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CLINICAL REPORT

Enzyme Replacement Therapy in Severe Fabry Disease with Renal Failure: A 1-year Follow-up

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We present here the course of clinical response of a 53-year-old haemodialysed Fabry patient who received recombinant human α-galactosidase A at a dose of 1 mg/kg every other week over a period of 1 year. The therapy was well tolerated by the patient, who revealed an impressive favourable cutaneous, gastrointestinal, neurological and psychiatric response and a dramatic improvement in his quality of life, but no improvement in cardiac and renal function. ***Key words: α-galactosidase A; angiokeratoma; dialysis; diarrhoea; depression; globotriaosylceramides; oedema.***

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Fabry disease (FD) is an X-linked lysosomal storage multisystemic disorder caused by mutations in the gene encoding the lysosomal enzyme α-galactosidase A (AGA) (1). In affected hemizygotes the resulting AGA deficiency causes a progressive accumulation of globotriaosylceramides and other glycosphingolipids with terminal α-galactosyl moieties in various organs throughout the body (2). This progressive lipid accumulation leads to the clinical manifestations of FD, which mainly include angiokeratomas, acroparaesthesias, hypohidrosis or anhidrosis, and to severe clinical sequelae in the cardiac, renal and cerebrovascular system resulting in early death (3).

The recent advent of enzyme replacement therapy (ERT) with recombinant human AGA (4, 5) has introduced a new and spectacular era in the treatment of FD, which, until recently, was limited to pain relief and palliative management of cardiac disease, renal failure and stroke. The efficacy and safety of ERT with recombinant human AGA have been demonstrated in two double-blind randomized controlled studies (6, 7). However, there is a paucity of information on its use in severe FD with chronic renal failure.

In this paper a severely affected Fabry patient undergoing haemodialysis is reported and his response to 1 year of ERT with human recombinant AGA is described in some detail.

CASE REPORT

In 1995, a 45-year-old Caucasian male patient with severe hypertension was admitted to the University Medical Center of Patras. He had a history of anhidrosis, heat intolerance and skin lesions since his early childhood. Since the age of 10 years he has had painful episodes with severe swelling of both hands and feet associated with low grade fever, abdominal and flank pain, diarrhoea, early feeling of fullness, anorexia, weight loss, general weakness and acroparaesthesias. He recalled having tonsillitis at the age of 15 with 'possible joint swelling a couple of weeks later' but gave no clear history of definite rheumatic fever or carditis or suggestive symptoms thereof. Since the age of 25 years he has experienced attacks of burning sensation at the proximal parts of the limbs that worsened in the summer, but revealed a progressive decline of their frequency and severity with advancing age. On dermatological examination, there were numerous typical angiokeratomas on the trunk and the penis, swelling of upper eyelids, multiple linear telangiectases on the face and a marked lymphoedema on both lower limbs. Based on these findings the clinical diagnosis of FD was made and confirmed by biochemical investigations that revealed a deficiency of AGA in plasma (1.63 nmol/ml/h; normal range 4–11) and skin fibroblasts (2.0 nmol/mg/protein/h; normal range 13–33) (8, 9). Molecular genetic investigations demonstrated a novel trinucleotide deletion located in exon 7 of the AGA gene (8, 9). Ophthalmological and otorhinolaryngological examinations were unremarkable, whereas severe left ventricular hypertrophy (LVH) with moderate valvular lesions and end-stage renal disease were diagnosed. The patient started symptomatic treatment for his cardiac disease (captopril 75 mg/day; glycerol trinitrate 5 mg/day; acetylsalicylic acid 100 mg/day) and a haemodialysis program (three times weekly). Since then he has been followed up in our University Medical Center. At the age of 50 years the patient suffered a transient ischaemic attack (TIA) with dysarthria and unsteadiness of gait. In the

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following 2 years he has had three more similar TIAs of 5–60 min duration each.

