RENAL TRANSPLANTATION IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 1 in 1,000 people in the general population. The natural history of ADPKD includes the progression of chronic kidney disease to end-stage renal disease (ESRD) in a large proportion of patients. Renal transplantation is the treatment modality of choice in these patients. However, there are some specific issues that should be addressed in ADPKD, and the aim of the current review is to describe the issues that need to be considered in the pre and post-transplant management of ADPKD patients, excluding routine procedures.

Keywords: Autosomal dominant polycystic kidney disease, intracranial aneurysms, native nephrectomy, renal transplantation.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is considered one of the most common genetic disorders. It affects approximately 1 in 1,000 people in the general population and, therefore, the number of patients is substantial, with more than 500,000 cases estimated for the whole of the European Union. The disease is due to a mutation in one of two genes: *PKD1* in Type 1 ADPKD and *PKD2* in Type 2 ADPKD. Mutation of *PKD1* is more prevalent and causes 85% of cases of the disease. The natural history of ADPKD includes the progression of chronic kidney disease to end-stage renal disease (ESRD) in a large proportion of patients.[1] Effectively, ADPKD is the fourth most common renal disease requiring renal replacement therapy (RRT), with a prevalence of 91.1 cases per 1 million individuals.[2] The average age of patients with ESRD depends on the type of the disease and amounts to 58.1 years in Type 1 ADPKD, and 79.7 years in Type 2 ADPKD.[3] Due to the extrarenal distribution of polycystins, encoded by *PKD1* and *PKD2* genes, ADPKD is a systemic disease with multiple extrarenal manifestations, including arterial hypertension, aneurysms, and cysts in solid organs such as the liver, pancreas, and spleen.[1]

Similar to other causes of ESRD, renal transplantation (RTx) is the treatment modality of choice in ADPKD patients who require RRT. However, there are some specific issues that should be addressed in these patients. The aim of the current review is to describe the issues that should be considered in the pre and post-transplant management of ADPKD patients, excluding routine procedures.

PRE-TRANSPLANT PROCEDURES

Native Nephrectomy

The first issue that should be addressed is whether the patient requires a native nephrectomy (NN); ADPKD is not an indication for this procedure per se. The indications for NN are: renal cyst infection, pain, suspicion of tumour, recurrent haematuria, and a lack of space for the

implantation of the transplant. In effect, only 20% of ADPKD patients require NN.[4] The volume of a native kidney decreases after transplantation.[5] Therefore, if the space for the renal graft is available at the moment of transplantation there is no need for NN due to the aforementioned indication. Maximal kidney length >21.5 cm was proposed as an optimal criterion in making decisions concerning NN in ADPKD patients.[6] The timing and the method of NN remain controversial. In general, nephrectomy may be performed before or at the moment of transplantation. Simultaneous nephrectomy and transplantation is considered a safe approach in experienced centres. It is associated with acceptable morbidity and does not affect patient and graft survival.[7-11] Additionally, some clinicians prefer post-transplant nephrectomy as the safest option.[12] The next question that should be raised is whether the patient requires unilateral or bilateral nephrectomy. Some clinicians report bilateral nephrectomy as a safe method,[9-11] but others prefer a unilateral procedure due to the perioperative complication rate.[7] Finally, a choice between conventional and laparoscopic nephrectomy is to be made; the latter is considered a safe option.[7,9] To reduce postoperative pain and the risk of incisional hernias, as well as to improve the cosmetic result of laparoscopy, laparoscopic nephrectomy with morcellation of the specimen was proposed.[13] Alternatively, embolisation of enlarged polycystic kidneys may be considered.[14]

Cardiovascular System

The involvement of the cardiovascular system is common in ADPKD. Vascular manifestations of the disease are due to the fact that both polycystins are expressed within arterial smooth muscle cells,[15-17] and a systemic vascular defect has been observed in the oligosymptomatic stage of the disease.[18,19] Arterial hypertension (AH) in ADPKD is common and has complex pathogenesis, with three main pathological mechanisms: i) activation of the renin-angiotensin-aldosterone system secondary to intrarenal ischaemia caused by growing cysts; ii) activation of the sympathetic nervous system; and iii) ciliopathy-related endothelial dysfunction.[20] Therefore, careful cardiovascular assessment, including AH and its complications, is of special value in ADPKD.

