Autosomal dominant polycystic kidney disease in a kidney transplant population

H. Hadimeri, G. Nordén, S. Friman and G. Nyberg

Transplant Unit, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden

Abstract

Aim. To define specific manifestations of autosomal dominant polycystic kidney disease in kidney transplant patients.

Methods. Of 874 consecutive first renal transplant patients 1985–1993, 114 (13%) had autosomal dominant polycystic kidney disease (ADPKD). Mean age was 53±8 years, 62% were men, and 83% received cadaveric kidneys. Control patients were matched for sex, age and donor type. Median follow-up time was 63 months. One patient was lost to follow-up. Medical records before and after transplantation were reviewed.

Results. Survival of patients and grafts was similar in ADPKD patients and controls. Twenty-five ADPKD patients died, four of causes not seen in the controls; two aortic aneurysms, one urothelial cancer, one colon perforation. Four more ADPKD patients but no control had diverticulitis (P = 0.03), two with perforation. Cardiovascular morbidity was not increased. Eight patients had subarachnoidal haemorrhage before transplantation and two during follow-up. Nineteen patients had undergone nephrectomy before transplantation, 11 because of voluminous kidneys, five for infection, pain or bleeding, two for suspected malignancy, one for hypertension. After transplantation, seven patients underwent nephrectomy, only one related to kidney size. During the first year, need of phlebotomy occurred in 14% of patients versus 4% of controls, P = 0.02. Urinary tract infection rates were not increased. No morbidity was related to liver cysts.

Conclusion. The specific features of kidney transplantation to patients with ADPKD were few: enlarged kidneys, relevant only before transplantation, erythrocytosis, and as rare but serious events, diverticulitis with perforation.

Key words: Autosomal dominant polycystic kidney disease; ADPKD; diverticulitis; kidney transplantation; phlebotomy

Introduction

The main feature of the kidney involvement in autosomal dominant polycystic kidney disease (ADPKD) is tubular dysmorphogenesis with formation of cysts secreting liquid [1–3]. Subarachnoidal arterial aneurysms are well-known extrarenal manifestations of the disease [4,5] but a series of other abnormalities have also been reported. These involve cardiovascular, gastrointestinal and other organ systems with manifestations such as arterial aneurysms, hernias and diverticula [1,4,6–12]. The systemic defects may be caused by changes in the extracellular matrix [3].

With some control of hypertension, progression of renal insufficiency occurs with loss of 1–5 ml/min GFR per year [10,13]. The disease accounts for approximately 7–10% of the total morbidity in end stage renal disease (ESRD) [10,14]. In our population of 874 first renal transplant patients 13% had ADPKD [15].

The aim of the present retrospective case-control study was to describe renal as well as extra-renal manifestations of the disease before and after transplantation.

Patients and methods

Patients

The cohort studied received kidney transplants in Sahlgrenska University Hospital, Göteborg, Sweden between January 1985 and January 1993. A total of 1095 kidneys were transplanted to 1000 patients. A detailed analysis and re-evaluation of the patients’ underlying renal diagnosis was performed, based on medical records from the transplant unit and from nephrology departments where patients had been seen initially. Details on this work has been published previously [15]. Of the total, 136 transplantations were performed to patients diagnosed with ADPKD. The diagnosis was based on the demonstration, by various radiographic methods, before transplantation, of enlarged polycystic kidneys, in individual patients further supported by the demonstration of liver cysts, and/or a family history of the disease. The mode of inheritance was established to be autosomal dominant in 67%, siblings or aunts were affected in another 4%, one of the patient’s parents had died.
young in 4%, a close questioning revealed no carrier or offspring with the disease in 10%, while the family history had not been properly elucidated in 15%. Of the patients received a combined heart and kidney transplant. This presentation is limited to the other 114 who received first kidney transplants alone.

**Control patients**

For each patient with ADPKD a matched control was picked from the consecutive file of transplant patients, all non-diabetic first transplant recipients. Matching was made for sex, age (+5 years) and kidney donor, cadaveric (CD) or living (LD). Table 1 shows demographic data for ADPKD patients and controls. As an effect of the matching, all variables are similar, except the proportion of pre-emptive transplantations that tended to be more frequent in the ADPKD patients (P=0.05). ADPKD patients had spent median 9 months in dialysis before transplantation.

**Transplantation data**

Maintenance immunosuppression was based on cyclosporin A and prednisolone. For the first 2 years, all our patients took part in a randomized study evaluating the effect of adding azathioprine. Since 1987, triple drug therapy has been the standard. Induction therapy with ATG for 7–10 days was given to patients with lymphocytotoxic antibodies to human lymphocyte antigens (HLA) or delayed onset of graft function. Anti-rejection therapy consisted of methylprednisolone in bolus doses on 4 consecutive days, followed by a second course of ATG or OKT 3 in resistant cases. The same principles were applied for ADPKD patients and their contemporary controls.

