Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): considerations for routine screening and management

Randy L. Luciano and Neera K. Dahl

Section of Nephrology, Yale University School of Medicine, New Haven, CT, USA

Correspondence and offprint requests to: Neera K. Dahl; E-mail: neera.dahl@yale.edu

ABSTRACT

Autosomal-dominant polycystic kidney disease (ADPKD) is a systemic disease, marked by progressive increase of bilateral renal cysts, resulting in chronic kidney disease (CKD) and often leading to end-stage renal disease (ESRD). Apart from renal cysts, patients often have extra-renal disease, involving the liver, heart and vasculature. Other less common but equally important extra-renal manifestations of ADPKD include diverticular disease, hernias, male infertility and pain. Extra-renal disease burden is often asymptomatic, but may result in increased morbidity and mortality. If the disease burden is significant, screening may prove beneficial. We review the rationale for current screening recommendations and propose some guidelines for screening and management of ADPKD patients.

Keywords: ADPKD, extra-renal, screening

INTRODUCTION

Autosomal-dominant polycystic kidney disease (ADPKD) patients comprise 5–10% of patients with end-stage renal disease (ESRD) and an equal percentage undergoing renal transplant. ADPKD is caused by a mutation in PKD1 or PKD2 genes, with allele frequencies of 1:500 to 1:1000 [1]. However, diagnosis of ADPKD may be much less common. Mutations in PKD1 comprise 85% of cases. PKD1 encodes polycystin-1 and a large integral membrane protein [2]. PKD2 encodes polycystin-2 and a transient receptor potential calcium ion channel [3, 4]. Together, these proteins function as a mechanosensory ion channel complex. Mutations of these proteins affect the development, polarity and environmental sensation of cells contributing to cyst formation through effects on the primary cilia [1, 5]. Polycystins have also been demonstrated to have roles in cell adhesion and extracellular matrix regulation [6]. Localization of these proteins extends outside of renal tubules to other epithelial and endothelial surfaces, and mutations result in extra-renal manifestations associated with ADPKD. ADPKD is a systemic disorder with cysts developing in the liver and pancreas as well as in the kidney. In addition, ADPKD is associated with an increased incidence of kidney stones, cerebral aneurysms, cardiac disease, colonic diverticula and male infertility. This review focuses on extra-renal manifestations of ADPKD describing complications and screening recommendations.

LIVER AND PANCREATIC CYSTIC DISEASE

The prevalence of hepatic cysts in ADPKD patients has been estimated to be as high as 80%. Cysts originate from bile duct epithelium. Cyst size and number increase with age [7]. Females tend to have more cysts and prior pregnancy and use of estrogen (hormone replacement therapy) increases cyst size and number [8]. Initial studies correlated an increase in liver cyst size with severity of kidney disease [9]. No correlation was noted between the liver cyst volume and the total kidney volume in the CRISP cohort when adjusted for age [7]. In the HALT-PKD Study A population, liver volume was associated with total kidney volume in women but not in men [10]. Hepatic involvement of ADPKD does not result in hepatic dysfunction. Laboratory tests of liver function (alkaline phosphatase and gamma glutamyl transferase) may be mildly elevated in asymptomatic patients, and the tumor marker CA 19-9 may also be elevated in response to hepatic cyst infection with no correlation to increased malignancy [11–13]. Increase in hepatic cysts may present as abdominal pain and distension, or with acute
compression leading to early satiety, nausea or vomiting. Compression of vascular or ductal hepatic structures can lead to jaundice, ascites or cholecystitis [14]. Patients may have functional limitations and decreased mobility due to enlarged livers, impairing quality of life [15]. Infection of hepatic cysts is potentially life-threatening, and best diagnosed with positron emission tomography–computed tomography (PET–CT) [16]. Complications of liver cysts continue to develop even after patients have developed ESRD or undergone renal transplant. Failure to thrive or unexplained weight loss post-renal transplant may trigger an evaluation for complications from liver cysts.

Medical management using somatostatin analogs (octreotide or lanreotide) has led to significant reduction in liver volume with continued use. In a randomized double-blinded placebo-controlled clinical trial looking at long-acting octreotide in patients with ADPKD, octreotide use leads to significant reduction in liver cyst volume (~5%) and renal cyst stability when compared with placebo over a 1-year period [17]. In the second year of treatment, there was no further reduction in liver volume and increased renal cystic volume in patients treated with octreotide for 2 years [18]. A study looking at lanreotide in patients with ADPKD or polycystic liver disease demonstrated a 4% reduction in cyst volume after 1 year of lanreotide use [19]. Hepatic cyst volume increased within 6 months of cessation of therapy. Symptomatic patients with poor functional status and large liver volumes (>3–4 L) may be appropriate candidates for medical treatment or radiologic intervention, cyst aspiration or sclerosis. Patients with kidney transplants may benefit from rapamycin as immunosuppressive therapy [20]. Cyst fenestration hepatic lobe resection or hepatic transplant may be considered in symptomatic patients with good functional status [11].

