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Full Review

Spanish guidelines for the management of autosomal dominant polycystic kidney disease*

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent cause of genetic renal disease and accounts for 6–10% of patients on renal replacement therapy (RRT). Very few prospective, randomized trials or clinical studies address the diagnosis and management of this relatively frequent disorder. No clinical guidelines are available to date. This is a consensus statement presenting the recommendations of the Spanish Working Group on Inherited Kidney Diseases, which were agreed to following a literature search and discussions. Levels of evidence found were C and D according to the Centre for Evidence-Based Medicine (University of Oxford). The recommendations relate to, among other topics, the use of imaging and genetic diagnosis, management of hypertension, pain, cyst infections and bleeding, extra-renal involvement including polycystic liver disease and cranial aneurysms, management of chronic kidney disease (CKD) and RRT and management of children with ADPKD. Recommendations on specific ADPKD therapies are not provided since no drug has regulatory approval for this indication.

Keywords: ADPKD, autosomal dominant polycystic kidney disease, guidelines, recommendations, management

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting one in 400–1000 live births [1]. Progressive cyst expansion leads to massive enlargement and distortion of the kidney architecture and, ultimately, to end-stage renal disease (ESRD) in most patients [2]. ADPKD accounts for ∼5–10% of cases of ESRD requiring renal replacement therapy (RRT) in Europe and the USA [3, 4].

ADPKD is genetically heterogeneous with two genes causing the disease, *PKD1* and *PKD2* [5, 6]. *PKD1* accounts for 85% of cases and *PKD2* for the remaining 15% [7, 8].

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PKD1 causes more severe disease, with a mean age at onset of ESRD of 58 years, compared with 79 years in cases due to *PKD2* [9]. ADPKD is a systemic disease. Cysts develop also in the liver, pancreas, spleen, seminal vesicles, ovary and arachnoid. Intra- and extra-cranial aneurysms, cardiac disorders and hypertension are more common in ADPKD patients than in the general population [10, 11]. Many molecules have been tested to treat ADPKD, but the only one approved is tolvaptan in Japan [12].

Prospective randomized controlled clinical trials and also clinical studies that incorporate an experimental design for the diagnosis and management of ADPKD are sorely lacking and difficult to undertake because of the relatively small numbers of patients at individual treatment centres and patient heterogeneity regarding stage of disease at presentation and organ involvement. Hopefully, the recent KDIGO controversies meeting on ADPKD will address the management of the disease and identify key research needs (http://kdigo.org/home/conferences/adpkd/). The present consensus recommendations are largely based on the experience and opinions of the authors, as well as on a literature search. The Cochrane Library, MEDLINE and Database Systematic Reviews (up to 1 December 2013) were searched using the search terms 'ADPKD' or 'polycystic kidney' in combination with the terms 'diagnosis' or 'imaging' or 'gene' or 'hypertension' or 'CKD' or 'chronic kidney disease' or 'chronic kidney failure' or 'ESRD' or 'end-stage renal disease' or 'dialysis' or 'transplantation' or 'infection' or 'pain' or 'liver' or 'aneurysm' or 'cancer' or 'pregnancy' or 'children'. We largely selected publications in the past 10 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than these guidelines have room for.

The authors are members of the Working Group on Inherited Kidney Diseases within the Spanish Society of Nephrology. They reached a consensus on the recommendations and considered that the benefits outweighed any potential risks. The levels of evidence are low: levels C and D according to the Centre for Evidence-Based Medicine (University of Oxford) (http://www.cebm.net/?O=1025). The following aspects of the disease are addressed: diagnosis, hypertension, pain, assessment of renal disease progression, ESRD, polycystic liver disease (PLD), intracranial aneurysms (ICA), other extra-renal features and ADPKD in children.

DIAGNOSIS

Since ADPKD is an autosomal dominant disease with high penetrance, offspring of affected parents have a 50% chance of developing the disease. Given the high penetrance, the skipping of a generation is highly unlikely. Currently, ultrasonography is used to screen for and diagnose the disease in persons with an affected relative. The diagnosis of sporadic cases, which account for ~10–15% of patients, relies on clinical features of the disease but sometimes requires genetic testing, especially in the early stages. ADPKD must be distinguished from other causes of renal cysts such as simple cysts, autosomal recessive polycystic kidney disease, *HNF1B*-related renal disease and other cystic diseases. In an adult, the presence of enlarged cystic kidneys, decreased glomerular filtration, hypertension and hepatic cysts is highly suggestive of ADPKD. However, frequently not all these clinical traits are present and the diagnosis becomes more complicated. In these cases, the genetic test is very helpful. Even in the absence of a specific treatment, early diagnosis in adults may improve cardiovascular risk factors.