**Records**

Detailed clinical information was given by the nephrologists when patients were referred for transplantation. Most often, copies of local records were provided. After transplantation, patients with functioning grafts were seen in the transplant unit at regular follow-up visits 6 months and 1, 3, 5 and 10 years after transplantation. Patients living in the Göteborg area were more closely followed at the out-patient clinic. For other patients, reports were sent at least annually from the local nephrology departments. One patient living abroad ceased to send reports after 3 years. No other patient or control was lost to follow-up except by death. Median follow-up time for ADPKD patients alive was 64 months, (range 23–135) and for controls 63 (21–118) months.

The available records were reviewed and data on the course of the disease before and after transplantation were analysed. Transplant data analysed were: age at the time of diagnosis; ESRD and transplantation; time in dialysis before transplantation; age of donor; and time and cause of graft loss and of death. Before and after transplantation data were collected on: ischaemic heart disease expressed as myocardial infarctions or clinical angina; cerebrovascular events causing hospital care; herniations in the abdominal; diaphragmatic and inguinal regions mentioned in the records; gastrointestinal morbidity with diagnosed diverticulitis of the colon or intestine; and nephrectomies performed and the indications. During the first year after transplantation the following were noted: number of days when any anti-rejection treatment was given; incidence of urinary tract infections as judged from laboratory tests and/or treatment; and phlebotomies performed. At the 1-year follow-up the following were measured: blood pressure; number of antihypertensive drugs; haemoglobin level; and glomerular filtration rate (GFR) as analysed by plasma clearance of 51chrome EDTA.

Control patients’ records were reviewed by the same investigator (HH) with respect to the majority of these variables and using the same criteria. The following variables were, however, not recorded: time in dialysis; nephrectomies; and other events before transplantation; and haemoglobin level and GFR 1 year after transplantation.

**Statistics**

Unless otherwise stated, values are mean ±SD. Statview 4.5 for Macintosh was used for calculations. Comparisons between groups for categorical values were made using Fisher’s exact test and for nominal values the Mann–Whitney test. Cumulative survival was calculated according to Kaplan–Meier and the significance of differences between groups tested by the log rank test (Mantel Cox). P-values >0.05 were considered not significant (NS).

**Results**

**Population characteristics**

Sixty-two percent of the ADPKD patients were men. Patients with established autosomal dominant inheritance had the same characteristics as those with a negative family history, e.g. 64% versus 55% were men and age at ESRD was 51±8 years versus 53±10. Age at ESRD was higher in women than in men, 54±8 years versus 50±8, P=0.039, but age at the time of diagnosis was not significantly different.

Seven percent of the ADPKD patients were reported to have suffered subarachnoidal haemorrhage before transplantation. Three percent had diverticulosis of the ileum or colon diagnosed due to diarrhoea and/or abdominal pain. There was no difference between ADPKD patients and controls in the incidence of ischaemic heart disease before transplantation, 8% versus 5%. Inguinal, abdominal and other herniations were reported in 13% of ADPKD patients versus 4% of controls, P=0.03.

<table>
<thead>
<tr>
<th>Table 1. Demographic data on ADPKD patients and the matched control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Men (%)</td>
</tr>
<tr>
<td>Scandinavian origin (%)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
</tr>
<tr>
<td>Age at ESRD (years)</td>
</tr>
<tr>
<td>Age at transplantation (years)</td>
</tr>
<tr>
<td>Pre-emptive transplantation (%)</td>
</tr>
<tr>
<td>Cadaveric donor (%)</td>
</tr>
<tr>
<td>Age of donor (years)</td>
</tr>
</tbody>
</table>
Survival

Survival of patients and grafts shown in Figs 1 and 2 did not differ between ADPKD patients and controls. Actual patient 5-year survival was 81% versus 83% and graft survival 62% versus 61% (n = 60 and 54). Survival rates for ADPKD patients with known dominant heredity were 82% and 62%, i.e., there was no difference from the total group. Causes of death and graft loss in ADPKD patients and controls are listed in Table 2. Two of 25 ADPKD patients died of aortic aneurysms, one of urothelial cancer and one after colon perforation. The other causes of death were as in a general transplantation population including the matched controls. Most graft losses in both groups were caused by patients’ death or rejection. No loss in the ADPKD group seemed to be related to the disease.