Additionally, intracranial aneurysms (ICANs) are attributable to complications specifically associated with ADPKD. Aneurysm formation is due to primary cilia dysfunction in a mechanism dependent on downregulation of survivin expression.[21] In effect, the frequency of ICANs is increased in ADPKD compared with the general population[22] and is estimated at 4-22.5%.[23,24] Additionally, ADPKD has been proven to be associated with increased risk of intracranial haemorrhage among ESRD patients.[25] To avoid complications associated with ICAN rupture, screening for ICANs is recommended: i) in those with family or past personal history of ICAN or its rupture; ii) in case of symptoms suggesting ICAN; iii) in patients with a job or hobby in which loss of consciousness may be lethal; iv) before major elective surgery; and v) when a patient is extremely afraid of possible ICAN.[26] Additionally, the risk of ICAN increases with the patient's age[27] and in Caucasians the prevalence is substantially increased after 45 years of age.[28] Irrespective of the type of ADPKD, the average age of ESRD patients is greater than 45 years. Therefore, most ADPKD patients should be considered as candidates for screening for ICANs during their preparation for RTx. Indeed, screening for vasculocerebral malformations in ADPKD patients is performed in numerous centres.[29] In some centres up to 91% of patients undergo such screening.[30]

The optimal method of screening for ICANs is magnetic resonance angiography (MRA) of the brain, due to the lack of X-ray exposure and no need for contrast media administration.[28] In patients with contraindications for MRA, the most important being implanted electronic devices or ferromagnetic foreign bodies, computed tomography angiography should be implemented as an alternative method. However, in such cases the risk of contrast-induced acute kidney injury, especially in patients with impaired renal function, must always be kept in mind and preventive measures must be implemented.

A patient with an ICAN detected on imaging should be referred to a specialist in neurosurgery in order to decide whether treatment is required, and when and how (endovascularly or surgically) it should be done. Due to the relatively low rate of progression and rupture of ICANs in ADPKD, only those at high risk of rupture require treatment. The decision is made on the basis of ICAN size and location, its morphology, the patient's age, and comorbidities. If the treatment is not conducted, the method and timing of follow-up must be determined.[31]

Liver

Polycystic liver disease (PLD) is observed in 75-90% of ADPKD patients.[32] ADPKD does not impact liver function and in most cases PLD is benign and asymptomatic.[33] However, in rare cases the condition may be complicated with massive hepatomegaly leading to mass effect with compression of the surrounding organs, or acute complications including torsion of the cyst, intraluminal haemorrhage, or infection.[32] Management of acute complications has been discussed previously.[34] In mass effect, when there is a lack of space for a renal graft, NN should be considered as a first-line treatment. When a reduction in liver volume is required, the treatment options include: i) interventional radiology with arterial embolisation or percutaneous sclerotherapy, and ii) surgical intervention with fenestration or hepatic resection. Liver transplantation (LTx), including combined LTx and RTx, should be reserved for the most severe cases, especially those with liver failure.[26,32]

In ADPKD patients with PLD, serum carbohydrate antigen 19-9 (CA19-9) may be increased due to its secretion by the biliary epithelium lining the liver cysts.[35] As exclusion of neoplastic disease is a part of pre-transplant assessment, levels of tumour markers are often examined in potential transplant recipients. Thus, in ADPKD patients a modest increase in serum CA19-9 need not be connected to cancer or inflammation.

Diverticular Disease

Due to the fact that RTx recipients with ADPKD are at risk of colonic diverticulosis and its complications, elective colonic resection should be considered before transplantation in patients with medical therapy for acute diverticulitis in their medical history.[36]

Living Related Kidney Donor

Living kidney donation should always be considered in candidates for RTx. However, exclusion of ADPKD is required in the potential living related kidney donor. Imaging studies may be insufficient for certain exclusion of ADPKD in a potential donor, especially if he or she is below 40 years of age. In such cases genetic testing is useful.[37]

POST-TRANSPLANT MANAGEMENT

Results

Graft and patient survival rates are at least not inferior in patients with ADPKD compared with those who underwent RTx for other reasons. One-year graft survival reaches 100%,[30] and 5-year graft survival exceeds 80%, which according to some is better when compared with other causes of ESRD.[29] Long-term graft survival is similar to other nephropathies.[38] Additionally, improved patient survival has been noted in recent years, which is connected with a decrease in cardiovascular mortality.[2] In effect, 1 and 5-year patient survival may exceed 90% and is not inferior compared with other causes of ESRD.[8,29,38] Similarly, no difference exists between ADPKD and non-ADPKD groups in patient survival at 10 and 15-year follow-up. Jacquet et al.[39] suggest that graft survival is even better in the ADPKD group, despite a higher risk of graft failure due to usually older donors and longer cold ischaemia times. According to most clinicians, ADPKD RTx recipients are older and their body mass index (BMI) is usually higher compared with non-ADPKD patients,[39,40] which may impact upon the long-term complications rate. In a study conducted by Jacquet et al.[39] ADPKD and non-ADPKD RTx recipient groups did not differ in terms of the incidence of biopsy-proven acute rejection, although the occurrence of metabolic disorders such as post-transplant diabetes, hyperlipidaemia, hypertension, and stroke was higher in ADPKD patients. Infections, cardiovascular disorders, and neoplasia are the main causes of mortality in patients with ADPKD after RTx.[40,41] There are no known examples of disease recurrence in the transplanted kidney.