Cystic involvement of the pancreas has been estimated to be ~10% in patients with ADPKD [21]. Pancreatic cysts were associated with increasing age, female sex and PKD1 mutation [22]. Pancreatic involvement is usually benign, with no reports of endocrine or exocrine dysfunction. However, cystic compression of the main pancreatic duct has resulted in chronic pancreatitis [23].

**CENTRAL NERVOUS SYSTEM CYSTS**

Arachnoid cysts are benign structures that have been found in ~8% of patients with ADPKD, relative to 0.8% in non-ADPKD-matched controls [24]. Cysts have been associated with increased risk of chronic subdural hematoma in case series and reports [25, 26]. Screening and follow-up examination are not necessary because arachnoid cysts grow slowly and are seldom associated with subdural hematoma [27]. Spinal meningeal cysts have also been reported, with an overall low prevalence (<2%) in patients with ADPKD [28].

**ANEURYSMS**

Asymptomatic intracranial aneurysms (ICAs) have been detected in ~6% of ADPKD patients without family history and approximately 20% of patients with a family history [29]. In contrast, the rate of ICAs in the general population is 1–2%. Aneurysmal rupture is a feared complication, resulting in a mortality rate of 60% and if the patient survives, significant morbidity. While rupture of aneurysms in the general population is largely based on size, location and prior rupture, the natural history of an ICA with ADPKD is less certain. The incidence of ICA rupture in ADPKD patients is approximately five times that of the general population. Given the 5-fold increased prevalence of ICA in the ADPKD population, this suggests that the risk of ICA rupture in patients with ADPKD is equivalent to the general population. In patients with ADPKD, ICA rupture has been shown to cluster in families, however with significant interfamilial heterogeneity [30, 31]. This association prompts a look at the rationale for screening based on the risk of ICA rupture in patients with ADPKD.

In a single-center study, all patients with ADPKD went through a presymptomatic MR screen for aneurysms from 1989 to 2002. Twenty-three aneurysms were found in 21 patients. The aneurysms were small (<7 mm), predominantly in the anterior circulation, and carried a 67% association with family history of ICA. In a mean imaging follow-up time of 81 months, 18 patients demonstrated no aneurysmal growth, one had a 1 mm increase in size, and one had interval development of an aneurysm, with no evidence of rupture in any patient [32]. An extension of this study through 2009 followed a total of 45 aneurysms from 38 patients, with an association of ICA in family members of 50%. Follow-up, initially at 6-month intervals, progressing to annually and then less frequently, demonstrated one new aneurysm, two aneurysms with increased growth, three surgically clipped aneurysms and no ruptures over a cumulative imaging follow-up time of 243 years [33].

There are fewer studies that look at indications for rescreening. One study looking at 20 patients, 11 with ruptured and 9 with intact ICAs over 15.2 years discovered a 25% incidence of new ICAs, a 10% rate of preexisting aneurysm growth and 1 patient with a repeat rupture, with no mortality [34]. This high percentage of patients with interval development of new aneurysms prompted a look at the incidence of aneurysms in 76 ADPKD patients with initial negative screens [35]. At a mean follow-up of 9.8 years, only two patients had interval development of ICAs. Based on these studies, the recommendation has been to rescreen patients with ADPKD for ICAs, with initial negative studies, at 10 years [1].

The cost-effectiveness of MRA-based ICA screening a 20-year-old patient with ADPKD has been evaluated previously with a decision analysis model. Although an older study, the perceived benefit of screening patients outweighed no screening, increasing the life expectancy, albeit by only 1 year, while decreasing societal costs [36]. This study calls into question the rationale for screening all patients with ADPKD for ICAs. Data do suggest that ADPKD patients with a family history of ICA have an increased prevalence of aneurysms. Although the risk of rupture in these patients may be equivalent to that of the general population, the higher prevalence makes this risk concerning. In a recent retrospective study looking at 355 patients with ADPKD screened for aneurysms, the prevalence of ICAs was 12.4%. In those with family history, prevalence
was 21.6% when compared with 11.0% in those without family history. Prevalence in this patient population is slightly higher, but approximately equivalent to other studies. However, as opposed to other studies, the authors recommend screening all patients with ADPKD over the age of 30 for ICAs [37]. There are limitations to this study, including the lack of follow-up data regarding aneurysm progression, new incidence or rupture.