Recommendations

(i) The patient with a secure or likely diagnosis of ADPKD should be advised to inform first-degree adult relatives of the diagnosis, and screening should be offered to them (D).

(ii) Genetic counselling should always be provided (C).

Imaging diagnosis

Ultrasonography is the most widely used imaging technique to diagnose and follow up ADPKD. Ultrasonography can detect cysts from 1 cm in diameter, is widely available, is inexpensive and does not require radiation or contrast material [13]. The new generation of ultrasonography scanners now provide resolution down to 2–3 mm, although this is dependent on the body habitus of the test subject, the operator and the centre. Ultrasonography is also useful for exploring abdominal extra-renal features of ADPKD, such as hepatic or pancreatic cysts, which support the diagnosis of ADPKD.

Ultrasonography diagnostic criteria are available for *PKD1* patients [14] and for patients with a family history of ADPKD but unknown genotype [15] (Table 1). The sensitivity of classic ultrasonography for *PKD1* patients is significantly higher than that for *PKD2* patients [15].

Computed tomography (CT) is more sensitive than classic ultrasonography and can detect cysts as small as 0.5 cm as well as stones; furthermore, it is better than ultrasonography at identifying renal tumours. However, CT exposes patients to radiation and is more expensive; therefore, it is not routinely used for diagnosis or for follow-up studies of ADPKD. Magnetic resonance imaging (MRI) is more sensitive than either ultrasonography or CT. MRI may be still more helpful in distinguishing renal cell carcinoma from simple cysts. MRI is the best imaging tool to monitor kidney size during treatment to assess progression. However, MRI is not routinely used because it is expensive and time-consuming, and extensive image analysis is required to calculate total kidney volume, which is not routinely available. Simpler MRI at a lower cost and with a shorter exposure time could be adequate for calculation of renal volume in a clinical setting [16].

Recommendations

(i) Ultrasonography is the recommended screening tool for relatives of an affected proband. Specific diagnostic

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Table 1. Diagnosis of ADPKD

Ultrasonography criteria (C)

Ravine's criteria (1994) for patients at risk of PKD1 mutation:

- At least two cysts in one kidney or one cyst in each kidney in patients younger than 30 years.
- At least two cysts in each kidney in patients aged 30–59 years.
- At least four cysts in each kidney in patients aged 60 years or older.

Pei's criteria (2009) for ADPKD patients with an unknown genotype and positive family history:

- Three or more (unilateral or bilateral) renal cysts in patients aged 15–39 years.
- Two or more cysts in each kidney in patients aged 40–59 years.

Presence of fewer than two renal cysts provides a negative predictive value of 100% and can be considered sufficient to rule out disease in at-risk individuals older than 40 years.

Indications for genetic testing in ADPKD (D)

(a) Individual patient characteristics

Potential living donor: individualize the testing decision based on age and severity of disease in the family, as well as imaging tests.

No family history of ADPKD. Especially when:

- Imaging findings are atypical (e.g. marked kidney asymmetry, multiple small cysts and renal failure in the presence of normal-sized cystic kidneys).
- Mild disease is present.
- There are atypical extra-renal symptoms.

Very early onset of the disease.

- Very early presentation within a family with typical ADPKD: genetic studies may identify a hypomorphic allele in addition to an allele with a pathogenic mutation.
- No family history of ADPKD and no detected mutations in the *PKHD1* gene (cause of autosomal recessive PKD) or with imaging features of ADPKD.

Pre-natal or pre-implantation genetic diagnosis in patients with or without a family history.

(b) Family characteristics

Families with many members with kidney cysts and atypical imaging findings

criteria should be used for different clinical questions: either diagnosis of ADPKD in members of families with *PKD1* as the disease-causing gene or diagnosis of ADPKD in families with an unknown genetic defect (Table 1) (C).

(ii) CT scanning should be used in uncertain cases or in those with suspicion of associated renal disease such as stones or tumour (D).

(iii) MRI should be reserved for monitoring renal volume in clinical trials and in certain cases to distinguish a renal cyst from a tumour (D).

Genetic diagnosis

At present, genetic testing for ADPKD is still expensive and it is not widely recommended. However, it is indicated in several situations: (i) when a definitive diagnosis is required in young individuals, such as a potential living-related donor in an affected family with equivocal imaging data; (ii) in patients with a negative family history of ADPKD, because of potential phenotypic overlap with several other kidney cystic diseases; (iii) in families affected by early-onset polycystic kidney disease, since in these cases, hypomorphic alleles and/or oligogenic inheritance can be involved [17, 18] and (iv) in patients requesting genetic counselling, especially couples requesting a pre-implantation genetic diagnosis. Testing patients in routine clinical care to determine whether the gene causing the disease in the family is *PKD1* or *PKD2*, or the type of mutation, is currently questionable as there is significant clinical variability within each gene and within each type of mutation, and the therapeutic approach will currently not be changed by the result. However, it is important to note that a strong genotype–phenotype correlation has been recently reported [9]. Truncating *PKD1* mutations have a more severe prognosis compared with in-frame *PKD1* mutations.