Table 2. Causes of death and of graft loss in APKD patients and the matched controls

<table>
<thead>
<tr>
<th>Cause</th>
<th>ADPKD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial, cardiac failure</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Sudden death/finded dead</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Circulatory, other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Intoxication/suicide</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Perforation of colon</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cachexia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total number of deaths</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

Graft losses

<table>
<thead>
<tr>
<th>Cause</th>
<th>ADPKD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's death</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Never functioning</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Renal artery thrombosis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total number of grafts lost</td>
<td>42</td>
<td>38</td>
</tr>
</tbody>
</table>

Post-transplant morbidity

Levels of arterial pressure did not differ between patients and controls at the 1-year follow-up, $147 \pm 18/88 \pm 10$ versus $151 \pm 20/88 \pm 10$ mmHg. The number of antihypertensive drugs was also similar, $1.7 \pm 1.0$ versus $1.9 \pm 1.0$. When ADPKD patients were arbitrarily separated into two groups according to mean arterial pressure (MAP) $\geq 105$ mmHg or below, there was no significant difference in survival of patients or grafts.

Morbidity following transplantation for ADPKD patients and controls is presented in Table 3. Coronary heart disease occurred at similar rates. Cerebrovascular events appeared to be more frequent in ADPKD patients, but the difference was not significant. Only two ADPKD patients had subarachnoidal haemorrhages diagnosed, and in one this was a recurrence. One thrombotic stroke was elicited by erythrocytosis. Need of phlebotomy occurred in more ADPKD patients than controls. Calculated only on patients with grafts functioning after 1 year ($n = 91$) the rate

Table 3. Post-transplant course for 114 APKD patients and 114 matched controls

<table>
<thead>
<tr>
<th></th>
<th>ADPKD</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection rate (%)</td>
<td>51</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Number of days treated</td>
<td>3.6±5</td>
<td>4.0±6</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection (%)</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Phlebotomy (%)</td>
<td>14</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Total follow-up Cerebrovascular events (%)</td>
<td>12</td>
<td>9</td>
<td>(0.52)</td>
</tr>
<tr>
<td>Diverticulitis (%)</td>
<td>4</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>14</td>
<td>20</td>
<td>(0.22)</td>
</tr>
</tbody>
</table>
was 21% versus 5% of controls, \( P = 0.01 \). At the 1-year follow-up visit haemoglobin values were 143 ± 19 g/l. This figure includes values in patients with poor renal function and those treated with phlebotomy. In addition to the patient who died following colon perforation, three ADPKD patients had new onset diverticulitis, complicated by perforation in two. Furthermore, one of the patients with pre-transplant symptoms had continued problems. No diverticulitis morbidity occurred in the controls. Hernias were noted in 10% versus 6% of controls (NS). Similar proportions of ADPKD and control patients had urinary tract infections during the first year. No morbidity was related to liver cysts.

Twenty-four ADPKD patients underwent nephrectomy, 11 bilateral and 13 unilateral. Nineteen had been operated on before and seven after transplantation, i.e. two of them had one kidney removed before and the other after transplantation. The reasons for nephrectomy are presented in Table 4. Four patients had several indications, all combinations with infection. Before transplantation, most nephrectomies were made because the kidneys were greatly enlarged, either to create space for a transplant or to relieve pressure. After transplantation, one nephrectomy was performed to facilitate retransplantation, but otherwise no kidney was removed because of enlargement. Infection and erythrocytosis were the most frequent causes in this phase.

None of the patients with both polycystic kidneys removed had any urinary tract infection during the first year. Haemoglobin values after 1 year did not differ between patients with bilateral nephrectomy and those without.

**Discussion**

Our study is the largest single-centre experience published and the only one restricted to the cyclosporine era, a period in which antihypertensive therapy also has been more efficient. The mean age of our patients at ESRD was comparatively high, 51 ± 8 years. Whether better control of blood pressure during the last decades plays a role for this remains uncertain [13,16–18]. Alternatively, it might be an effect of selection, because more elderly patients have been accepted for transplantation in the cyclosporine era.

Although ADPKD is inherited as an autosomal dominant, women were in the minority in our population. This may be explained by a more benign course of the disease in women [6,16–17,19], also illustrated by the fact that the women were older than the men at the time of ESRD.

We found no differences in patient or graft survival between ADPKD patients and controls. The same result was reported from a case-control study in 54 ADPKD patients from the Mayo Clinic [14] and 101 ADPKD patients in Leiden who were compared with a larger, younger control group [8]. In the latter study, a multivariate analysis showed the relative risk of cerebrovascular events and of myocardial infarction after transplantation to be increased in ADPKD patients, however, this was only clearly so in the subgroup treated with azathioprine. We could not confirm this result with respect to ischaemic heart disease. Rather, the morbidity tended to be reduced in ADPKD transplant patients. Reduced mortality in cardiac disease has also been reported in the dialysis ADPKD population [20]. Thus, cardiac manifestations directly connected to ADPKD do not constitute a severe clinical problem, at least not in comparison with the high cardiovascular morbidity in patients with renal failure in general.

