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Case Report

Should living related kidney transplantation be considered for patients with renal failure due to Fabry's disease?

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Introduction

Fabry's disease is an X-chromosomal hereditary storage disease characterized by the pathological accumulation of glycosphingolipids (GSL) [1]. A defect in the lysosomal enzyme α-D-galactosidase A blocks the catabolism of neutral GSL with terminal α-galactosyl residues and leads to the systemic accumulation of globotriosylceramide, galabiosylceramide, and some blood group B substances. A ected hemizygous males display massive deposition of these GSL in body fluids and various organs, including kidney, heart and brain. Patients develop characteristic angiokeratomas, hypohidrosis, corneal deposits and su er from painful acral crises and paraesthesiae. The kidney is invariably involved and patients generally develop end-stage renal disease within the fourth decade of life [2].

Heterozygous female carriers may show subtle renal abnormalities due to the accumulation of GSL. Severe renal impairment has been described, however, in a few patients [3]. Due to random X-inactivation of the α-galactosidase A gene in heterozygous females the level of enzymatic activity can vary significantly, making accurate carrier detection sometimes di cult.

Controversy exists as to whether living related kidney donation should be considered for patients with Fabry's disease [4]. Recently we were faced with such a situation where the mother of a male patient with chronic renal failure due to Fabry's disease wanted to be considered for living related kidney donation. Despite being asymptomatic clinically, she displayed marked GSL deposition in a kidney biopsy and was therefore excluded from being a donor.

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Case

A 27-year-old male patient diagnosed with Fabry's disease during his adolescence was referred to our centre for kidney transplantation. At age 14 he was noted to be unable to sweat and he therefore avoided all sports. When exposed to hot outside temperatures his body temperature rose to 41°C and he then developed seizures. He also had typical cutaneous lesions (angiokeratomas) on the scrotum, where a skin biopsy showed characteristic changes compatible with the diagnosis. A determination of the α-galactosidase activity in blood leukocytes was performed, showing a very low level of 0.024 mU/mg protein (normal range 0.41–0.76), confirming the enzymatic defect. One year before referral he had a serum creatinine of 312 μmol/l, but 1 month prior to admission this value had increased to 602 μmol/l with a calculated clearance of 12 ml/min. Proteinuria was 2 g/24 h and a renal ultrasound showed bilaterally small kidneys (9 cm length on the right side, 8.5 cm on the left) with increased echogenicity. Plans to initiate haemodialysis were made shortly before referral.

The patient has a 4-years-younger brother who has also been diagnosed with Fabry's disease and who has been successfully transplanted with a kidney from his healthy father at age 17 with an uneventful subsequent course. Because of the favourable outcome of the paternal living related kidney transplantation in the brother, the mother of the referred patient now wanted to be considered as a living donor for her 27-year-old son.

The mother of the patient is a 48-year-old healthy female carrier of Fabry's disease. Her α-galactosidase A activity in blood leukocytes was 0.38 mU/mg protein, which is below the normal range, consistent with a heterozygous state. She has been completely asymptomatic and therefore underwent preliminary screening for renal allograft donation, which was initially favourable, including matching blood groups. Careful ophthalmological evaluation (slit lamp), however, revealed slight deposition of whorl-like corneal opacities (suspi-

cion of cornea verticillata). Nephrological tests showed a normal urinary sediment without proteinuria, a normal serum creatinine, and a normal renal ultrasound. Inulin and PAH clearances were then performed, revealing a GFR of 120 ml/min/1.73 m^2 and a RPF of 563 ml/min/m^2 (both considered normal). The patient then underwent percutaneous renal biopsy to test for evidence of GSL accumulation in the kidney.

Figure 1 demonstrates that glomerular epithelial cells and some proximal tubular cells were filled with typical clear vacuoles in a mosaic pattern, representing the GSL deposits. The immunofluorescence staining showed no IgG, IgM, or C3 deposition (not shown). Electron microscopy examination of the biopsy also revealed typical vacuoles filled with lamellated electron-dense myelin figures in visceral and parietal glomerular epithelial cells. Inclusions were also found in endothelial cells. Overall the GSL deposition was extensive and contrasted with the unremarkable clinical presentation.

Because of the remarkable GSL deposition in the kidney of the heterozygous mother it was decided not to proceed with living related organ donation but to consider this 27-year-old patient for cadaveric allograft transplantation instead. Several months later he was successfully transplanted with a cadaveric kidney and so far has had an uneventful course.

Discussion

The situation of an a ected male hemizygous patient with Fabry's disease presenting with his asymptomatic mother for living related kidney donation illustrates the problems transplant physicians are faced with when examining clinically normal heterozygous donors of hereditary diseases for renal allograft transplantation. Although the mother did not show clinical or laboratory signs of kidney disease on routine examination she was found to have abundant osmiophilic electron-dense inclusions in glomerular epithelial and in some proximal tubular cells.

In the literature a few reports have shown that female heterozygous carriers of Fabry's disease can develop renal disease which is characterized by proteinuria and haematuria and later by the development of chronic, and very rarely of end-stage renal failure [3,5–9]. The majority of female carriers do not develop renal disease, however, and negative GSL deposition has been documented by Gubler *et al*. in a biopsy of a female carrier [5]. Since it is impossible to predict which carrier will develop renal involvement one needs to perform a renal biopsy to determine the extent of renal involvement.