Recommendations

(i) Genetic testing for ADPKD is not recommended in routine clinical care when the clinical and imaging diagnosis is clear (ungraded statement).

(ii) Specific situations in which genetic testing for ADPKD may be valuable are related living donor transplantation, uncertain *de novo* cases, very early-onset disease and pre-implantation genetic diagnosis (Table 1) (D).

(iii) The method for genetic testing may be chosen based on the clinical presentation, the characteristics of the family and the availability of genetic testing techniques (ungraded statement).

Genetic linkage analysis

The major drawback of linkage analysis is that it can only be used in familial cases. It is imperative that at least three members of the family are diagnosed with ADPKD with absolute certainty. Only certain families are large enough for the study to confirm the linkage to one of the genes and discard the linkage to the other gene. Phenomena that may complicate the diagnosis include the presence of *de novo* mutations, the presence of hypomorphic alleles [17, 19], recombinations and mosaicism [20]. Once the risk haplotype has been identified within a family, at-risk individuals may be tested based on the presence/absence of that haplotype.

Recommendations

(i) In order to perform linkage analysis in a family, it is imperative that at least three members of the family have been diagnosed with ADPKD with absolute certainty and that the family is large enough to be informative (C).

(ii) In order to diagnose an individual by linkage analysis, linkage in the family should be exclusive to *PKD1* or *PKD2* (C).

Mutation analysis

DNA sequencing is generally considered to be the preferred methodology for genetic testing as compared with linkage analysis. Of the various possible approaches for the mutation study of *PKD1* and *PKD2* genes, Sanger sequencing is the most commonly used technique today [21, 22]. When a pathogenic mutation is not identified by Sanger sequencing of

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PKD1 (cursiva) and PKD2 (cursiva), multiplex ligation-dependent probe amplification analysis should also performed to search for a potential insertion or deletion. However, the upcoming next generation of sequencing techniques will significantly reduce costs and times [23]. The advantages of mutation detection compared with linkage testing are that single individuals, small families and uncertain cases can be analysed. Difficulties of mutational diagnosis include the high degree of allelic heterogeneity, the fact that 75% of the *PKD1* gene is reiterated on the same chromosome with a high degree of homology (pseudogenes), the presence of mosaicism and the difficulty of classifying an amino acid change or small in-frame insertions or deletions as pathogenic, neutral or hypomorphic. It is important to refer the samples to laboratories with the appropriate expertise. The main limitation of mutational screening is the sensitivity of <100%, although it is close to 94% according to the latest studies [9].

Recommendations

(i) Mutational screening of *PKD1* and *PKD2* can be used for both sporadic and familial cases, even when the diagnosis is uncertain (C).

(ii) Mutational screening of *PKD1* and *PKD2* is preferred to linkage analysis, especially when the indication is prenatal or pre-implantation diagnosis (D).

(iii) Mutational screening of *PKD1* and *PKD2* is highly recommended in very early-onset cases as well as in transplant donors (D).

HYPERTENSION AND CARDIOVASCULAR RISK MANAGEMENT

Arterial hypertension is highly prevalent in ADPKD patients compared with patients with other renal diseases. Nearly 60% of ADPKD patients have hypertension before the glomerular filtration rate (GFR) decreases [24]. The use of ambulatory blood pressure monitoring may help to make an early diagnosis of hypertension and to identify patients with masked hypertension, which is highly prevalent among ADPKD patients [25]. Hypertension occurs earlier and more frequently in *PKD1* than in *PKD2* and in those ADPKD patients whose affected or unaffected parents also have hypertension [26]. Target organ damage is more prevalent in ADPKD than in matched patients with essential hypertension, even though the prompt diagnosis and treatment of hypertension and the extensive use of renin–angiotensin–aldosterone system (RAAS) blockade have drastically diminished the prevalence of left ventricular hypertrophy [27–29].

Activation of the RAAS seems to play a major role in the pathogenesis of hypertension in ADPKD patients. Plasma renin activity and aldosterone concentration are increased in ADPKD patients compared with matched essential hypertension patients [30]. Also, there is strong evidence for the activation of a local intrarenal RAAS. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers alone fail to completely suppress the RAAS. The safety and efficacy of combining both classes of the drug is being evaluated in the HALT trial [31]. Additional contributors to the development of hypertension include intrarenal ischaemia, which impairs tubular sodium handling and increases the activity of the sympathetic nervous system, endothelial dysfunction, extracellular volume expansion and alteration of the urine concentration ability [32, 33].