Given these aforementioned studies and the 5–10-fold increased prevalence in patients without family history and upwards of 20-fold increased prevalence of those with a family history of ICA, we suggest definite screening of ADPKD patients for ICAs who have a family history of ICA with or without rupture. Since most patients with ADPKD will not have a family history of ruptured ICA, the patient should be aware of his or her increased risk of ICA relative to the non-ADPKD population. As the prevalence in those without family history is still substantial, we are inclined to offer screening to these patients, especially those with special circumstances as outlined in Table 1. Patients found to have ICAs should be followed with periodic rescreening or should have an intervention depending on the size or location of the ICA and patient characteristics (age, functional status and morbidity risk).

Mutational analysis of *PKD1* and *PKD2* genes has been examined to determine if genotype differences can lead to a vascular phenotype [38]. Mutations in either gene were associated with ICAs. *PKD1* mutations resulting in a vascular phenotype tended to cluster in a more 5’ (N-terminal) location relative to controls. However, vascular phenotypes, including rupture, were still present in 3’ (C-terminal) mutations, making mutational analysis a problematic screening tool.

Aneurysms have been found in non-cranial arteries of ADPKD patients, including the aorta, popliteal, splenic and coronary arteries. The presence of abdominal aortic aneurysms (AAAs) has been reported in ADPKD patients to be as high 5–10% when compared with 2–4% in the general population [39]. However, these groups tend to be biased towards hypertensive patients. In a study of ADPKD patients, ultrasonography of the abdominal aorta showed no statistical difference in aorta diameter relative to controls [40]. Aorta diameter did increase with age in both groups; however, across all age cohorts there was no difference in diameter. Currently, there are no recommendations to screen ADPKD patients for AAAs, and screening should mirror current recommendations for the general population: any male between the ages of 65–75 who has smoked >100 cigarettes in a lifetime or male >60 years with a family history of AAA should undergo one-time screening with abdominal ultrasonography [41].

### CARDIAC COMPLICATIONS

Cardiac manifestations, including early-onset hypertension, left ventricular hypertrophy (LVH), pericardial effusions and cardiac valvular abnormalities occur in a high percentage of ADPKD patients. Mortality is estimated to be 1.6- to 3.2-fold higher in ADPKD patients than the general population, with cardiac-related death being the most common cause of mortality [42]. These complications, while worse with declining GFR, may be present before apparent renal dysfunction, making diagnosis and risk management critical.

Hypertension is very common in patients with ADPKD, occurring in upwards of 70% of patients even before renal dysfunction is observed [43, 44]. Hypertension is diagnosed in the fourth decade of life in the majority of patients with ADPKD when compared with the fifth or sixth decades of life in non-ADPKD patients. Hypertension is also present in ~20–30% of children with ADPKD, before significant cyst burden [45]. The association between hypertension and renal volume has been examined in 147 patients with ADPKD, and it was found that there was a significant greater renal volume in hypertensive versus normotensive patients (volume: hypertensive 624 ± 47 cm³ versus normotensive 390 ± 43 cm³, P < 0.0005) [46]. More recent data in the CRISP cohort magnetic resonance imaging (MRI) showed a positive correlation between total renal, cystic volume and elevated blood pressure [47].

One complication of hypertension in ADPKD is LVH, leading to progressive cardiac dysfunction and increased morbidity and mortality. LVH has been demonstrated in young patients before hypertension develops [48]. Also, studies using 24-h ambulatory blood pressure monitoring demonstrated increased systolic, diastolic and mean blood pressure in seemingly normotensive ADPKD patients [49]. LVH in ADPKD patients is most likely multifactorial with increased angiotensin II levels possibly contributing to cardiac myocyte growth [50]. In addition, insulin resistance, not uncommon in ADPKD, has been associated with increased left ventricular mass in normotensive ADPKD patients [51]. Earlier studies demonstrated a prevalence of LVH of 37% (women) to 46% (men). Patients with LVH tended to be older, weigh more and have more loss of kidney function and higher blood pressures [52]. Angiotensin converting enzyme inhibitor (ACEI) use was limited. In contrast, Study-A patients from the HALT-PKD cohort had a very low prevalence of LVH (0.93–3.9%). These patients tended to be younger and most patients had been treated with an ACEI or angiotensin receptor blocker (ARB) prior to enrollment [53]. This suggests that blood

<table>
<thead>
<tr>
<th>Table 1. Screening considerations for intracranial aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who should be screened for ICAs?</td>
</tr>
<tr>
<td>(i)</td>
</tr>
<tr>
<td>(ii)</td>
</tr>
<tr>
<td>(iii)</td>
</tr>
<tr>
<td>(iv)</td>
</tr>
<tr>
<td>(v)</td>
</tr>
<tr>
<td>(vi)</td>
</tr>
</tbody>
</table>
pressure control with blockade of the renin–angiotensin system is critical in LVH progression.

