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Case report

Control of proteinuria with increased doses of agalsidase alfa in a patient with Fabry disease with atypical genotype–phenotype expression

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ABSTRACT

Fabry disease is a rare X-linked lysosomal storage disorder of glycosphingolipids, caused by the partial or complete deficiency of the lysosomal enzyme alpha-galactosidase A (a-Gal A). The missense mutation pN215S usually causes a milder form of the disease with isolated cardiac involvement. We report a case of a male Fabry patient with the pN215S mutation and a generalized disease. He suffered a relapse in proteinuria which responded to increased doses of the administered recombinant enzyme. Individualization of enzyme replacement therapy must be considered in selected cases characterized by clinical deterioration.

Control de la proteinuria con aumento de dosis de agalsidasa alfa en un paciente con enfermedad de Fabry y expresión de genotipo-fenotipo atípica

Palabras clave:
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RESUMEN

La enfermedad de Fabry es un trastorno hereditario raro ligado al cromosoma X, que se caracteriza por un almacenamiento lisosómico de glucoesfingolípidos causado por una deficiencia parcial o completa de la enzima lisosómica α-galactosidasa A (a-Gal A). La mutación sin sentido pN215S suele provocar una forma más leve de la enfermedad, con afectación cardíaca aislada. Se describe un caso de enfermedad de Fabry en un paciente varón con la mutación pN215S y enfermedad generalizada. El paciente presentó una recidiva de la proteinuria que respondió al aumento de dosis de la enzima recombinante administrada.

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Debe considerarse la posible conveniencia de una individualización de la terapia sustitutiva enzimática en casos seleccionados que presenten deterioro clínico.

Introduction

Fabry disease is a rare genetic lysosomal storage disorder of glycosphingolipids with X-linked transmission and an estimated incidence of 1:40,000–1:117,000 live male births.[1] Partial or complete deficiency of the enzyme alpha-galactosidase A (a-Gal A) results in altered metabolism and progressive lysosomal accumulation of the substrate (mostly globotriaosylceramide, Gb_3).[2] The responsible gene is located on the long arm of the chromosome X (Xq22). More than 600 mutations have been identified with variable phenotypical expression.[3]

Clinically we distinguish the classical form and two variants, cardiac and renal. In the classical form clinical manifestations appear during childhood or early adolescence including acroparesthesias, angiokeratomas and corneal opacities.[4] Progressive accumulation of Gb3 in the kidneys, heart and central nervous system lead to renal failure, hypertrophic cardiomyopathy and cerebral vascular accidents limiting life expectancy. The cardiac variant of the disease is associated with residual alpha-galactosidase A activity (>1%), appearing later in life. The patients suffer from left ventricular hypertrophy and hypertrophic cardiomyopathy with decreased systolic function. Other cardiac manifestations include valvular disease with thickened valves (especially left-sided) and regurgitation, myocardial ischemia, arrhythmias (frequently supraventricular) and ECG changes such as voltage criteria for LVH and repolarization abnormalities, shortened P-R, A-V block or bundle branch block.[5] The clinical picture is dominated by the aforementioned cardiac manifestations, while the classical signs and symptoms are usually absent. Some patients may present a degree of proteinuria without severe renal failure.[6]

Advances in the application of molecular genetic techniques have enabled the development of directed protein therapies for lysosomal storage diseases. In case of Fabry disease two formulations of recombinanat enzyme are currently available. Agalsidase-alfa (Replagal®, Shire) is derived from human skin fibroblasts and is administered intravenously at dose of 0.2 mg/kg every 14 days. Accordingly, agalsidase-beta (Fabrazyme®, Genzyme) is produced by Chinese Hamster ovary cell line and is given intravenously at dose of 1 mg/kg every 14 days.

We present the case of a male Fabry patient who was diagnosed with the missense mutation pN215S who in addition to cardiac involvement also presented serious extracardiac clinical manifestations. In our case, twenty months after the initiation of agalsidase-alfa in the conventional dose, an increment of proteinuria and left ventricular mass were noted. Switching the patient to double dose of the enzyme led to reduction of proteinuria and reestablishment of the cardiac indexes.

Case report

A 41-year old male was presented in the Renal Outpatient Clinic with proteinuria of 0.5 g/d and left ventricular hypertrophy. His renal function was normal (eGFR 122 ml/min/1.73 m^2). The patient underwent a renal biopsy which showed glomeruli with enlarged podocytes displaying abundant fine, granular and lucent protoplasm. Some tubular epithelial cells had a vacuolated and lucent cytoplasm or atrophy while mild interstitial fibrosis was also present (<10%). Immunofluorescence showed IgM deposition in mesangium of two glomeruli with granular distribution. Histological findings in association with the clinical manifestations led to further investigation toward diagnosis of Fabry disease. Indeed, low activity of α-Gal A in plasma and in leucocytes (0.3 nmoles/ml/h and 1.5 nmoles/mg protein/h, respectively) led to the aforementioned diagnosis. The subsequent familiar genetic investigation revealed that both he and his mother, a 70-year old female, had the pN215S missense mutation, corresponding to adenine replacement in the position 10135 with guanine (10135A → G).

Monitoring of the patients, performed twice a year, included biochemical exams of renal function and 24-h measurement of proteinuria, cardiac ultrasound and pro-BNP levels, plasma and urine levels of Gb3 as well as the titer of the anti-agalsidase antibodies and brain MRI scan every other year. The female suffered from left ventricular hypertrophy, without renal or CNS involvement. On the contrary, male patient had a complex phenotype with left ventricular hypertrophy, proteinuria and CNS lesions. Brain imaging with MRI scan showed vascular dolichoectasia in the vertebrobasilar junction and punctuated white matter lesions in the frontal lobe as well as in the basal ganglia.

The male patient was administered agalsidase-alfa (Replagal®, Shire) in the recommended dose of 0.2 mg/kg/d every 2 weeks and an ACE inhibitor in the maximum tolerated dose (ramipril 5 mg daily). Enzyme replacement therapy began 3 months after the histologic diagnosis.

During the first 20 months both renal and cardiac indexes remained stable and no other relevant event was noticed. At that point in the male patient a steep increase of proteinuria (from 560 to 2536 mg/d) as well as an increase in left ventricular mass (from 412 to 464.5 g) and pro-BNP levels (from 190 to 266.5 pg/ml) were observed. After measurement of Gb3 levels in plasma (5.86 nmol/ml) and exclusion of development of neutralizing anti-agalsidase-a IgG and IgA antibodies we considered to adapt the therapeutic regimen. Thus we administered, with the same frequency, double dose of enzyme (0.4 mg/kg/d). Seven months later, proteinuria decreased from 2536 to 986 mg/d and the indexes of cardiac size were reestablished. Accordingly plasmatic levels of Gb3