More in accordance with the Leiden study, the total incidence of cerebrovascular events in ADPKD patients after transplantation tended to be increased in our series. We were not able to establish to which extent this morbidity was related to the formation of aneurysms or other abnormalities related to ADPKD, such as arterio-venous malformations or carotid artery aneurysms [4,5]. Subarachnoid haemorrhage was diagnosed in only two cases, caused by rupture of an intracranial aneurysm in one, but may have occurred in a few other patients as this possibility was not always ruled out in case of stroke. An even greater uncertainty pertains to the pre-transplant data because in most instances the actual records were not available. An adequate blood pressure control, which was maintained in the majority of our patients, is important and has probably helped to reduce morbidity [21].

**Table 4. Nephrectomies performed in 24 of 114 ADPKD patients**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Before transplantation</th>
<th>After transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Kidneys</td>
</tr>
<tr>
<td>Numbers</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Volume</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pain, bleeding</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Suspicion of malignancy</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Erythrocytosis is an important characteristic for transplant patients with ADPKD. This is due to an inappropriately high production of erythropoietin in the remnant kidneys and can be cured by nephrectomy of the native kidneys [4,20,22]. Several drugs, among them ACE-inhibitors, may be used to control the disorder but with variable efficacy and side effects. Repeated phlebotomy is effective but requires monitoring of haemoglobin levels. Such surveillance may fail when a patient is dehydrated as in our case complicated by stroke.

Although survival rates were not reduced, individual patients died of diseases for which the risk is, or may be, increased in ADPKD, such as aortic aneurysms and perforation of the colon. Colonic screening of renal transplant candidates over the age of 50 showed an increased prevalence of colonic diverticula in ADPKD patients [12]. In another series the prevalence of diverticula and also the incidence of diverticulitis with perforation of the colon was reported to be increased in a dialysis population with ADPKD [11]. Perforation of the colon is a most serious complication and could be even more dangerous with immunosuppressive therapy. Corticosteroid treatment might render the diverticulum wall more vulnerable and perhaps less resistant to the bacterial flora. So far there has been no consensus on the clinical relevance of ADPKD diverticula after transplantation. One study reports diverticulitis as a post-transplant complication in only one of 1019 transplant patients [12]. However, patients with a history of diverticulitis had been refused transplantation in that centre unless they underwent colectomy. Furthermore, the only case occurred in a patient with ADPKD and was complicated by perforation. A large patient series and detailed follow-up, as in our study, was required to demonstrate the fact that there is an increased risk.

In ADPKD, arterial aneurysms occur in increased frequency in the subarachnoid space [4,5] and maybe in other regions. The two lethal ruptures of aortic aneurysms in our series suggest but do not prove an over-representation. There are other suggestive reports based on sporadic cases in ADPKD patients [7,9,23] but screening for abdominal aortic aneurysms revealed no increase in ADPKD patients compared with healthy controls [24].

Herniations were reported more frequently in the records before transplantation in ADPKD patients than in controls. This observation reinforces the notion of ADPKD as a systemic disease, possibly with different properties of the peritoneal and other membranes. After transplantation hernias were not reported to be significantly increased in frequency, but this may be due to the comparatively short follow-up.

Enlarged kidneys did not create significant technical problems pre-operatively. Thus, palpation was sufficient to evaluate the need of nephrectomy. Following transplantation, remnant kidneys have been reported to undergo volumic regression [25]. In line with this concept, only one patient required nephrectomy on space-creating indication after transplantation, in order to enable retransplantation. One may speculate that the immunosuppressive therapy may interfere with the pathogenetic mechanisms involved in the altered cell growth [26].

Urinary tract infections were not more frequent in ADPKD patients than in controls, which may seem surprising. However, some patients with increased risks had undergone nephrectomy on this indication before transplantation.

The liver is also often involved in the disease. Although the majority of our patients had liver cysts, none had any morbidity related to liver cysts in the post-transplant period. Women, especially, may develop hepatomegaly due to cyst formation, but the condition rarely leads to liver insufficiency [27,28]. None of the ADPKD patients in this series required special evaluation with respect to hepatomegaly before or after transplantation. Recently, however, two ADPKD patients with this problem, both women, have undergone successful combined liver and kidney transplantation in our department.

An unclear point is whether the two different genotypes causing ADPKD differ in the expression of extrarenal manifestations. If, for instance, some rare but severe manifestation occurs only in the rarer form of the disease, the risk may be very relevant for that subgroup. Further DNA linkage analyses may therefore prove to be of value to identify risk patients [4,6,29].

In conclusion, this large case-control single-centre study of transplantation to patients with ADPKD, all treated with cyclosporine, shows good results with respect to survival of patients and grafts. The specific features were enlarged kidneys (a problem only relevant before transplantation), post-transplant erythrocytosis, and diverticulitis with perforation of the colon, as rare, but serious events.

References

Received for publication: 12.8.96
Accepted in revised form: 17.3.97