According to the recent KDIGO definition of CKD, every ADPKD patient has CKD even when GFR and urinary albumin excretion are normal (http://kdigo.org/home/guidelines/ckd-evaluation-management/). Accordingly, guidelines for the management of cardiovascular risk in CKD, including blood pressure (http://kdigo.org/home/guidelines/blood-pressure-in-ckd/), lipids (http://kdigo.org/home/guidelines/lipids/), anaemia (http://kdigo.org/home/guidelines/anemia-in-ckd/) and CKD mineral bone disorder (http://kdigo.org/home/mineral-bone-disorder/), should be applied until ADPKD-specific evidence becomes available. However, there are some discrepancies between guidelines regarding blood pressure targets for individuals with CKD. Recommendations from the recently released JNC8 guidelines for the management of blood pressure in CKD differ from those of KDIGO in that JNC8 does not recommend different blood pressure targets depending on the magnitude of albuminuria. In this regard, until new evidence becomes available, such as might be provided by the HALT clinical trial, there is no firm evidence to recommend specific blood pressure targets for patients with ADPKD. It is not known whether a low-salt diet in normotensive ADPKD patients is clinically beneficial. However, higher sodium intake in subjects participating in the CRISP cohort was associated with more rapid progression of the disease [34]. Also, the European guidelines of hypertension say that reduction of salt intake to 6 g per day achieves a modest reduction of blood pressure [35].

Recommendations

(i) Lifestyle changes (maintenance of ideal body weight, regular aerobic exercise and a diet limited to a maximum intake of 6 g of salt daily) should be encouraged to prevent and to treat hypertension as in essential hypertensives (D).

(ii) Ambulatory or home blood pressure monitoring is recommended for early diagnosis of hypertension (D).

(iii) The clinic blood pressure target for ADPKD patients should be similar to other CKD patients until results from the HALT trial become available (D).

(iv) Pharmacological regimens for hypertension should include a RAAS inhibitor as the first option based on its theoretical advantages (C).

(v) Cardiovascular risk should be assessed, and all modifiable cardiovascular risk factors treated according to the CKD guidelines (ungraded statement).

RENAL DISEASE PROGRESSION BEYOND BLOOD PRESSURE CONTROL

Progressive deterioration of renal function determines the prognosis of ADPKD [10]. The GFR typically remains within

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the normal range for several decades, despite progressive renal enlargement [2].

The currently unmodifiable factors that determine progression of CKD in ADPKD are the gene (worse in cases due to *PKD1*) and severity of the mutation (worse if truncating), renal volume (rapid progression when total kidney volume exceeds 1500 mL) [36], gross haematuria before the age of 30 and an abnormal renal concentration capacity [37]. Gender does not seem to exert a significant effect in terms of renal outcome [3]. Modifiable factors affecting CKD progression in ADPKD are hypertension and proteinuria, which are not a hallmark of the disease, but might develop as functioning renal mass decreases [37]. Increased free water intake may lower vasopressin levels, inhibit kidney cell cAMP synthesis and thus might contribute to slowing the increase in kidney volume and the rate of deterioration of renal function, although no human data are available and the amount of water that may make a significant impact is unknown [38, 39].

Recommendations

(i) Currently, no drug has regulatory approval for the specific indication of slowing progressive loss of renal function in ADPKD (C).

(ii) A high free water intake (2–3 L per day) is recommended for CKD Stages 1–3 (D).

(iii) Long-term administration of nephrotoxic drugs should be avoided (ungraded statement).

(iv) Follow-up visits should be scheduled according to CKD stage. ADPKD adults without renal failure and controlled blood pressure should be followed up on a yearly basis (D).

(v) Total renal volume is the best predictor of renal outcome in ADPKD patients but, for the moment, should be restricted to patients enrolled in a clinical trial. In routine clinical practice, ultrasonography is recommended due to its cost and lack of contraindications. Simplified MRI may be of use in renal volume follow-up in a near future (D).

(vi) Patients with large polycystic kidneys should avoid contact sports and situations that carry a high risk of abdominal trauma (D).

ACUTE AND CHRONIC PAIN, CYST INFECTION AND BLEEDING

Acute pain may result from pyelonephritis or cyst infection, cyst bleeding or passage of stones [11]. Both kidney and liver cysts may be symptomatic. Cyst bleeding or rupture usually presents with acute pain that may be accompanied by macroscopic haematuria or/and anaemia. Cyst infection usually presents with fever and back pain. Imaging may help diagnose cyst infection whereas urine or blood culture may be negative [40, 41]. Gram-negative enteric bacteria are the usual causative agents. Acute renal pain may also be due to nephrolithiasis, which occurs in 20–36% of patients. Uric acid stones are more common than calcium oxalate stones [42]. Predisposing factors include hypocitraturia, acid urine pH and possibly in a few patients hypercalciuria or a distal acidification defect and, especially, compression of the collecting system by expanding cysts leading to urinary stasis.

