Acta Clin Croat 2005; 44:59-63 Review

KIDNEYS IN ANDERSON-FABRY DISEASE

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SUMMARY – Anderson-Fabry disease is an X-linked recessive glycolipid storage disease caused by deficient activity of the lysosomal enzyme alpha-galactosidase A. Numerous mutations are responsible for development of the disease. Clinical manifestations include acroparesthesia from childhood, corneal dystrophy, angiokeratomas, hypohidrosis, hearing loss and, with aging, development of cardiovascular and renal disease. Renal failure typically begins in the third decade of life. A young male patient presents with proteinuria and impaired urinary concentrating ability, or reaches end-stage renal disease of unknown origin without prior supervision of nephrologist. Polyuria and nicturia are the first signs of disease caused by urinary concentration defect. Proteinuria begins in the second decade of life, and is usually below the nephrotic level. Urinalysis is characterized by hematuria and lipiduria. Urinary sediment contains lipid globules and characteristic "Maltese crosses". Enzyme replacement therapy has recently become available. Two formulations of alpha-galactosidase A have received marketing authorization. It seems possible to halt and probably even reverse the progression of Fabry disease before the irreversible organ damage has set in. Clinical trials have proved the efficacy and safety of treatment with agalsidase alpha or beta. Besides its beneficial effect on renal function, enzyme replacement therapy improves cardiac parameters and quality of life in patients with Anderson-Fabry disease. The main disadvantage of enzyme replacement therapy is the very high cost of treatment, posing a challenge even to the most industrialized countries in the world.

Key words: *Fabri disease – complications; Fabri disease – genetics; Kidney disease – therapy; Kidney disease – diagnosis*

Introduction

Anderson-Fabry disease is an X-linked recessive glycolipid storage disease caused by deficient activity of the lysosomal enzyme a-galactosidase A[1]. Numerous mutations are responsible for the disease development[2-4]. Most of them occur individually or are limited to several families. The incidence of Anderson-Fabry disease has been estimated to range from 1 *per* 40,000 to 1 *per* 117,000 male live births[5]. The phenotype of heterozygous females varies widely, from asymptomatic state to severe signs of disease due to random X-chromosome inactivation. The true incidence is unknown due to the under-recognition of disease (especially in women) and variable clinical expression. Based on these estimates, there would be at least 50 patients with Anderson-Fabry disease in Croatia.

Globotriaosylceramide, the glycolipid substrate for a-galactosidase A, accumulates in different cells and tissues[6]. Clinical manifestations include neuropathy with painful episodes present from childhood, corneal dystrophy, angiokeratomas, hypohidrosis, hearing loss and, with aging, development of cardiovascular and renal disease. The mean survival is 40-50 years for hemizygous males, and 70 years for female carriers, with death resulting from cardiac, renal, or cerebrovascular complications[7].

Recently, with the advent of molecular genetic techniques, enzyme replacement therapy has become available. Two formulations of a-galactosidase A have received marketing authorization.

In this review, we will provide a brief overview of the manifestations of Anderson-Fabry disease. Treatment options will be discussed, with the hope that our doctors will consider this disease in the differential diagnosis of end-

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Received January 24, 2005, accepted February 28, 2005

stage renal disease (ESRD) and/or unexplained heart hypertrophy in suspected individuals.

Genetic Background of Renal Disease

The type of mutation may influence the age at onset of chronic renal failure in patients with Anderson-Fabry disease[8]. Scientists from the National Institutes of Health (NIH), USA, found the patients with conservative substitution mutations (one amino acid substituted by another amino acid from the same structural group) to have a higher residual a-galactosidase A activity and to maintain normal renal function during the follow up period. Patients with nonconservative mutations had a lower residual enzyme activity, and 35% of them developed chronic renal failure by age 22[9,10].

Renal Failure in Anderson-Fabry Disease

Renal failure typically begins in the third decade of life in patients with Anderson-Fabry disease. A young male patient presents with proteinuria and impaired urinary concentrating ability, or in another scenario, with ESRD of unknown origin. Such unfortunate patients are the most suitable candidates for the misdiagnosis of "chronic glomerulonephritis – without biopsy". For this reason, the diagnosis of Anderson-Fabry renal disease is often made by recognition of extrarenal manifestations. Positive family history significantly contributes to the diagnosis of the disease.

