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Fabry's disease, an eye-kidney disease review

Doença de Fabry, revisão de uma doença olho-rim

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ABSTRACT

Fabry's disease is a recessive X-linked disorder that results from a deficiency of the hydrolase alpha--galactosidase A (α-Gal A). The absence of α-Gal A enzyme activity leads to accumulation of glycosphingolipid globotryaosylceramide (GL-3) in the lysosomes of a variety of cell types. It can cause skin and ocular lesions, progressive renal, cardiac or cerebrovascular disorders. The authors report the case of a 39-year-old female who was referred to a nephrology appointment by her ophthalmologist, after the diagnosis of *cornea verticillata* and posterior subcapsular cataract. This case illustrates the importance of a multidisciplinary evaluation to an effective clinical screening. In males, most symptoms begin in childhood; in females the onset can be observed later and presentation is more variable. Various manifestations often lead to misdiagnosis or are frequently delayed for many years. Enzyme replacement therapy highlights the importance of early diagnosis so that treatment can be initiated before irreversible organ damage occurs.

Key-Words: Beta agalsidase; Fabry's disease; globotryaosylceramide; microalbuminuria.

RESUMO

A Doença de Fabry é uma doença hereditária recessiva ligada ao X, que resulta da deficiência da enzima hidrolase α-galactosidade A (α-Gal A). A ausência de actividade da α-Gal A leva à acumulação de glicoesfingolípidos globotriaosilceramida (GL-3) nos lisossomas das células. É responsável por lesões cutâneas e oculares, bem como doença renal, cardíaca e cerebrovascular. Os autores apresentam uma doente de 39 anos, género feminino que foi referenciada pelo seu Oftalmologista à consulta de Nefrologia, após o diagnóstico de córnea *verticillata* e catarata subcapsular posterior. Este caso ilustra a importância de uma equipa multidisciplinar na detecção da doença. No homem, a maioria dos sintomas inicia-se na infância; no género feminino, o início da sintomatologia ocorre mais tarde e a sua apresentação é mais variável. A heterogeneidade das manifestações leva ao erro ou atraso diagnóstico. O diagnóstico precoce é fundamental para que a terapêutica enzimática de substituição seja iniciada antes da lesão irreversível.

Palavras-Chave: Agalsidase beta; doença de Fabry; globotriaosilceramida; microalbuminúria.

CASE REPORT

The authors report a case of a 39-year-old female who was referred to a nephrology appointment by her ophthalmologist, after the diagnosis of *cornea verticillata* and posterior subcapsular catarat. She presented with progressive decrease of visual acuity, chronic fatigue, and mild periorbital oedema. She denied other symptoms like dermatologic, neurologic or cardiac ones. Her past medical history was unremarkable, however, her maternal grandmother died with end-stage renal disease (ESRD) on regular haemodialysis programme (no cause was identified at that time). Chronic medication: Ginera ® id. She had normal blood pressure, normal cardiopulmonary auscultation, normal urine output and mild malleolar and periorbital oedema. The review of systems was otherwise negative. Blood laboratory investigation showed mild mixed dyslipidaemia, normal renal function, as well as normal's blood count. Urinalysis showed 9 leucocyte/hpf and 11 erythrocyte/hpf, glomerular hyperfiltration (140 ml/min/1.73 m^2) and proteinuria (1254 mg/24h). Eletrocardiogram, chest X-ray, abdominal ultrasound and echocardiogram were normal. Renal ultrasound presented normal morphology and dimensions of both kidneys, with milimetric parapielic cysts. Brain magnetic resonance imaging (MRI) revealed images of small dimensions related to outbreaks of gliosis resulting from small vascular sequelae. Urinary GL3 excretion was increased. Biochemistry analysis confirmed low leucocytes α-Gal A activity. Molecular study identified the mutation c.317_27del11(pL106fs).

Genetic study of her family found both parents being negative. Concerning her descendants, she has one 5-year-old girl and one 8-year-old boy that were positive and negative for the mutation, respectively. They are being followed in a genetic paediatric consultation.

After the diagnosis confirmation, she was started on enzyme replacement therapy (agalsidase beta 1 mg/kg every 15 days). Adjuvant therapy was started with an aldosteron receptor blocker (Losartan 50 mg id) and colecalcipherol (15000 UI/week).

The patient has been under therapy for one year, and is asymptomatic, with normal renal function (serum urea 4 mg/dL, creatinine 0.71 mg/dL, eGFR 155 ml/min), and a proteinuria of 1.4 grs/day.

REVIEW

Fabry's disease (FD) is a rare, inherited, recessive X-linked disorder caused by mutations in the gene encoding the acid hydrolase enzyme alpha--galactosidase A (EC 3.2.1.22), which causes deficiency of the lysosomal hydrolase alpha-galactosidase A (α-Gal A)[1]. More than 700 types of mutations have been identified, but they are usually family specific. Most of the described mutations are associated with the classic Fabry's phenotype, in which there is multisystem involvement[2]. The genetic study of our patient's family was made and her parents were both negative, meaning that she has a *de novo* mutation. Some authors have found some correlation between specific mutational and enzyme activity levels and have proposed that a classification related to this association will facilitate the diagnosis of Fabry's disease[3].

The incidence of FD hemizygosity is generally estimated as 1 in 40,000 to 50,000 males[4,5]; however, recognition of atypical forms of the disease and neonatal screening[6] suggest that the actual figure may be much higher.

Regarding pathophysiology, the absence or deficient of α-Gal A enzyme activity leads to accumulation of glycosphingolipid globotryaosylceramide (GL-3) in the lysosomes of a variety of cell types including capillary endothelial, renal (podocytes, tubular cells, glomerular endothelial, mesangial and interstitial cells), cardiac (cardiomyocytes and fibroblasts) and nerve cells[5] causing cellular dysfunction and microvascular pathology. The lysosomal storage starts before birth and is the only feature during the first stage of the disease (primary disease). After some years, the disease progresses to cellular dysfunction, which defines the second stage (secondary disease). It is characterized by compromised energy metabolism[7-9], small vessel injury[10], K/Ca 3.1 channel dysfunction in endothelial cells[11], oxidative stress[12], impaired autophagosome maturation[13] and tissue ischaemia. The last and worse stage of FD is caused by cellular death with the development of irreversible cardiac[14-16] and renal[17] tissue fibrosis (tertiary disease). These three stages of the disease reflect a heterogeneous, progressive clinical picture. In the primary stage, patients have no symptoms and the only evidence of disease is through a tissue biopsy where is seen a lysosomal accumulation of Gb3 and related glycosphingolipids. The secondary stage is

characterized by mild symptoms and the evidence of the disease is often found through complementary exams that translate cellular dysfunction of the affected organs. The tertiary stage reflects the target organs failure with end-stage renal disease, heart failure or acute myocardial infarction and stroke, which are irreversible[18-20].

During the natural course of the disease, several symptoms may begin according to the target organs affected that may vary among patients, contributing to the called "classical or atypical variants" according to the dominant manifestations. In classically affected male patients, clinical onset occurs in childhood; however, this may not be true for females because the X inactivation is incomplete and the enzyme activity level can be from zero to almost normal[21].

Early neuronal damage of small nerve fibres of the peripheral somatic[22] and autonomic nerve systems[23] correlates with the onset of episodic abdominal pain crises ("Fabry crises"), as well as, chronic pain, hypohidrosis/anhidrosis and paresthesias[24]. Cerebrovascular disease evidence starts with asymptomatic white matter lesions in the magnetic resonance imaging (MRI), but symptoms like dizziness, transient ischaemic attacks, and stroke are representative.

Skin lesions, mainly angiokeratomas, can be found in several forms, locations and sizes, which usually increase with age[25].

Regarding eye disease, the most specific, almost pathognomonic and common finding is *cornea verticillata* (corneal deposits) but other abnormalities can occur, like vascular tortuosities and posterior subcapsular cataract[26]. The main differential diagnosis causing *cornea verticillata* is a side-effect of chronic amiodarone that was excluded.

Heart and kidney are the two remaining affected organs that most compromise life expectancy. Cardiac disease starts with concentric hypertrophy and remodelling of myocardium, which leads to irreversible endocardic fibrosis, conduction abnormalities, valvulopathy and myocardial infarction[2]. The best complementary diagnostic exam to evaluate cardiac involvement is cardiac MRI, which highlights fibrosis. However it is worth to mention that electrocardiogram often shows a shortened PR interval when there is a conduction compromise[2].

Sphingolipids play an important role in modulating podocyte function, so nephropathy is one of the major complications of FD. Approximately 30–35% of females have proteinuria[5,27], 13% have stage 3 CKD[28] and 1–4% have ESRD[29]. The decline in renal function over time is related to the degree of proteinuria and, in untreated patients, is more rapid when the eGFR is below 60 ml/min/1.73 m^2. Before renal replacement therapies were available, the mortality rate was 100% between the ages of fifties and sixties[30]. Nowadays, the prevalence of patients with ESRD due to FD starting dialysis probably underestimates the reality because not all patients undergo a renal biopsy. Additionally, the prevalence among young males who initiate dialysis before the age of 40 years, for example, may be higher. According to both American and European databases, FD patients that initiate dialysis have a worse survival compared with non-Fabry controls[31]. Although these patients have a higher cardiovascular risk due to cardiac increased adiposity, hypertension, dyslipidaemia and immunosuppression side-effects, when they undergo renal transplantation, their overall and graft survival is comparable to matched controls[31].

One of the earlier signs of nephropathy is microalbuminuria. Over time, the proteinuria under the nephrotic range is the most typical form of presentation and is an independent risk factor affecting the extent of renal decline, as well as determining the success of ERT[32,33]. A proteinuria level above 1 g/d is associated with a worst prognosis[18,34]. Other features are glomerular hyperfiltration; impaired concentration ability due to distal tubular involvement; and increased urinary Gb3 excretion[35]. Urinalysis may be quite variable and microscopy may be useful in the diagnosis because vacuolated epithelial cells filled with glycosphingolipids give the appearance of a 'Maltese cross' when polarized light microscopy is used[36], and they are very specific. Although pathogenesis is not known, renal ultrasound presents parapielic cysts in up to 50% of patients[37]. A wide range of renal histopathology could be found due to diffuse deposition of glycosphingolipid in the glomeruli, tubules, and vasculature. Light microscopic findings include a "foamy" appearance of the glomeruli with diffuse swelling and vacuolization of visceral podocytes[38]; mesangial expansion and progressive segmental and global glomerulosclerosis[39-41]. Electron microscopy shows podocytes and mesangial cells filled with lysosomal electron dense granules

arranged in a lamellar, myelin pattern[38]. One study found that podocyte Gb3 inclusion volume and density, as well as foot process width were shown to increase with age and to be directly correlated with proteinuria[42]. Although not yet confirmed, this evidence illustrates that a podocytopathy plays a key role in FD.

As seen with other nephropathies, glomerular sclerosis and tubulo-interstitial fibrosis, although not specific, are the histological features that best correlate with the progression of renal disease[43]. A glomerular sclerosis above 50% predicts a worst prognosis[44].

Concerning diagnosis of FD, enzymatic analyses of dried blood spots allow population screening and an initial diagnosis in males[45], while in heterozygous females, in whom alpha-galactosidase A activity is highly variable, genotyping is essential for a diagnosis. Adding to this, a target organ biopsy that reveals deposition of the glycosphingolipid can also confirm the diagnosis. Although not vital for diagnosis, kidney biopsy may have an important role to assess and monitor disease progression[46]. It should also be undertaken if there is the possibility of double pathology (e.g., diabetes or other glomerular diseases), especially if the patient is hypertensive; or there is a sudden, unexplained decline in renal function[47].

With age, progressive damage to vital organ systems develops and life-threatening renal, cardiovascular or cerebrovascular complications limit life-expectancy of untreated males and females to approximately 50 and 70 years, respectively[2].

Management of FD relies on enzyme replacement therapy (ERT)[48,49], but adjuvant therapies[50,51] are also important. It has been shown to improve the clinical outcome of patients with FD, including stabilization of kidney function[52-54]. However, because clinical trials are difficult to carry out in rare disorders, such as FD, adding to the heterogeneous presentation, no evidence is available to support the optimal timing to initiate it or to identify which patients are most likely to gain significant benefit from therapy[55]. The ERT appears not to have beneficial effect on overt proteinuria in adults[56,57], especially in men, but stabilization of renal function may be seen with ERT if proteinuria can be controlled using renin-angiotensin system blockers[58]. No biomarker or monitoring strategy has been identified until now. The ERT is currently available with recombinant A-galactosidase, including agalsidase-α (Replagal; Shire Pharmaceuticals) and agalsidase-β (Fabrazyme; Genzyme Corporation), the second one being the only approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for specific treatment of FD[52,59]. Recent data[46] described a reduction, and even clearing, of podocyte GL-3 deposits that was related to the cumulative dose of ERT received, and the reductions in urinary albumin excretion paralleled the reductions in podocyte GL-3 deposits.

CONCLUSIONS

This case illustrates the importance of a multidisciplinary evaluation to an effective clinical screening. It should be noticed once more that a negative family history does not exclude the diagnosis because a *de novo* mutation can happen at any time.

Although most women are heterozygous and remain asymptomatic[60], this case confirms that women should not be considered silent carriers of the mutation and they are potential victims for severe organ damage and death due to heart and kidney involvement.

At the present time, available evidence emphasizes the importance of the podocyte in relation to proteinuria, an important indicator of disease progression[61]. In this setting, this disease should not be forgotten in the differential diagnosis of proteinuria (especially under the nephrotic range) of uncertain origin, mainly based on the importance of starting ERT early, before there is major irreversible organ damage. We are hopeful that additional biomarkers will be validated in the future and will assist in the treatment decisions and patient monitoring.

Conflict of interest statement: None declared.

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