Chronic pain may result from kidney or liver enlargement. The indications, advantages and limitations of different imaging techniques in ADPKD patients with pain, fever or bleeding are summarized in Table 2.

Recommendations

(i) Bleeding

(a) Treatment of cyst bleeding is symptomatic and consists of bed rest, analgesics and, in the case of kidney cysts, hydration sufficient to increase the urinary flow rate to 2–3 L per day (D).

(b) Patients should be encouraged to self-treat and not to go to the emergency department unless bleeding is severe, persistent or with a change in pattern (ungraded statement).

(c) Depending on the magnitude and persistence of bleeding, the following treatment options may be considered: intravenous fluids, desmopressin if GFR is <15 mL/min/1.73 m^2, packed red cells in case of anaemia, endovascular catheter to avoid ureteric obstruction, percutaneous embolization or nephrectomy if there is life threatening bleeding (D).

(d) There should be careful evaluation of risks and benefits prior to initiation of anticoagulation or antiplatelet therapy in patients with a history of gross haematuria (D).

(ii) Cyst infection

(a) Symptomatic cyst infection requires hospitalization (D).

(b) Diagnosis of cyst infection may be based on the association of (1) fever >38°C, (2) local pain in the flank and (3) C-reactive protein (CRP) of >5 mg/dL (D).

(c) Increased alkaline phosphatase and/or CA19.9 is often associated with liver cyst infection (C).

(d) Urine and blood should be cultured (C).

(e) Empirical lipophilic antibiotics with good cyst penetration (quinolones) should be started and adjusted according to evolution and sensitivity testing (D).

(f) Duration of treatment should be 4–6 weeks (D).

(g) Addition of a second antibiotic (cephalosporins or carbapenems) and imaging for re-evaluation for complications should be considered if there is no improvement within 72 h (D).

(h) Further imaging assessments should be done if infection persists, in order to localize the infected cyst. A positron emission tomography (PET)–CT would be the recommended technique in this case (D).

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Table 2. Imaging in ADPKD patients with pain, fever or bleeding

Test	Advantages	Advantages beyond evaluation of pain, fever or bleeding	Disadvantages	Indication
Plain abdominal X ray	Cheap, accessible		Cysts not visible	Initial evaluation of abdominal pain
Ultrasound	Identification of urinary tract obstruction, lithiasis and complicated cysts	Diagnosis of ADPKD; information on kidney size	No discrimination between cyst infection and bleeding	Initial evaluation of abdominal pain or fever
CT scan	Sensitive for diagnosis of lithiasis; may yield images suggestive of recent bleeding or, sometimes, of infection (gas, intra-cystic level, increased density of surrounding fat)	Estimation of kidney volume; estimation of interstitial fibrosis	Frequently identifies multiple complicated cysts; may not adequately differentiate infection from older bleeding; contrast may not be used because of renal insufficiency; contrast can illuminate pericystic normal parenchyma	Initial evaluation of abdominal pain or fever
MRI	T1 and T2 sequences similar to CT scan. DWI MRI may identify infected cysts	Precise estimation of total kidney volume and growth rate; quantification of cyst number	Low availability; T1/T2 sequences do not adequately differentiate infection from bleeding; contrast may not be used because of renal insufficiency; contrast can illuminate pericystic normal parenchyma	Evaluation of fever when CT scan is not informative
^{18}F-FDG PET/CT	Test of choice to precisely locate infected renal or liver cyst; can locate other sources of infection		Expensive; low availability; no defined criteria for diagnosis and monitoring of infected cysts; also detects tumours and haematoma; possible interference of renal failure in marker removal	Therapeutic decision-making when CT and MRI are not informative especially in cases of persistent fever
Radioactive gallium- or indium-labelled leucocyte scintigraphy	Locates inflammation		Low availability; preparation takes 48 h; requires leucocyte external manipulation; low accuracy; low sensitivity (50%)	Alternative when PET–CT is not available and CT and MRI are not informative
Arteriography	Diagnostic and potentially therapeutic if there is severe active bleeding		Invasive; potential radiocontrast nephrotoxicity	Serious bleeding

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; DWI, diffusion-weighted imaging. ^{18}F-FDG PET, fluorine-18 fluorodeoxyglucose positron emission tomography.