Polyuria and nicturia are the first signs of the disease, and are caused by the urinary concentration defect. Proteinuria begins in the second decade of life and is usually below the nephrotic level. Urinalysis is characterized by hematuria and lipiduria[11]. Urinary sediment contains lipid globules and characteristic "Maltese crosses". The mean age at onset of clinical nephropathy has been reported at 27 years[12]. In the NIH series, development of chronic renal failure has been reported at a mean age of 43 years. Anderson-Fabry disease may rarely cause ESRD in teenagers[13]. Progression of chronic renal failure to ESRD occurred over a mean of 4±3 (range 1 to 13) years[14]. The mean rate of decline in glomerular filtration rate was 12.2 ml/min *per* year. The patients did not receive angiotensin-converting enzyme (ACE) inhibitors or angiotensin II antagonists, which could possibly slow down the disease progression[10]. All NIH patients who survived to age 50 developed ESRD, and none survived past 60 years of age[10].

Treatment of Anderson-Fabry Disease

Enzyme replacement therapy

The development of a-galactosidase A formulations has significantly modified the treatment of patients with Anderson-Fabry disease. In the past, the management of this disease was limited to symptomatic treatment of different complications. Two randomized trials of enzyme replacement therapy with different a-galactosidase A formulations have been published[15,16]. Studies are hardly comparable, yet both suggested that enzyme replacement therapy for Anderson-Fabry disease was safe and effective.

Agalsidase beta (Fabrazyme) was administered in 11 doses every two weeks for 20 weeks in a dose of 1 mg/kg. The primary study endpoint was the percentage of patients in whom renal microvascular endothelial deposits of globotriaosylceramide were significantly reduced. Patients from the treatment group had significantly less endothelial deposits in the kidneys, skin and heart as compared with the placebo group. Plasma globotriaosylceramide concentrations were unchanged in the placebo group. Treatment group had undetectable concentration of globotriaosylceramide[16].

Agalsidase alfa (Replagal) was administered intravenously every other week for 6 months (12 doses) in a dose

Table 1. Characteristics of two recombinant a-galactosidase A formulations

	Agalsidase beta	Agalsidase alpha
Trade name	Fabrazyme®, Genzyme	Replagal®, TKT Europe
Enzyme source	Chinese hamster ovary cells	Human cells
Dose	1 mg/kg iv over 4 to 6 hours every 2 weeks	0.2 mg/kg iv over 40 minutes every 2 weeks
Infusion reactions	Premedication necessary	No premedication
Development of antibodies	88%	85%

of 0.2 mg/kg. The primary endpoint was the change in the worst neuropathic pain compared with baseline. Significant improvements compared with placebo were recorded. The overall pain sensitivity and quality of life as well as creatinine clearance and cardiac conduction were improved. Plasma globotriaosylceramide concentrations were reduced by 54% as compared with 7% on placebo ($p=0.005$)[15]. Details of two different enzyme formulations are given in Table 1.

Rigor and fever occurred significantly more frequently in the treatment groups than in the placebo groups. Transient mild to moderate infusion associated reactions occurred in 59% of patients. In all patients, the occurrence of infusion reactions was appropriately controlled by reduction of infusion rate and premedication.

Development of IgG antibodies to agalsidase A occurred in almost 90% of patients in both studies. Only three patients withdrew from the extension study due to positive serum IgE or skin test. They successfully resumed therapy. There was no anaphylaxis associated with the use of agalsidase[17]. Antibody formation had not interfered with therapeutic outcome.

Treatment of patients with renal failure caused by Anderson-Fabry disease

Clinical trials with agalsidase formulations investigated changes in kidney histology associated with the use of enzyme replacement therapy. The NIH searched for changes in glomerular structure, and found a decreased concentration of globotriaosylceramide in renal tissue[15]. Scientists from the Mount Sinai Study Group looked for lipid deposits within the capillaries, and found that, compared with the placebo group, patients treated with enzyme replacement therapy had a significantly decreased renal concentration of globotriaosylceramide[16]. Different histologic study endpoints make it difficult to compare the trials, however, the results of both studies indicate that an early intervention before the onset of renal fibrosis has a potential to halt the progression of the disease.