The patient gave his informed consent to receive ERT with recombinant AGA (agalsidase beta; Fabrazyme, Genzyme Corp., Cambridge, MA, USA), which was started at the Department of Dermatology, University of Patras, in January 2002 at a dose of 1 mg/kg every other week and at a rate of 10 mg/h. The treatment protocol had been approved by the institutional ethics committee. As the patient experienced a moderate hypersensitivity reaction (rigors, fever, hypertension and tachycardia) to the sixth infusion, he was thereafter pretreated 1 h before each infusion with 100 mg nimesulide and 10 mg cetirizine. With this pretreatment the reaction to the seventh and eighth infusion was less severe, and at the following stages of ERT no reaction was observed.

Gastrointestinal response

After the third infusion there was a clear decrease in the frequency of painful diarrhoea episodes, with complete remission after the sixth infusion. A progressive remission of the early feeling of fullness and an increase of appetite were also observed. After 1 year of ERT the patient could eat larger portions of meals without any complaints and an increase of his body weight to 52.5 kg (baseline: 48 kg) and of his body mass index (BMI) to 17.7 kg/m^2 (baseline: 16.2 kg/m^2; height: 172 cm) was observed.

Cutaneous response

After the third infusion a progressive reduction in the size and number of angiokeratomas and telangiectases became evident. After 1 year of ERT the number of facial telangiectases was clearly decreased, whereas an almost complete remission of the trunkal and penile angiokeratomas was observed (Fig. 1). After the fifth infusion a progressive reduction of limb lymphoedema was seen. After 1 year of ERT there was a complete remission of the oedema in the right limb and a dramatic improvement of that in the left limb. For the first time in his life the patient experienced sweating (after the seventh infusion), that gradually became more pronounced with further treatment. After 1 year of ERT a complete normalization of the patient's sweat gland function was observed, accompanied by a full remission of heat intolerance. Additionally, histochemical examination of biopsy specimens derived from the apparently normal skin of the patient before and 12 months after commencement of ERT and stained with Bandeiraea Simplicifolia Lectin I (BSL I), which specifically binds to α-D-galactosyl residues, revealed a complete clearance of glycosphingolipid accumulation in the sweat glands (Fig. 2).

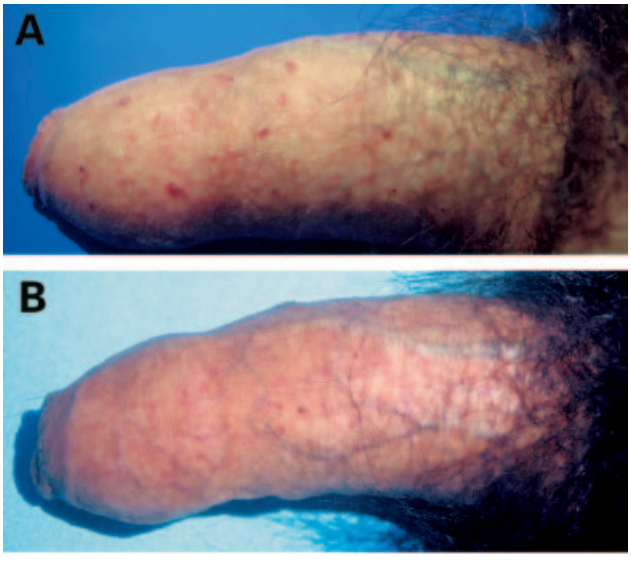

Fig. 1. Clinical aspect of penile angiokeratomas before (A) and 1 year after onset of enzyme replacement therapy (B).