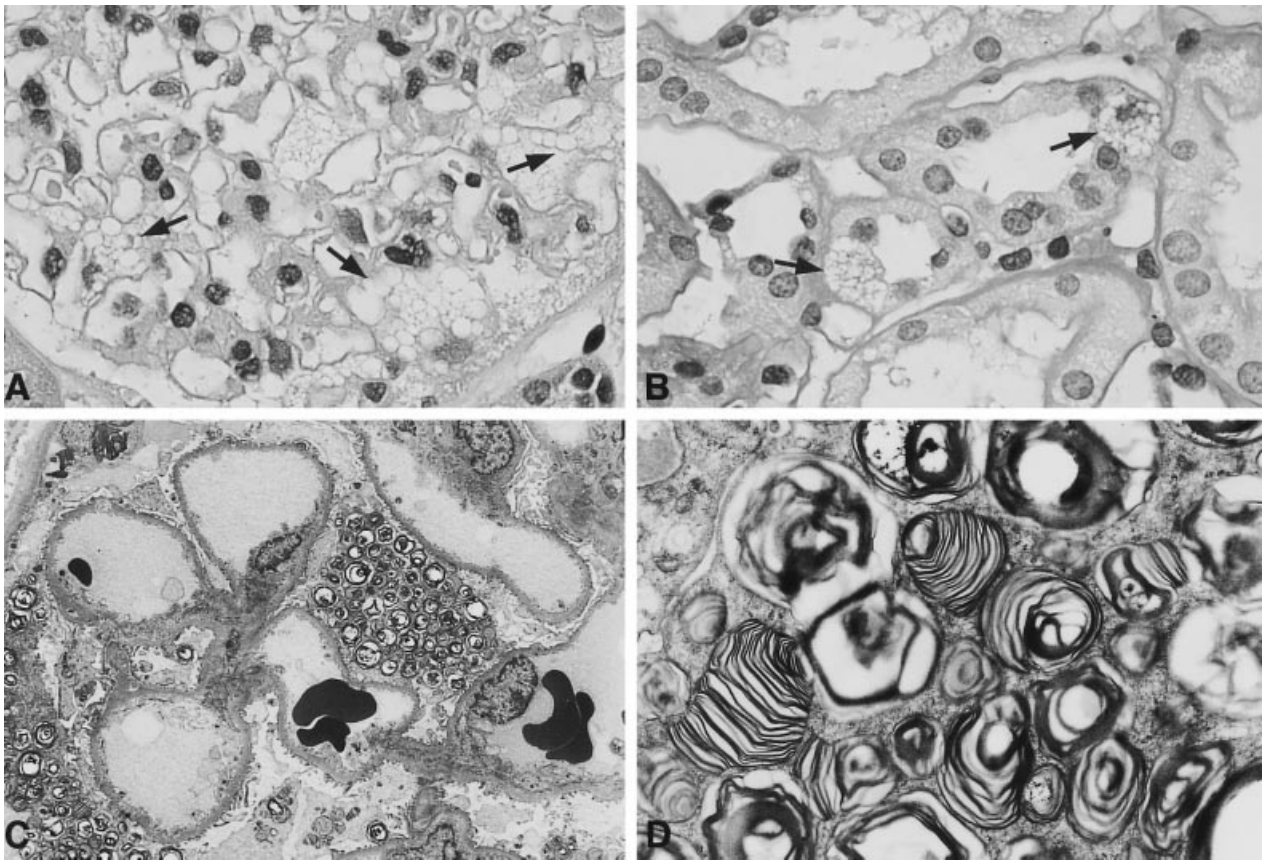

Fig. 1A-D. Renal biopsy of the 48-year-old potential heterozygous female donor. (**A**) Glomerulus with visceral epithelial cells which are filled with clear vacuoles (arrows) (H&E ×400). (**B**) Individual cells in proximal tubules are also filled with clear vacuoles (arrows) (PAS ×400). (**C**) Overview by electron microscopy, demonstrating 'myelin figures' in podocytes (×1850). (**D**) Electron micrograph demonstrating the lamellated structure of the 'myelin figures' (×8200).

A case has been reported where living related renal transplantation has been performed from an asymptomatic female heterozygotic carrier to her una ected daughter who developed renal failure due to chronic glomerulonephritis with nephrotic syndrome [10]. The typical lesions of Fabry's disease, which were seen in the graft at the time of transplantation, remained unchanged in successive biopsies, suggesting that hyperfiltration in a normal α-galactosidase environment did not a ect renal morphology adversely. The donor's subsequent course over 7 years was also favourable and the renal function stayed stable. Another case of living related donation has been reported where a normal una ected sister donated a kidney to her hemizygous a ected brother [4].

Most transplants reported for patients with Fabry's disease have been performed from cadaveric donors. The outcome for these patients has been satisfactory with 1-year graft and patient survival times of over 80% and 90% respectively [11]. What is clear from the literature is that a recurrence of GSL deposition is detectable when a normal cadaveric kidney is transplanted into a patient with Fabry's disease, suggesting that these storage products can accumulate in a transplanted organ despite possessing enzymatic activity for α-galactosidase A (reviewed in [12]). GSL accumulation is usually confined to the endothelium, although more widespread graft involvement can occur. It is therefore quite possible that a heterozygous kidney with signs of renal involvement could become severely a ected after a short time with danger of subsequent allograft loss when transplanted into an α-galactosidase-deficient environment.

Some authors have suggested that living related donation should always be avoided in patients with Fabry's disease [4]. Based on our experience with the reported case we would recommend the performance of a kidney biopsy to evaluate the extent of renal involvement in heterozygous females with absence of proteinuria, haematuria, or signs of renal failure. In case of a positive biopsy, living related kidney donation should not be performed because of the danger for allograft loss due to 'recurrent' disease and because of a possible risk of the donor's developing chronic renal failure.

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