Women with Alport syndrome: risks and rewards of kidney donation*

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Insights gained during the last 30 years of research in Alport syndrome have influenced the way potential related kidney donors for Alport patients with end-stage renal disease (ESRD) are assessed. Awareness of Alport syndrome among clinicians and families has increased greatly, so the disease is more likely to be suspected in patients with haematuria and in kindreds with renal disease. Widespread application of electron microscopy, immunohistochemistry and molecular genetics has enhanced diagnostic accuracy, with the result that we are more likely to know which patients and families truly have Alport syndrome. We have learned that Alport syndrome is primarily an X-linked disorder (∼80% of families) and that only ∼10% of affected males represent de novo mutations, meaning that the mother of a boy with Alport syndrome is most likely a heterozygous carrier. Over 95% of heterozygous women with X-linked Alport syndrome (XLAS) exhibit haematuria, so detection of affected women in XLAS kindreds is a straightforward process [1]. Finally, it has been demonstrated that, contrary to the conventional wisdom of the 1980s and 1990s, heterozygous females with XLAS carry a substantial risk of developing chronic renal failure and ESRD [1].

It has been the practice in our transplant centre to counsel carriers with XLAS against kidney donation, based in part on the paucity of long-term outcome data in carriers who have undergone nephrectomy [2]. In this issue of NDT, Gross and colleagues describe six mothers with Alport syndrome who donated kidneys to their children with the disease [3]. Five mothers with XLAS donated to their sons and one mother who was a carrier of autosomal recessive Alport syndrome (ARAS) donated to her daughter. Renal function declined 25–60% in four of the six donors over 2–14 years of observation following nephrectomy, although no donor’s creatinine clearance was <40 ml/min at the time of follow-up evaluation. Four of the six developed microalbuminuria or proteinuria, and hypertension was diagnosed in four of six donors. These cases were collected from several European centres, so they presumably do not reflect a single prevailing protocol for kidney donor evaluation and approval.

Yachnin and colleagues previously described a 44-year-old carrier of XLAS who donated a kidney to her son [4]. Fifty-four months after transplant, the donor had no signs of renal disease other than microscopic haematuria. It is legitimately possible to draw divergent conclusions from these observations. Clearly, the rates of hypertension, proteinuria and reduced renal function in this small group of donors are much higher than in the general donor population [5–7]. Since proteinuria is an important risk factor for progression to ESRD in Alport heterozygotes [1,8], it is very possible that one or more of the women who developed proteinuria after nephrectomy will ultimately progress to terminal renal failure. From this perspective, the risk associated with nephrectomy in an Alport heterozygote may be prohibitive for many clinicians.

On the other hand, it is likely that none of these mothers will ever regret her decision to donate. Whether due to inherent inclination or societal expectation or both, women are more likely to be living kidney donors than men, and mothers are more likely to donate kidneys to their children than fathers [9–13]. Add to this the possibility that a mother with XLAS may feel that she has somehow caused her child’s renal disease, it is not difficult to appreciate the powerful forces motivating women with XLAS to minimize the risks of kidney donation to their physical well-being. A clinician who stands in the way of a mother’s determination to help her child must recognize that ‘protecting’ the mother may have painful emotional and psychological consequences.

When it is impossible to ‘do no harm’, clinicians must endeavour to do as little harm as possible. A blanket policy of rejecting women with XLAS as kidney donors may be excessively rigid. On the other hand, criteria for accepting these women as donors should be stringent so as to minimize the risk of progression to ESRD after nephrectomy. First, women with XLAS should be donors of last resort, mothers are more likely to donate kidneys to their children than fathers [9–13]. Add to this the possibility that a mother with XLAS may feel that she has somehow caused her child’s renal disease, it is not difficult to appreciate the powerful forces motivating women with XLAS to minimize the risks of kidney donation to their physical well-being. A clinician who stands in the way of a mother’s determination to help her child must recognize that ‘protecting’ the mother may have painful emotional and psychological consequences.

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are risk factors for progression to ESRD [1,14,15]. This author has further recommended that only women over 45 years of age should be considered as potential donors, since the prevalence of proteinuria in XLAS heterozygotes increases with age, eventually developing in 75% of one large cohort of women with XLAS [14,15]. A history of gross haematuria in childhood may be an additional risk factor for progression in heterozygous women with XLAS [8].

With an approach such as this, the number of heterozygous females with XLAS who undergo nephrectomy should be small. Gross and colleagues suggest initiation of treatment with angiotensin-converting enzyme inhibitors immediately after nephrectomy, in the hopes that this will prevent or delay the development of proteinuria and hypertension [3]. This recommendation is reasonable, but it highlights the ethical issue: if a potential donor will predictably require medical therapy as a result of donation, should that person be allowed to be a donor? The answer to this question may be very much influenced by the particular moral and ethical beliefs held by the reader. In this writer’s opinion, kidney donation by women who are heterozygous for XLAS should be a rare event. Alport syndrome registries in Europe, North America and elsewhere should try to track these donors to determine their long-term outcomes.

Carriers of ARAS, who are heterozygous for mutations in COL4A3 or COL4A4, frequently have haematuria and thin glomerular basement membranes on renal biopsy. These heterozygotes have a much lower risk of progression to ESRD than women with XLAS. However, proteinuria and renal insufficiency can develop in people with thin glomerular basement membranes who are heterozygous for COL4A3/COL4A4 mutations [16], so urine protein excretion and family history should be taken into account in evaluating these individuals as potential kidney donors.

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