Development of proteinuria in a patient with Anderson-Fabry disease demands aggressive control of hypertension. It is expected that angiotensin antagonists may slow down the disease progression. Development of ESRD demands initiation of renal replacement therapy. In the USRDS analysis of incident dialysis patients between 1995 and 1998, 64% of patients started hemodialysis, 22% continuous ambulatory peritoenal dialysis, and 12% continuous cycling peritoneal dialysis[18]. In the ERA-EDTA analysis, the initial treatment modality was hemodialysis in 78%, peritoneal dialysis in 18%, and preemptive transplantation in 1% of patients[19].

The 3-year survival of patients with Anderson-Fabry disease on dialysis is slightly better than the survival of patients with diabetes (63% *vs.* 53%) but significantly lower than in nondiabetic controls (74%) ($p=0.01$)[18].

Kidney transplantation is not universally accepted as the treatment of choice for ESRD patients with Anderson-Fabry disease. Previous reports considered these patients as being at a too high cardiovascular risk for transplantation. The burden of cardiovascular risk is high, considering the original cardiovascular involvement by Anderson-Fabry disease, the increased risk of the development of cardiovascular disease that is well known among dialysis patients, and finally, the additive risk effect of immunosuppressive medications. Published reports on kidney transplantation in patients with Anderson-Fabry disease are contradictory[12,20,21]. There are case reports of recurrence of Anderson-Fabry disease in transplanted kidney recipients[22]. However, overall data suggest that the graft and patient survival in patients with Andesron-Fabry disease is comparable to matched controls.

Symptomatic treatment

The additional and until recently the only treatment for Anderson-Fabry disease is directed against specific symptoms caused by damage to different organs and tissues. Carbamazepine and phenytoin may relieve pain[23]. The management of cardiac dysfunction includes pharmacological control and implantation of electrostimulator in case of severe conduction abnormalities.

Conclusion

It may be possible to halt and probably even reverse the progression of Fabry disease before the irreversible organ damage has set in. Clinical trials have demonstrated the efficacy and safety of treatment with agalsidase alpha or beta. It has been clearly shown that enzyme replacement therapy has beneficial effects on renal function as well as on cardiac parameters and quality of life in patients with Anderson-Fabry disease. However, the enormously high price is a big challenge even for the most developed countries in the world. Timely diagnosis and treatment initiation may spare funds necessary for symptomatic and supportive therapies, while keeping the patient capable of working. This should be our goal.

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Sažetak

Bubreg u Anderson-Fabrijevoj bolesti

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Anderson-Fabrijeva bolest se nasljeđuje recesivno putem X kromosoma. Nedostatna aktivnost lizosomskog enzima a-galaktozidaze A uzrokuje nakupljanje glikolipida u različitim tkivima i organima. Dosad su prepoznate brojne mutacije odgovorne za razvoj bolesti. Kliničke manifestacije uključuju akroparestezije od djetinjstva, distrofiju mrežnice, angiokeratome, hipohidrozu, slabljenje sluha, te razvoj kardiovaskularne i bubrežne insuficijencije. Zatajenje bubrega započinje u trećem desetljeću života. Obično mladi muškarac dolazi s proteinurijom i poremećenom sposobnošću koncentriranja mokraće ili nastupa završno zatajenje bubrega bez prethodnog nadzora nefrologa. Poliurija i nikturija su prvi znakovi bolesti uzrokovani poremećenom sposobnošću koncentriranja mokraće. Proteinurija počinje u drugom desetljeću života i obično je ispod nefrotske razine. Analizom mokraće nađu se hematurija i lipidurija. U sedimentu su prisutne nakupine lipida i znakoviti "malteški križevi". Odnedavno je u kliničkoj praksi dostupna enzimska nadomjesna terapija za liječenje Anderson-Fabrijeve bolesti. Dosad su na tržištu registrirana dva pripravka rekombinantnog enzima a-galaktozidaze A. Čini se da je moguće zaustaviti i možda čak ispraviti poremećaje u ciljnim organima pogođenim Anderson-Fabrijevom bolešću ako u njima nisu nastupile nepovratne promjene. Klinička istraživanja su dokazala učinkovitost i neškodljivost liječenja agalsidazom alfa ili beta. Uz povoljan učinak na bubrežnu funkciju, enzimska nadomjesna terapija je značajno poboljšala srčanu funkciju i kvalitetu života bolesnika. Glavni nedostatak nadomjesne terapije je vrlo visoka cijena liječenja koja predstavlja izazov čak i za najrazvijenije zemlje svijeta.

Ključne riječi: