CARDIAC VARIANT OF FABRY DISEASE RESPONDING TO DOUBLE DOSE OF AGALSIDASE ALFA

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ABSTRACT

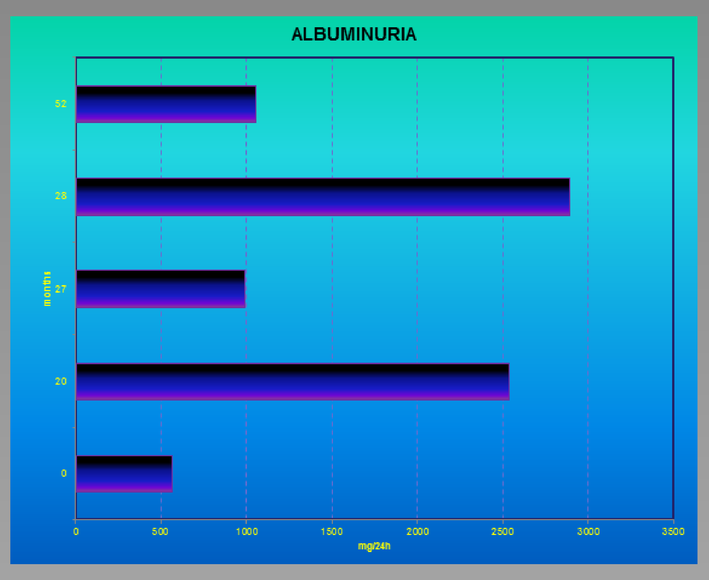
Introduction and aims: A 41-year old male (M) was presented in the nephrological outpatient clinic with proteinuria. He underwent a renal biopsy which revealed Fabry disease and in the subsequent genetic and enzymatic investigation both he and his mother, a 70-year old female (F), were diagnosed with the cardiac variant (pN215S mutation, 10135A→G).
Methods: Thus the patients initiated on enzyme replacement therapy with agalsidase- alfa (Replagal®, inj 0,2 mg/kg/d every 2 weeks, iv). Monitoring of the patients, performed twice a year, included biochemical exams of renal function, proteinuria, cardiac ultrasound, pro-BNP levels, plasmatic and urinary Gb_3 as well as the titer of the anti-agalsidase antibodies and MRI scan every other year.
Results: For the following 20 months both renal and cardiac indexes remained stable or slightly improved in both patients. At that point in patient M a steep increase of proteinuria (from 560 to 2536 mg/d) was noted. Moreover, in the cardiological follow-up an increase in left ventricular mass (from 412 to 464,5 gr) and pro-BNP (from 190 to 266,5 pg/ml) was observed. Possible causes of this deterioration (i.e. uncontrolled hypertension, urinary tract infection, drugs) were excluded. In literature, in similar cases, is reported improvement by means of more frequent administration of the same enzymatic dose. For better compliance and social reasons we were led to the decision to pursue the same goal administering double dose of enzyme with the same frequency. Thus the patient switched to agalsidase-alfa (Replagal®) dose of 0,4 mg/kg/d every 2 weeks, iv. In the following 7 months a progressive reduction of proteinuria (from 2536 to 986 mg/d) and reestablishing of the indexes of cardiac size was observed. Targeting to verify this apparent dose effect, conventional dose (0.2 mg/kg/d every 2 weeks) of agalsidase-alfa was readministered. One month later proteinuria increased again (2886 mg/d). Consequently we decided to continue with the double of the conventional dose of agalsidase-alfa and today, 24 months later, the patient presents albuminuria 1053 mg/d and stable cardiac size and function (LV mass=414,8 gr, pro-BNP=166,5pg/ml).
Conclusions: Substitution therapy in conventional dose usually controls the progression of Fabry disease. Nonetheless the administration of enzyme's replacement in higher dose may be helpful in selective cases.

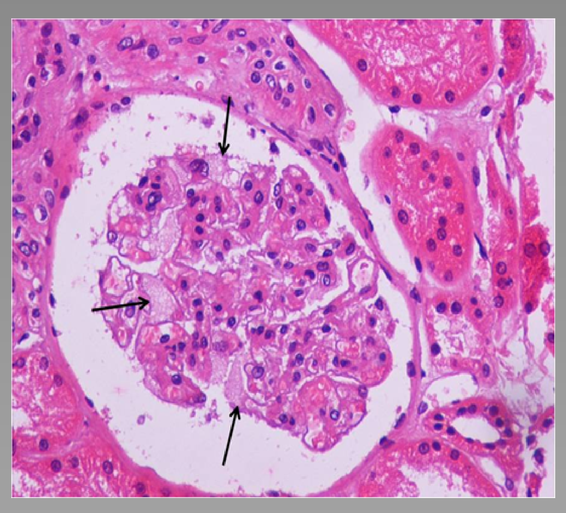
INTRODUCTION

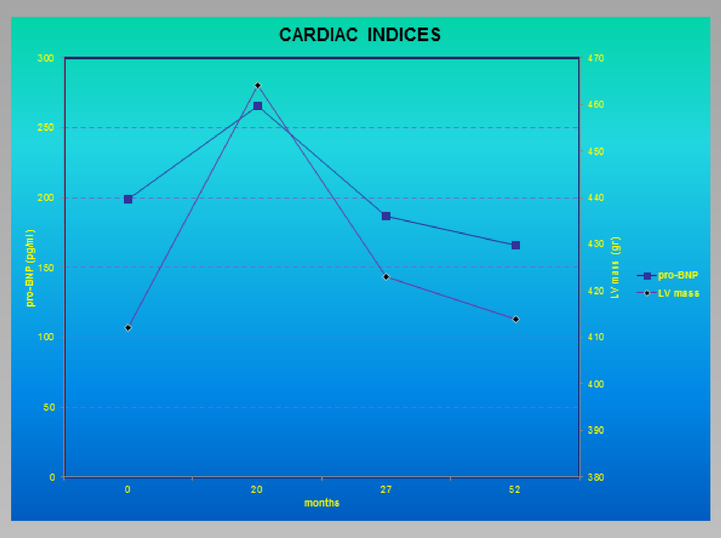
Fabry disease is a rare X-linked storage disorder of glycosphingolipids with an estimated incidence of 1:40000-1:117000 live male births[1]. It is caused by the partial or complete deficiency of the lysosomal enzyme alpha-galactosidase A[2] resulting in lysosomal accumulation of glycosphingolipids (mostly globotriaosylceramide, Gb_3). The responsible gene is located on the long arm of the chromosome X (Xq22). More than 400 mutations have been identified with variable phenotypical expression. The spectrum of the genetic lesions ranges from absence of the gene, manifested with severe disease, to missense mutations with residual alpha-galactosidase A activity and milder phenotype[3].
Gb_3 is progressively deposited in endothelial cells and smooth muscle cells of the capillaries as well as in various tissues throughout the body (i.e. CNS, heart, kidneys, lungs, eyes), leading to ischemic microvascular disease. In the course of the disease, inflammatory and neurohormonal tissue reactive mechanisms contribute to the development of hypertrophy and fibrosis, resulting in organ dysfunction.
Clinically we distinguish the classical form and the variants of Fabry disease (cardiac and renal). In the classical form the clinical manifestations appear during childhood or early adolescence and include neuropathic pain (acroparesthesias), angiokeratomas, corneal opacities (cornea verticilata) and hypohidrosis or anhidrosis[4].
Although, all types of renal cells as well as the endothelium of the blood vessels may be affected, podocytes and epithelial cells of the loop of Henle and distal convoluted tubule are the most commonly injured sites. Accumulation of the sphingolipids forms cytoplasmic vacuoles and inclusions. Other non-specific findings are hyperplasia of the mesangium and mesangial matrix, glomerular sclerosis, interstitial fibrosis and tubular atrophy. Clinically, isosthenuria may be the first manifestation. Non-nephrotic range proteinuria is developed frequently during the 3rd decade of life and renal failure in the 4th-5th decade which progresses to end stage renal disease after 1-13 years[5].
Progressive accumulation of Gb-3 inside the heart tissue and subsequent fibrosis lead to the development of 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[6].
The cardiac variant of the disease is associated with a residual alpha-galactosidase A activity (>1%) appearing later in life. The clinical picture is dominated by the aforementioned cardiac manifestations while the classical signs and symptoms are usually absent. The patients may present some degree of proteinuria without severe renal failure[7].
Heterozygotes females may remain asymptomatic (carriers) but severe disease with CNS, kidney or heart involvement occurs in up to 20% with a mean age of onset of 46 years, approximately a decade later than men[8].