Cardiac response

Before initiation of ERT, the patient reported exertional dyspnoea, atypical chest pain, fatigue and dizziness. Cardiologic examination revealed severe concentric LVH, moderate aortic stenosis and regurgitation, moderate mitral and mild tricuspid regurgitation, moderate pulmonary hypertension and severe thickening and calcification of the aortic and mitral

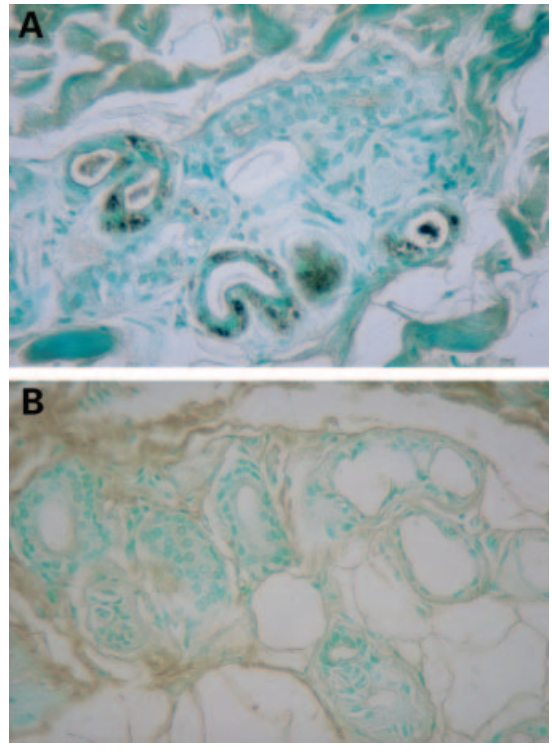

Fig. 2. (A) Accumulation of glycosphingolipids in the sweat glands of the patient before commencement of enzyme replacement therapy (ERT). (B) Complete clearance after 1 year of ERT. (Histochemical staining with BSL-I; ×400.)

valves without any significant stenosis of coronary vessels. After 1 year of ERT the patient exhibited a significant improvement of his cardiac symptoms. However, echocardiography failed to demonstrate any significant improvement of the pretreatment findings.

Renal response

Before the onset of ERT the patient was on hospital haemodialysis three times per week using a 1.62 m^2 polysulphone surface as dialyser and had no residual renal function. Adequacy of dialysis expressed as single-pool Kt/V ratio (spKt/V) was 1.23 (K = dialyser blood water urea clearance; t = dialysis session length; V = urea distribution volume) (10). After 1 year of ERT, apart from a rise in spKt/V value (1.34), no significant change in the patient's renal function could be detected.

Neurological response

Before the commencement of ERT, neurological examination showed a lower left-sided facial paresis, suppressed reflexes and extensor plantar responses. Pain and vibration sense in the distal limbs was bilaterally depressed. Brain MRI showed dolichoectasia of the basilar artery and several periventricular lacunar infarcts. Electroneurophysiological evaluation revealed a sensorimotor length-dependent axonal polyneuropathy (Table I). In addition, there was an impairment of the autonomic nervous system. After 1 year of ERT the results of the neurological examination and brain MRI showed no significant change, as compared to the pretreatment phase. Nevertheless, electroneurophysiological examination disclosed improvement mainly of the sensory parameters (Table I), whereas the impairment of the autonomic nervous system remained unchanged.

Psychiatric response

Before commencing ERT the patient revealed a major depressive disorder (DSM-IV) [Hamilton Depression Scale Score (HDS score) = 31] (11), but refused to take the prescribed antidepressant. After the seventh infusion the patient was found to be clearly less withdrawn, sad or anxious and reported experiencing pleasure from relationships and having good appetite and concentration. After 1 year of ERT a major depressive disorder could no longer be diagnosed (HDS score = 7).

