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CLINICAL, BIOCHEMICAL AND MOLECULAR STUDIES: STEPWISE TO ACHIEVE DIAGNOSIS OF FABRY DISEASE

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Introduction: Fabry disease (FD, OMIM # 301500), a treatable X-linked storage disorder, is caused by deficient activity of the lysosomal enzyme ?-galactosidase A (?-Gal A). Over 400 pathogenic mutations in *GLA* gene have been associated with FD. Enzymatic deficiency leads to lysosomal accumulation of globotriaosylceramide (Gb3) and lyso-Gb3. The first clinical manifestations of FD (pain in the extremities, corneal changes and angiokeratoma) develop in childhood. Progressive renal insufficiency and cardiovascular involvement are the main causes of premature death.

Aims: This work provide evidence for the needful of combining biochemical and molecular tests to diagnose hemizygotes, heterozygotes and symptomatic female carriers of FD.

Methods: FD diagnosis methodologies underlay in three approaches:?-Gal A activity: measured in capillary Dried Blood Spots (DBS), peripheral blood plasma and total leukocytes, and in cultured skin fibroblasts;GB3: urinary excretion measured in 24 hour urine;Genotype analysis: *GLA* gene mutations identified by sequencing of exons and exon-intron boundaries.

Results: This work report clinical, biochemical and molecular data of 105 patients from 51 unrelated Portuguese families. Partial reduction or absence of ?-Gal A activity confirmed diagnosis in all male patients. Mutated alleles associated with ?-Gal A pseudodeficiency may also result in low/reduced ?-Gal A activity. Wide phenotypic variability in clinical manifestations and biochemical parameters was observed in these cases, which remain to be classified as Fabry patients. In female carriers, ?-Gal A activity may range from zero to control values, thus, FD diagnosis in females can only be made through molecular genetic tests.

Conclusions: FD diagnosis is not straight forward through ?-Gal A enzymatic activity, and frequently requires a combination of different technical approaches, even in male patients due to ?-Gal A pseudodeficiency. X chromosome inactivation can mask obligate carriers, leading to normal ?-Gal A activity, so molecular analysis is the only effective approach to overcome this obstacle. Identification of a ?-Gal A mutation associated with a clinically relevant phenotype would be extremely useful for disease progression evaluation, as well as for enzyme replacement therapeutic decisions.

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HUNTER SYNDROME, THE MOST PREVALENT MUCOPOLYSACCHARIDOSIS IN PORTUGAL

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Introduction: Lysosomal storage diseases (LSD) is a group of rare diseases which involves more than 50 inherited metabolic diseases, being Hunter disease - Mucopolysaccharidosis type II (MPS II)- MIM 309900, an inherited X-linked LSD. MPS II is due to iduronate-2-sulfatase (IDS) enzymatic deficiency, that leads to impaired hydrolyses of terminal iduronate 2-sulfate esters into heparan and dermatan sulfate. More than 300 mutations have been reported in *IDS* gene, located at Xq28, and MPS II has an estimated prevalence of 1 in 170 000 male live births. As well as in other MPS disorders, there is a wide clinical variability, ranging from mild to severe clinical phenotype. The availability of enzyme replacement therapy improves many of the symptoms and signs of the disease.

Aim: To report the MPS II prevalence in the Portuguese population and present data from enzyme replacement in treated patients.

Methods: MPS II diagnosis as a three steps analytical approach: screening for quantitative and qualitative urinary glycosaminoglicans accumulation, definitive diagnosis iduronate-sulphatase activity determination in blood or cultured fibroblasts and genotype identification by *IDS* gene sequencing to ascertain causal mutations.

Results: MPS II is the most prevalent MPS in Portugal. Since 1984, 33 index patients, belonging to 28 families, were diagnosed and 8 of them were submitted to enzyme replacement therapy. Apparently clinical variability among MPS II patients is a mere reflection of molecular heterogeneity, as patients with an *IDS* gene complete deletion seem to have a more severe form of the disease. A more profound clinical evaluation is required as, until now, no female patients have diagnosed.

Conclusions: Some LSD have a overlapping clinical phenotype with MPS. However, clinicians faced with male affected members in different family generations, should consider MPS II as the first hypothesis in the differential diagnosis. Once the genotype has been ascertained, genetic counseling should include female carrier identification in the affected families. Although the incidence of these genetic diseases is quite low, their combined incidence is 1 in 7000 births, which is in the range considered to be feasible for a newborn screening.