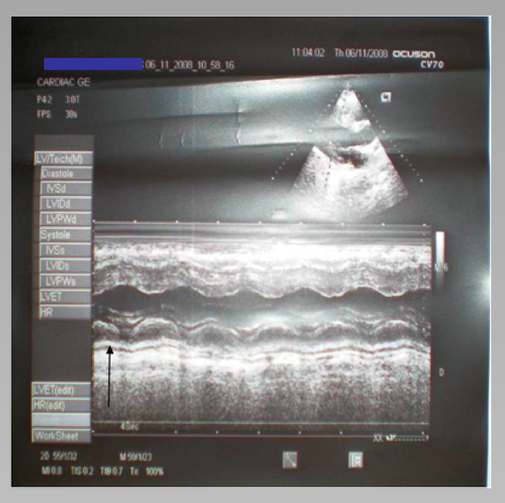
CASE REPORT

A 41-year old male (M) was presented in the nephrological outpatient clinic with proteinuria of 0,5 g/d, arterial hypertension and left ventricular hypertrophy. The patient underwent a renal biopsy with findings of a lysosomal storage disease. The subsequent genetic and enzymatic investigation revelead that both he and his mother, a 70-year old female (F), suffered from the cardiac variant of Fabry disease. The genetic defect was identified as the pN215S mutation (10135A→G) of the gene of a-galactosidase A, while the serum enzyme's activity was 0,3 nmoles/ml/h (normal range: 4-21 nmoles/ml/h).
The patients initiated substitution therapy with agalsidase-alfa (Replagal®, Shire) in the recommended dose of 0,2 mg/kg/d intravenously every 2 weeks and an ACEi in the maximum dose was administered. Monitoring of the patients, performed twice a year, included biochemical exams of renal function and 24-hour measurement of proteinuria, cardiac ultrasound and pro-BNP levels, plasmatic and urinary levels of Gb3 as well as the titer of the anti-agalsidase antibodies and MRI scan every other year.
During the first 20 months of treatment both renal and cardiac indexes had remained stable or slightly improved in both patients. At that point in patient M 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 gr) and pro-BNP (from 190 to 266,5 pg/ml) were observed. After exclusion of possible causes of this deterioration (i.e. uncontrolled hypertension, urinary tract infection, development of neutralizing anti-agalsidase-a antibodies) we decided to change the therapeutic regimen. For better compliance and social reasons we administered double dose of enzyme with the same frequency and the patient switched to biweekly injections of 0,4 mg/kg/d of agalsidase-alfa. Seven months after the switch, proteinuria decreased from 2536 to 986 mg/d and the indexes of cardiac size were reestablished (Graphics 1,2). Targeting to verify this apparent dose effect, the conventional dose of agalsidase-alfa (0.2 mg/kg/d every 2 weeks) was re-administered and one month later proteinuria increased again (2886 mg/d). Consequently the patient switched again to the double dose of the recombinant enzyme. After 24 months, the patient presents albuminuria of 1053 mg/d and stable cardiac size and function (LV mass=414,8 gr, pro-BNP=166,5pg/ml).









DISCUSSION

Advances in the application of molecular genetic techniques have enabled the development of directed protein therapies. In the case of Fabry disease two formulations of recombinant enzyme are currently available: Agalsidase-alfa (Replagal®, Shire) and agalsidase-beta (Fabrazyme®, Genzyme). Agalsidase-alfa is derived from human skin fibroblasts and is administered intravenously at dose of 0,2 mg/kg every 14 days. Accordingly, agalsidase-beta is produced by Chinese Hamster ovary cell line and is given intravenously at dose of 1 mg/kg every 14 days[9].
Long-term enzyme replacement therapy (ERT) appears safe and effective leading to stabilization of the renal function, reduction of left ventricular site, pain relief and improved quality of life as well as clearance of microvascular renal and cardiac endothelial deposits of Gb3[10]. The effectiveness of ERT is maximized when it is initiated early in the course of the disease before the development of irreversible organ damage[11].
Despite the favorable therapeutic response observed in the clinical trials, there are still controversies regarding the appropriate ERT regimen (i.e. dose and frequency of administration) in case of progressive clinical deterioration. In an open label, prospective clinical trial of 11 male patients with Fabry disease and rapid annual decline of eGFR, switching agalsidase-alfa regimen from the conventional biweekly dosing to weekly infusions of 0,2 mg/kg slowed eGFR's decline[12].
In our case administration of more enzyme by doubling the recommended dose of agalsidase-alfa was followed by a significant decrement of proteinuria as well as decrease of the left ventricular mass. The relapse of albuminuria after returning to the original therapeutic dosage as well as well as the re-improvement of cardiovascular and renal indexes following the increased dose of agalsidase-alpha in 0,4mg/kg provide evidence on the efficacy of the modulated therapy.

CONCLUSIONS

Although individualization of ERT is not supported by the literature, it should be considered in selected cases of Fabry disease when conventional ERT dosing and symptomatic treatment are not effective to control proteinuria and thus delay the progression of renal disease. However, accounting on the rise of the cost of the therapy, additional investigation is required in order to evaluate cost-effectiveness of such a therapeutic intervention.

REFERENCES

1. Mehta A, Ricci R, Widmer U et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004; 34: 236-42
2. Kint JA. Fabry's disease: alpha-galactosidase deficiency. Science 1970; 167: 1268-1269
3. Clarke JT. Narrative review: Fabry disease. Ann Intern Med 2007; 146 (6): 425-33
4. Ries M, Ramaswami U, Parini R et al. The early clinical phenotype of Fabry disease: A study of on 35 European children and adolescents. Eur J Pediatr 2003; 162: 767-772
5. Ortiz A, Oliveira JP, Waldek S et al. Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. Nephrol Dial Transplant 2008; 23 (5): 1600-7.
6. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart 2007; 93: 528-535
7. Sachdev B, Takenaka T, Teraguchi H et al. Prevalenve of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002; 105: 1407-1411
8. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab 2008; 93 (2): 112-28
9. Lee K, Jin X, Zhang K et al. A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease. Glycobiology 2003; 13 (4): 305-313
10. Alfadhel M, Sirrs S. Enzyme replacement therapy for Fabry disease: some answers but more questions. Therapeutics and clinical risk management 2011; 7: 69-82
11. Breunig F, Weidemann F, Strotmann J et al. Clinical benefit of enzyme replacement therapy in Fabry disease. Kidney Int 2006; 69: 1216-1221
12. Schiffmann R, Askari H, Timmons M et al. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. J Am Soc Nephrol 2007; 18: 1576-1583