(i) Invasive procedures should be considered when there is no response to antibiotics following imaging identification of the affected cyst. These include percutaneous or surgical drainage if the cyst diameter is >3–5 cm and nephrectomy in the case of an emphysematous cyst, recurrent infections, recent refractory cyst infection in a transplant candidate or staghorn calculus causing recurrent urinary tract infections in a poorly functioning or non-functioning kidney (C).

(j) If fever recurs after stopping antibiotics, complicating features such as obstruction, perinephric abscess and stone should be excluded. If none is identified, several months of antibiotic treatment might be needed to eradicate the infection (D).

(iii) Lithiasis

(a) Renal lithiasis may benefit from potassium citrate when hypocitraturia is present, as well as from urine alkalinization (D).

(b) Percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy can be used in an individualized setting (D).

(iv) The cause of chronic pain should be evaluated and corrected if possible.

(a) Mechanical back pain or pain due to renal enlargement should be managed symptomatically (D).

(b) Narcotic analgesics should be reserved for acute episodes (D).

(c) Invasive procedures may be considered in the presence of intractable pain due to cyst enlargement (D).

RENAL REPLACEMENT THERAPY

Survival of ADPKD patients on RRT is higher than that of non-ADPKD patients. Renal complications may persist even after reaching ESRD but rarely result in serious problems [3, 43]. Cardiovascular disease is the main cause of death [3, 43]. Recurrent gross haematuria, cyst infection and kidney volume may require nephrectomy. Gross haematuria in an ADPKD patient with ESRD is usually due to cyst bleeding, but screening for renal cell carcinoma should be considered, especially if the haematuria is recurrent. It has been suggested that peritoneal dialysis may be associated with a better prognosis in ADPKD than in non-ADPKD patients [44, 45]. However, in patients with very large kidneys and/or livers, lack of space may restrict the available area for peritoneal exchange and increase the chances of hydrothorax and abdominal hernias, and haemodialysis is a better option [46]. The same is true for

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patients with recurrent diverticulitis. Renal transplantation in ADPKD has similar outcomes to those in non-diabetic patients [3, 47]. The main difference resides in the need to screen for ICA and to evaluate for removal of one or both kidneys [47]. It remains controversial whether routine screening for ICA should be done prior to kidney transplantation. There is insufficient available evidence to choose whether native nephrectomy should be performed before or at the time of kidney transplantation [48]. Hand-assisted laparoscopic nephrectomy is a good option, provided the centre has experience in this type of surgery. Although mTOR inhibitors were suggested to reduce kidney volume after renal transplantation, there is not enough evidence to recommend mTOR inhibitors as first-line immunosuppression in ADPKD [49].

Recommendations

(i) Both peritoneal dialysis and haemodialysis are suitable for most ADPKD patients with ESRD (C).

(ii) Heparin should be avoided during haemodialysis in patients with recurrent gross haematuria (C).

(iii) Transplantation is the recommended form of RRT. Pre-emptive renal transplantation from living donors is encouraged (D).

(iv) Elective nephrectomy of native kidneys should be considered prior to renal transplantation when the kidney size prevents adequate placement of the graft. Timing (pre-transplant or simultaneous with transplantation) should take into account the experience of each centre (D).

(v) Native kidney nephrectomy may also be indicated to treat complications such as bleeding or persistent infection (D).

KIDNEY CANCER

Renal carcinoma does not occur more commonly than in other CKD populations but may be more difficult to diagnose [50].

Recommendations

(i) If gross haematuria lasts longer than 1 week or if the initial episode occurs after the age of 50 years, imaging should be performed to screen for kidney cancer (D).

(ii) A solid mass on ultrasonography, speckled calcifications on CT, contrast enhancement, tumour thrombus or regional lymphadenopathies on CT or MRI should raise suspicion of a carcinoma (C).

POLYCYSTIC LIVER DISEASE

PLD is the most common extra-renal manifestation and is defined by the presence of at least 20 simple cysts in the liver [51]. Risk factors for the development of hepatic cysts are age >25 years, female gender, previous pregnancies, increased renal volume and oestrogen intake [51]. Liver cysts are usually asymptomatic. However, increased liver volume may cause abdominal pain, gastro-oesophageal reflux, early satiety, nausea and vomiting, dyspnoea, orthopnoea, hernia, back pain, venous obstruction (hepatic inferior vena cava, portal) and bile duct obstruction. Liver failure is exceptional. Laboratory tests for liver function (gamma-glutamyltransferase, aspartate aminotransferase and alkaline phosphatase) and CA 19.9 may show mildly increased levels even in asymptomatic patients. Treatment to decrease liver volume is only indicated in highly symptomatic patients (Table 3) [52–54].

