Alpha-galactosidase A deficiency (Fabry's disease) in a black Zimbabwean

M. Z. BOROK, R. GABRIEL

Abstract **We describe a patient with Fabry's disease with renal and myocardial involvement. He has been followed up for 10 years. This metabolic defect has not been noted before in southern Africa; the clinical course is similar to that of western European and American cases.**

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Fabry's disease is an X-linked recessive disorder resulting from deficient activity of the lysosomal hydroxylase, α-galactosidase A. Hemizygous men are severely affected. A complementary DNA that encodes mature α-galactosidase A has been cloned and sequenced.[1] There is a progressive accumulation of neutral glycosphingolipids and terminal α-galactosidase moieties, predominantly within lysosomes of endothelial, peri-epithelial and smooth-muscle cells of the cardiovascular and renal systems and brain.[2] In addition there are typical findings in the conjunctiva, retina and lens.[3] Fairly characteristic progressive changes develop in many organs. Hemizygous men die of renal failure in their fourth or fifth decade.[4] The deposition may be confined exclusively to the myocardium.[5] Comparable conditions include Niemann-Pick disease (sphingomyelin), Gaucher's disease (glucocerebroside) and metachromatic lipodystrophy (sulphate). Renal involvement is minimal or non-existent in these latter three autosomal recessive conditions.[6]

Confirmation of the diagnosis is obtained by demonstration of low α-galactosidase A serum activity. We report such a patient, investigated as part of our study of nephrotic patients in Zimbabwe.

Case report

An 18-year-old Shona man presented to Parirenyatwa Hospital, Harare, Zimbabwe, in January 1982 with headaches, anorexia and joint discomfort of 2 months' duration, as well as puffiness of the face, eyes and ankles of 2 weeks' duration. The patient's parents are alive as are 3 brothers and 3 sisters.

Examination revealed the following: weight 50 kg, puffy eyes, normal skin and conjunctivae, blood pressure 120/80 mmHg, modest peripheral oedema, no arthropathy. Slit lamp examination and assessment of colour vision were normal in 1982 and were still normal in 1992.

Urine microscopy revealed granular casts, no red cells, a serum creatinine level of 65 μmol/l, creatinine clearance 80 ml/min, a serum albumin level of 29 g/l and a urine protein value of 4,4 g/day. Concentrations of serum immunoglobulins C4 and C3 were normal. The patient was successfully treated with diuretics. In January 1983, his serum creatinine level was 102 μmol/l and clearance 74 ml/min. By 1987 the creatinine level was 135 μmol/l and clearance 57 ml/min. In June 1992, the serum creatinine level had risen to 428 μmol/l and the clearance had fallen to 13 ml/min. Urine protein content was 1,2 g/day and serum albumin level 51 g/l.

In May 1983 unusual limbal markings with some endothelial folds were noted on the right conjunctiva: they have not altered during follow-up. Visual acuity was and remains normal. The patient was last seen in March 1992, at which time he was normotensive and had developed no further stigmata of the condition.

He has not experienced the limb pain and paraesthesiae which are common in this sphingolipidosis.[7]

Results of special investigations

Renal biopsy (June 1982)

Light microscopy revealed 29 glomeruli of which 4 (14%) were obsolete; the remainder were enlarged. The visceral epithelial cells were prominent and contained vacuolated cytoplasm. Some tubules were atrophic with foci of fibrosis and moderately dense groups of mononuclear cells. Some of the convoluted tubular epithelial cells contained vacuolated cytoplasm. Arterioles, interlobular arteries and veins were normal. There was no glomerular deposition of immunoglobulin or complement components except for granular C3 in arteriolar walls. Electron microscopy showed a normal capillary basement membrane with no electron-dense deposits. Abnormalities were confined to epithelial, endothelial and mesangial cells. All contained osmiophilic inclusions which were most prominent in the greatly enlarged visceral epithelial cells. They contained numerous laminated osmiophilic inclusions, the majority of them free within the cytoplasm, although some appeared membrane-bound. These findings are characteristic of Fabry's disease.[2] Other glomerular structures were normal except for widespread foot process fusion of parietal epithelial cells.