Native Kidneys

The volume of the native kidneys after transplantation tends to decrease;[5] however, vigilance is required due to cases of recurrent cyst infections and mechanical compression of the transplanted kidney and ureter by an enlarged native kidney,[42] recurrent lumbar pain,[43] and possibility of carcinogenesis.[44] Native kidneys produce erythropoietin that induces higher haemoglobin levels at Month 3 post-transplant in ADPKD compared with other nephropathies.[45,46] On the other hand, excessive secretion of erythropoietin may lead to erythrocytosis, which is defined as an increase in haematocrit above 51%.[40]

Cardiovascular System

Research results contradict the idea that hypertension is more frequent in transplant recipients with ADPKD compared with patients with other nephropathies,[40] and some studies indicate improved arterial pressure control after transplantation in ADPKD.[41] Although cardiovascular events are the second biggest cause of death in patients with ADPKD after transplantation,[40] they do not occur more frequently in this group compared with the control,[29] and according to some researchers myocardial infarction and heart failure are even less frequent in patients with ADPKD who reached ESRD compared with non-diabetic controls with ESRD.[46] Valvular abnormalities (mitral valve [MV] prolapse and MV regurgitation), however, are characteristic in ADPKD transplant recipients.[47] Also, pericardial effusion incidents occur more frequently in these patients.[48]

ICANs are more common in patients with ADPKD than in the general population[23] and ADPKD is a well-documented risk factor for intracranial haemorrhage among patients undergoing dialysis and after transplantation.[25,49] The potential for aneurysm formation in other arteries should not be forgotten, including aortic aneurysms. Thus, ADPKD RTx recipients should undergo periodic screening for abdominal aortic aneurysms. In the case of rupture, emergency endovascular repair is suggested to be superior compared with open surgery.[50,51] Among the vascular complications present in ADPKD patients after transplantation, thromboembolic disease (venous thrombosis and pulmonary embolism) should not be neglected due to its more frequent occurrence compared with other RTx recipients, which applies to patients with increased BMI in particular.[39]

Liver

Hepatic cysts are frequent but rarely symptomatic in ADPKD transplant recipients.[39] In contrast to native kidneys, the volume of a polycystic liver increases after RTx.[5] In the case of massive liver enlargement, therapeutic options include somatostatin analogues or surgical treatment, such as aspiration combined with sclerotherapy, laparoscopic or laparotomic fenestration, liver resection, or even LTx.[52] Additionally, hepatic cyst infection, enlargement, or rupture should be considered in the differential diagnosis of abdominal or chest pain in this group of patients.[53]

Diverticular Disease

The incidence of diverticulitis and colon diverticulum perforation is increased in RTx recipients with ADPKD when compared with patients after RTx for other reasons.[54,55] In RTx recipients these complications of diverticular disease are associated with higher mortality rates than in the general population, reaching up to 100% of patients hospitalised for this reason.[56] Early symptoms of inflammation and perforation of the diverticulum may be less tangible due to the patient receiving immunosuppressive therapy.[57] Therefore, we must remain vigilant in cases of abdominal pain in this group of patients, especially in the lower abdomen quadrants, and appropriate imaging must be carried out, with abdominal computed tomography as the method of choice. In the case of a positive diagnosis, some researchers recommend early surgical treatment.[36]

New Onset Diabetes after Transplantation

New onset diabetes after transplantation (NODAT), previously referred to as 'post-transplantation diabetes mellitus', is a frequent post-transplant complication that diminishes recipients' quality of life and has an adverse impact on graft and patient survival. In a large prospective study, 12-year graft survival was 48% in patients that developed NODAT compared with 70% in patients who were not affected by diabetes after RTx.[58] A case-control study from the Cleveland Clinic showed an increased rate of graft rejection in patients with NODAT (47%) compared with control patients (23%).[59]

According to some researchers ADPKD may be a predictor of NODAT, yet available data are controversial. A study conducted by de Mattos et al.[60] demonstrates a significant association between ADPKD and development of NODAT within the first year following RTx (17% versus 7.4%). Similar conclusions can be drawn from a Portuguese study where NODAT occurred in 33.3% of patients with ADPKD compared with 17.1% of the non-ADPKD control group.[40] In addition, a UK retrospective study showed that 13.4% of patients with ADPKD developed diabetes, whereas NODAT occurred in only 5.2% of the patients with other nephropathies. Moreover, twice as many patients with ADPKD and NODAT required treatment with insulin compared with the non-ADPKD diabetic group.[61] Additionally, according to the analysis

of Caillard et al.,[62] ADPKD is associated with risk factors for NODAT.

However, other studies do not support the concept that ADPKD is associated with a higher incidence of NODAT. In a retrospective cohort study conducted in 505 transplant recipients, there was no significant difference in NODAT incidence between ADPKD and non-ADPKD groups,[63] and several other studies yielded similar results.[64-66] Irene et al.[67] examined the incidence of NODAT and impaired glucose tolerance (IGT) in 65 renal allograft recipients with ADPKD compared with a gender and year of transplantation-matched control group and found no differences between groups. There was also no difference in the number of acute rejections between groups. Interestingly, a higher risk of NODAT development in RTx recipients with ADPKD may be associated with the HLA-B27 antigen.[65] Nevertheless, periodical assessment for NODAT should be performed in RTx recipients with ADPKD, especially when additional risk factors for NODAT exist, including BMI exceeding 25 kg/m^2, pre-transplant IGT, and acute rejection.[62]

Infections

Infections are an important class of complications arising in kidney recipients with ADPKD, and for most clinicians are considered as one of the main causes of death in this population. However, except for urinary tract infections (UTIs), they do not occur in this group with higher prevalence than in RTx recipients with other nephropathies.[29,68] Immunosuppression favours the spread of infections, including into the graft. Ascending UTIs and cyst infections occur mainly in patients who have not undergone a pre-transplant nephrectomy.[43] Due to immunosuppressive therapy, opportunistic pathogens should be included in the differential diagnosis of native kidney infection, including *Mycobacterium tuberculosis*.[69] Interestingly, renal graft recipients with ADPKD were suggested to be less prone to BK virus infection due to a lower cellular permissivity of the renal tubular epithelial cells in this disease.[70]

Neoplastic Diseases

Neoplastic lesions occur with increased frequency in patients receiving immunosuppressive therapy after transplantation, regardless of its cause, and cancer is one of the major causes of death in this group.[71,72] ADPKD appears to be a risk factor for renal tumours in the pre-transplant period, although the available studies do not provide consistent data.[44,73,74] In this context it is important to keep in mind the possibility of kidney tumours in patients who have not undergone nephrectomy. The increased risk of cancer in organ-transplant recipients with ADPKD has not been the subject of many studies. Recently, Wetmore et al.[75] compared the incidence of cancer in 10,166 RTx recipients with ADPKD and 107,339 without polycystic disease. Although the overall incidence of cancer was higher in patients with ADPKD, it was shown to be lower after adjustment for the higher age of recipients in this group. In a study by Vega et al.[38] the rate of cancer was similar in ADPKD and non-ADPKD RTx recipients. Other studies show no difference between the incidence of kidney cancer in recipients with ADPKD and control patients.[39,76] However, ADPKD may be a risk factor for non-melanoma skin cancer (NMSC) in patients after RTx. In a study conducted in 1,019 patients, a significantly higher risk of NMSC (both basal and squamous cell cancer) was demonstrated in RTx recipients with ADPKD compared with other nephropathies, regardless of age, sex, phenotype of the skin, or immunosuppression. In the same study, no relationship between ADPKD and solid tumours after transplantation was reported.[77]

Immunosuppressive Treatment

Although potential benefits of proliferation signal inhibitors in post-transplant immunosuppressive regimens in ADPKD patients have been suggested,[78] to date there are no data supporting their routine use. Despite results from experimental studies, sirolimus does not impact the growth of hepatic cysts after RTx.[79] Its benefits were only proven in casuistic reports, for example in the rare association of ADPKD with tuberous sclerosis.[80] Therefore, there are no special recommendations concerning immunosuppressive therapy after RTx in ADPKD patients, and they should be treated according to the general rules.

CONCLUSION

RTx in ADPKD is currently associated with excellent results. However, to obtain satisfactory outcomes several specific issues should be addressed in pre-transplant assessment and post-transplant management. Native kidneys, the cardiovascular system, and the gastrointestinal system require special attention in these patients. Immunosuppression should be administered according to the general rules.

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