DISCUSSION

Recent clinical trials have demonstrated the efficacy and safety of intravenous AGA in FD (4 – 7). However, to the best of our knowledge, no studies have been published on the efficacy and safety of ERT in dialysis patients with a severe phenotype of FD. One of the earliest signs of response to ERT in our patient was the decrease in the frequency of painful diarrhoea episodes after the third infusion, which completely resolved after the sixth infusion. This favourable response markedly contributed to the improvement of patient's quality of life and is probably associated with an ERT-induced mobilization and clearance of glycosphingolipids accumulated in the gastrointestinal smooth muscle, autonomic nervous and vascular tissue elements (12 – 14). In the studies published so far on the efficacy and safety of ERT in FD no data are provided about the gastrointestinal response of the treated patients, whereas with regard to the cutaneous response only a reduction in the concentration of glycosphingolipids in the superficial capillaries of skin and an 'increased ability to sweat' are mentioned (4 – 7). In our patient, 1-year ERT resulted in a normalization of sweat gland function with full remission of heat intolerance, complete remission of the oedema in the right limb and dramatic improvement of that in the left limb, almost complete resolution of angiokeratomas and a marked numerical decrease of facial teleangiectases. This favourable response to ERT is obviously associated with the decline in glycosphingolipid deposition in the cutaneous blood and lymphatic vessels. As the impairment of the autonomic nervous system remained unchanged under ERT, it seems reasonable to assume that the complete recovery of sweating is exclusively due to the clearance of glycosphingolipids from the sweat glands.

Eng et al. (6) reported a decrease in the concentration of glycosphingolipids in heart biopsy specimens of the treated Fabry patients after the 20th infusion of AGA but found no significant changes in echocardiograms and electrocardiograms, whereas Schiffmann et al. (7) observed a significant decrease in QRS complex duration after ERT. In view of the history of possible

Table I. *Neurophysiological findings: the patient's sensory conduction before and after 1 year of enzyme replacement therapy with recombinant α-galactosidase A*

	Ulnar nerve			Sural nerve		
Parameter	Normal limits	Before	After	Normal limits	Before	After
a-SAP (μV)	≥5	2	5.8	≥7	nd	4.5
SCV (m/s)	≥45	40	45	≥42	nd	44.4

a-SAP, amplitude of sensory action potential; SCV, sensory conduction velocity; nd, not detectable.

rheumatic fever in the childhood of our patient, the possibility that rheumatic heart disease might also be involved in the pathogenesis of his valvular lesions cannot be definitely ruled out. This could explain the lack of significant improvement in left ventricular wall thickness and other echocardiographic abnormalities after ERT.

In Fabry patients with preserved renal function ERT was found to reduce glycosphingolipid storage in the vascular endothelium of the kidneys and to prevent or delay the progression of renal involvement, leading to an improvement in renal pathology and function (5–7). Data on the efficacy of ERT in Fabry patients undergoing dialysis are missing. One year of ERT had no significant influence on the renal function of our severely affected patient; however, as he refused a kidney biopsy before and during treatment, the possible effects of AGA on his glomerular histology and renal glycosphingolipid deposition remain unknown.

Apart from a decline in neuropathic pain score and an improvement in the pain-related quality of life (5–7), no objective data are available with regard to the neurological response of Fabry patients to ERT. The unusual severity of neurophysiological abnormalities found in our patient could be attributed to an extensive glycosphingolipid deposition in his nervous and vascular tissues and to his chronic renal failure, which is a known cause of distal polyneuropathy (15). As the renal function of our patient remained unchanged after 1 year of ERT, the improvement of his neurophysiological picture, which is reported here for the first time, can be explained only in terms of mobilization and clearance of glycosphingolipids stored in the vasa nervosum cells and of reversion of lumen stenosis and ischaemia in peripheral nerve tissue.

About 18% of FD patients develop psychiatric disorders, mostly depression, that may have a major impact on the morbidity of FD (16). Interestingly, data on the psychiatric response of FD patients to ERT have not been reported previously. The beneficial effects of ERT on our patient's major depressive disorder became evident as soon as 3.5 months after the onset of AGA administration. Thereafter, the improvement in his mood and behaviour was rapid and impressive. After 1 year of ERT the criteria for diagnosis of a major depressive disorder were no longer fulfilled.

The results of this study demonstrate an impressive favourable cutaneous, gastrointestinal, neurological and psychiatric response of our severely affected FD patient to ERT and a dramatic improvement in his quality of life. Although 1 year of ERT produced no significant beneficial effects on the patient's cardiac disorder and renal disease, the possibility that this well tolerated treatment may have resulted in a stabilization of his cardiac and cerebral status and in a lower risk for development of further cardiovascular and cerebrovascular complications cannot be ruled out.

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