Echocardiography

In 1988, the patient had normal left ventricular end-diastolic and systolic dimensions, a posterior wall thickness of 12 mm and good left ventricular function. In 1992, end-systolic and diastolic dimensions of 23 mm and 46 mm respectively indicated good myocardial function but the intraventricular septum measured 14 mm and the posterior wall 12 mm. These dimensions fulfil the criteria for left ventricular hypertrophy. The myocardium was very echogenic. Blood pressure was normal at 125/75 mmHg.

Enzyme studies

Serum was obtained from the patient, his father, a brother and, for control purposes, from a man of comparable origin who had proteinuria due to minimal-change glomerular disease. The samples were assayed for total β-hexosaminodase and α-galactosidase A activities according to the method of Rietra *et al.*[8] Results are shown in Table I.

The father and brother had no evidence of renal disease and their α-galactosidase A serum activity was

Department of Medicine, University of Zimbabwe, Harare
M. Z. BOROK, M.B., M.R.C.P.
Renal Unit, Parirenyatwa Hospital, Harare
R. GABRIEL, B.A., M.SC., M.B., F.R.C.P.

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normal. Another brother had normal urine. Unfortunately it has not been possible to investigate the mother or sisters of the index patient.

TABLE I.
Total β-hexosaminodase and α-galactosidase A activity in the patient, his father, brother and a nephrotic black Zimbabwean control. Normal ranges of the above enzymes await confirmation in the Shona people

	Total β-hexosaminodase (μmol/ml/h)	α-galactosidase A (nmol/ml/h)
Control	2,5	26,5
Patient	0,8	0,3
Father	2,1	10,3
Brother	2,6	9,6

Discussion

There are a number of points worth discussing in this case of Fabry's disease, the first reported in southern Africa. The importance of establishing a diagnosis in a patient with nephrotic range proteinuria is emphasised. Nephrotic patients are common in our country.[9] One attitude is not to perform renal biopsy because treatment and follow-up can be impossible. Secondly, this nephropathy has been described very infrequently outside white populations — only a few cases have been recorded in black Americans, Latin Americans and orientals. Our patient, 1 of 118 black Zimbabwean nephrotics that we studied, is the only one with this abnormality. In a series of 98 renal biopsies on black Zimbabweans no comparable case was reported.[9] Likewise there have been no reports of this condition in a study of 140 South African black nephrotics,[10] a further study of 74 similar patients,[11] or in 34 black Malawian nephrotics.[12] Nevertheless, because electron microscopy was not used in either of the South African studies or the Malawian series the morphological diagnosis could have been missed.

The echocardiographic observations are entirely compatible with myocardial infiltration, a well-recognised feature of Fabry's disease.[13,14]

Dialysis and transplantation are available for this man, but some authorities consider grafting to carry an unacceptable risk of sepsis for patients with this enzyme deficiency.[15] The view has been challenged.[16,17] It has been demonstrated in some patients with Fabry's disease that the serum concentrations of total β-hexosaminodase and α-galactosidase rise after successful transplantation.[18] This is believed to be because of enzyme produced by the donor kidney. Not all studies have demonstrated this.[17] In our patient, the presumed myocardial infiltration by cerebrosides may seriously diminish the chance of long-term management.[19]

Fabry's disease is very rare in Europe and America. A retrospective study of 12 large renal centres over a 5-year period found only 12 proven patients with Fabry-related chronic renal failure.[17] The incidence of this condition in Zimbabwe and elsewhere is unknown and the prevalence conjectural. The clinical course of this man is entirely comparable with descriptions thereof in other studies. It is of note that α-galactosidase A deficiency does occur in the Shona population.

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Addendum

The patient was last seen in January 1993, when the serum creatinine value was 659 μmol/l and the clearance was 7 ml/min. He was still normotensive and had developed no further stigmata of the condition.

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