PLD may also cause acute complications such as cyst infection and bleeding. *Liver cyst infection* is clinically characterized by right-sided abdominal pain with fever. The causative agents are usually enterobacteria ascending from the bile duct. Blood tests may show leucocytosis, elevated CRP and elevated alkaline phosphatase and CA19.9. The best tool for diagnosing liver cyst infection is a PET after administration fluorine-18 fluorodeoxyglucose (FDG PET) [40, 55]. *Cyst bleeding* is rare and may mimic the symptoms of an infected cyst, although fever and signs of infection are uncommon. *Rupture of liver cyst* is exceptional and may cause acute abdominal pain and ascites [54]. PLD may also be associated with ascending cholangitis.

Recommendations

(i) Patients with moderate-to-severe PLD should avoid oestrogens and drugs that stimulate cAMP accumulation (e.g. caffeine) (D).

(ii) In patients with mild cystic liver disease, in whom hormonal RRT is planned, the lowest effective dose should be used. Transdermal route is preferred as it may exert a different biological effect on liver cysts by avoidance of the first-pass effect (D).

(iii) A CT scan is recommended when a liver cyst infection is suspected. The recommended treatment is an antibiotic regimen with quinolones for at least 6 weeks. A third-generation cephalosporin should be added if fever persists after 72 h. When signs of infection persist after 3–5 days on antibiotics, FDG PET should be performed in order to locate the infected cyst in the event that CT or MRI is unable to localize it. Percutaneous drainage may be advisable if infection persists and the causative cyst is identified and accessible. Cyst haemorrhage should be diagnosed with MRI and treated with non-opioid and opioid analgesics and rest (D).

(iv) Treatment aimed at reducing liver volume is only indicated when the patient is highly symptomatic. Available options are described in Table 3. Surgery on a polycystic liver should only be performed by a surgeon with expertise in PLD owing to the abnormal anatomy of the liver and the high morbidity of these surgical procedures (C).

INTRA-CRANIAL ANEURYSMS

The prevalence of ICA in ADPKD patients is ~8%, five times higher than in the general population [10, 11, 52]. ICAs are usually asymptomatic, located in the anterior circulation

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Table 3. Treatment options for complications caused by increased polycystic liver volume

Procedure	Method	Indication	Results	Complications
Aspiration and sclerotherapy	Cyst aspiration followed by injection of sclerosing agent (ethanol is the most commonly used; minocycline and tetracycline are alternatives) Destroys the epithelial lining of the cyst	Symptomatic dominant cysts (usually with diameter >5 cm)	70% disappearance or improvement of symptoms 22% total/19% partial cyst regression: up to 21% recurrence	Minor. Abdominal pain is the most common, due to peritoneal irritation during ethanol instillation
Fenestration	Aspiration plus resection of superficial cyst walls Laparoscopic or open approach	Dominant cyst as an alternative to percutaneous sclerosis	92%: reduced severity of symptoms 24% recurrences	23%: ascites, pleural effusion, arterial or venous bleeding May complicate future liver transplantation Factors predicting failure: previous abdominal surgery, deep-seated cysts, diffuse cystic disease
Segmental liver resection	Resect the more affected liver segment Usually combined with cyst fenestration	Severe involvement with at least one unaffected hepatic segment	86%: reduced severity of symptoms	50%: ascites, bleeding, bile leaks 3% perioperative mortality May complicate future liver transplantation
Liver transplantation	Liver transplantation or combined liver and kidney transplantation	Severe liver involvement with hepatic insufficiency or with untreatable complications	Curative therapeutic option	5-year survival rate: 92%

and measure <6 mm. The rupture of an ICA results in a subarachnoid haemorrhage, which may cause death (30–40%) or disability (30%) [56, 57]. The clinical presentation is a severe headache and frequent loss of consciousness. The risk of rupture correlates with the size of the aneurysm, presence of relatives with ADPKD and ICA [57, 58], the location, presence of a daughter sac, hypertension, tobacco or cocaine abuse, and the use of oestrogens and anticoagulants [57–61].

Magnetic resonance angiography (MRA) without gadolinium is the preferred imaging technique for diagnosis of ICAs. Screening with MRA has specific indications, shown in Table 4 [57]. Management of unruptured aneurysms is also summarized in Table 4 [62]. There is currently controversy over when to rescreen if initial screening has been negative: some propose rescreen at 10 years in those with a family history of ruptured ICA whereas others favour no rescreen at all [58, 63].

Recommendations

(i) The preferred imaging technique to screen for ICAs is MRA. If MRA is not feasible, CT angiography is an acceptable alternative (C).

(ii) Screening for ICA should be performed in any of the situations listed in Table 4 (D).

(iii) Unruptured ICA should be managed in collaboration with the neurosurgery department according to the guidance in Table 4 (C).

(iv) An urgent CT scan is mandatory when an ADPKD patient develops an acute severe headache with or without loss of consciousness (C).

(v) All symptomatic ICA should be treated (C).

(vi) The type of treatment once an ICA needing surgery has been identified should be decided in a personalized multidisciplinary setting and may include surgical clipping or endovascular coiling (C).

Table 4. Intracranial aneurysms: management in ADPKD

Indications for ICA screening in ADPKD patients

- Family or past personal history of stroke or ICA
- Symptoms suggestive of ICA
- Job or hobby in which loss of consciousness may be lethal
- Preparation for major elective surgery
- Extreme anxiety of the patient regarding the risk of having ICA

Management of unruptured ICAs *(modified from Williams and Brown 2013)*

Strongly consider treatment
- UIA ≥12 mm in diameter
- Symptomatic UIA
- Enlarging UIA

Possibly consider treatment
- UIA 7–12 mm in diameter and any of the following features
  - Young patients
  - Higher-risk locations (posterior circulation or posterior communicating artery)
  - Daughter sac
  - Family history of SAH
- UIA <7 mm in diameter in younger patients and any of the following features
  - Higher-risk locations (posterior circulation or posterior communicating artery)
  - Daughter sac
  - Family history of SAH

Do not recommend treatment
- UIA <7 mm in diameter in anterior circulation without family history of SAH and without daughter sac
- Asymptomatic cavernous internal carotid aneurysms

Intervention must be personalized: it may be surgical clipping or an endovascular coiling. ICA, intracranial aneurysm; SAH, subarachnoid haemorrhage; UIA, unruptured intracranial aneurysm.

OTHER EXTRA-RENAL FEATURES

Cysts in the pancreas, seminal vesicles and meninges are usually asymptomatic [64, 65]. Less common extra-renal

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features include abdominal hernias, bronchiectasis, mitral valve prolapse and diverticular disease [52, 54].

Recommendations

Screening for additional extrarenal manifestations is not recommended (ungraded statement).

PREGNANCY IN ADPKD

Women with ADPKD and renal failure or hypertension are at higher risk of developing pre-eclampsia during pregnancy [66].

Recommendations

(i) Pregnancy is not recommended in ADPKD women with CKD Stages 3–5, excluding transplanted patients (D).

(ii) Hypertensive pregnant ADPKD women should be followed up as a high-risk pregnancy (C).

(iii) Non-hypertensive ADPKD pregnant women may not be followed up as a high-risk pregnancy, although special attention to hypertension should be paid (ungraded statement).

CHILDREN WITH ADPKD

Typically, the clinical manifestations of ADPKD, both renal and extra-renal, occur during adulthood and children have few or no symptoms. Diagnosis of asymptomatic children, due to the limited sensitivity of radiological imaging, particularly in children <5 years of age, may require a genetic test, but this remains controversial because it raises ethical issues in the absence of any specific treatment (see diagnosis section). It is necessary to differentiate between an early diagnosis of the disease, which is usually associated with typical ADPKD progression and a very early-onset ADPKD. This latter scenario occurs in 1–2% of children with ADPKD and may be clinically indistinguishable from autosomal recessive polycystic kidney disease [67]. They may show a Potter sequence and significant morbidity, as well as perinatal or neonatal mortality. Recently, it has been demonstrated that these severe ADPKD cases can be caused by the presence of incompletely penetrant alleles in both *PKD1* gene copies [17, 19] or by a combination of mutations in multiple 'cystogenes' [18].

In general, children who present with enlarged kidneys on ultrasonography tend to have more clinical manifestations than children with normal-sized kidneys [67], including hypertension, which is the main issue in children [68, 69]. Hypertensive ADPKD children have an increased risk of left ventricular hypertrophy and decreased kidney function over time when compared with children with ADPKD and blood pressure below the 75th percentile [70, 71]. ACE inhibitors are the drug of choice for treating hypertension in children.

Recommendations

(i) Screening for ADPKD in children at risk is questionable due to ethical issues in the absence of a specific available treatment (ungraded statement).

(ii) Radiological imaging should be pursued in at-risk children with hypertension, haematuria and/or proteinuria (ungraded statement).

(iii) Children with unusually severe very early-onset ADPKD should undergo genetic testing to evaluate the contribution of other cystic genes to the phenotype (D).

(iv) All ADPKD children with symptomatic disease should be followed by a paediatric nephrologist (D).

(v) Blood pressure should be measured in asymptomatic, at risk ADPKD children starting in childhood (D).

(vi) In the event hypertension is detected, the diagnosis of ADPKD should be pursued and treatment with ACEI initiated (ungraded statement).

(vii) Evaluation for extrarenal features of the disease is not recommended during childhood (ungraded statement).

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CONFLICT OF INTEREST STATEMENT

None declared.

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