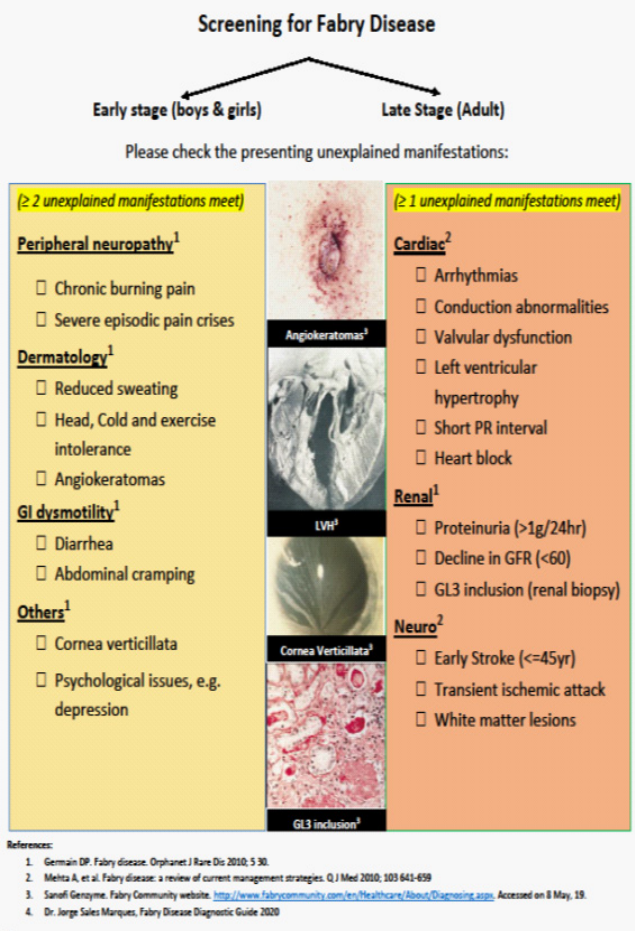

Figure 1: Fabry disease – Dried blood spot.

Consensus criteria to stop ERT

1 - Non-compliance >50% of infusions.

2 - Failure to attend regularly (according to local guidelines) at FU visits.

3 - Persistent life threatening or severe infusion reactions that do not respond to prophylaxis, e.g. anaphylaxis.

4 - Patient request.

5 - End stage renal disease, without an option for renal transplantation, in combination with advanced heart failure.

6 - End stage FD or other comorbidities with a life expectancy of <1 year.

7 - Severe cognitive decline of any cause.

8 - Lack of response for 1 year when the sole indication for ERT is neuropathic pain while receiving maximum supportive care.

Consensus criteria to not start ERT

1- Advanced cardiac disease with extensive fibrosis.

2- End stage renal disease, without an option for renal transplantation, in combination with advanced heart failure.

3- End stage FD or other comorbidities.

4- Severe cognitive decline of any cause with a life expectancy of <1 year [1-6].

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