Given these findings, there is very little evidence to support routine echocardiogram screening for LVH in patients with hypertension (HTN). Instead, screening should focus on detecting masked hypertension in patients with ADPKD. Blood pressure screening should be consistent with a standard sphygmomanometer for all young patients with ADPKD and ambulatory blood pressure recording, if there is concern for masked hypertension. If hypertension is diagnosed, an electrocardiogram is appropriate.

Blood pressure control with antihypertensive agents, especially blockade of the renin–angiotensin system has shown improved LVH and mortality in ADPKD patients [54]. Imaging modalities to detect LVH should be reserved for patients with symptoms or signs of heart failure with conventional echocardiography, which is more cost-effective than cardiac MRI.

The prevalence of valvular abnormalities is fairly consistent between various studies: ~15% of patients with mitral prolapse (MVP), 30% with mitral regurgitation, 10–20% with aortic regurgitation and 5% with tricuspid prolapse [55]. Valvular disease was statistically significant when compared with non-affected family members. The presence of hypertension and LVH in ADPKD raises the question as to whether valvular disease is the consequence of polycystin mutation or the effects of longstanding cardiovascular comorbidity. A study looking at the echocardiographic evidence of valvular disease demonstrated MVP in those with evidence of ADPKD as defined by either genomic linkage analysis or ultrasonography findings [56]. Patients with MVP tended to be older (>10 years) and have more renal involvement (>10 cysts). Blood pressure was statistically higher in ADPKD patients with MVP relative to those with normal valves. In another study, MVP decreased with age and was not associated with hypertension [57]. In these patients, mitral regurgitation increased with age and was associated with worsening blood pressure. The presence of MVP in younger children and in those with normal blood pressure suggests that it is a reflection of polycystin’s role in cardiac development and integrity as opposed to underlying structural defects and valvular complications from hypertension. Any cardiac murmur in an ADPKD patient, whether new or established, should be evaluated by echocardiography.

DIVERTICULAR DISEASE

The association of colonic diverticula with ADPKD has been examined in patients with chronic kidney disease (CKD), end-stage renal disease (ESRD) and transplant recipients. The incidence of diverticulosis in the general population has been estimated to be ~45% in both autopsy studies and barium enema studies [58]. Autopsy studies in ADPKD patients reveal a prevalence of 40%, consistent with that of the general population [21].

In a study looking at diverticular disease in CKD patients with and without ADPKD, there was no difference in the prevalence of diverticula between the two groups, and no difference in the diverticula in patients with ADPKD who had high versus low GFR [59]. These results contrast data from ESRD ADPKD patients. A single-center retrospective study found diverticulosis in 10 of 12 patients with ADPKD (83%) as opposed to only 10 of 31 non-ADPKD patients (32%) [60]. In addition, colonic perforation developed in four of the ADPKD patients but in none of the non-ADPKD patients. However, the number of ADPKD patients is rather small and the reason for imaging was unclear. A similar retrospective study looked at diverticulitis in ADPKD ESRD patients over a 12-year period that demonstrated 20% of ADPKD patients and only 3% of non-ADPKD patients with diverticulitis. Severity differed with 50% of ADPKD patients requiring surgical intervention versus 0% of the non-ADPKD patients [61]. Data from ADPKD renal transplant recipients remain strikingly polar. One study demonstrates a clear increased prevalence of diverticulitis in post-transplant patients with ADPKD with very high mortality rates [62]. A second single-center study demonstrated no difference in diverticulosis or colonic perforation between transplant recipients with and without ADPKD [63].

Screening of ADPKD patients for diverticula has not been addressed in the literature directly; however, the utility of screening colonoscopy has been evaluated in renal transplant recipients. In a single-center study, records from 118 patients >50 years were examined, representing 12% of all transplants over 10 years. Out of the 118 patients, 20 were found to have diverticular disease with 35% of those having ADPKD [64]. A review of all 1019 patients transplanted during this time yielded a colonic complication rate of 1.4%. Out of these 14 patients, 4 had complications related to diverticula requiring surgical intervention. Of the 4, 1 patient had ADPKD. It is unclear whether screening would have changed outcomes or altered management. Currently, screening colonoscopy in ADPKD patients is no different than the general population, focusing on the detection of colorectal cancer and not diverticula.

ABDOMINAL HERNIAS

ADPKD patients have an increased prevalence of hernias. A single-center study looking at 85 ADPKD ESRD patients or transplant recipients, found a 45% prevalence of all type abdominal hernia (25% inguinal, 6% incisional and 7% paraumbilical), when compared with a rate of 8% for matched non-ADPKD ESRD or transplant and 3% for general surgical patients [65]. The etiology of increased abdominal wall hernias is most likely multifactorial with contribution of decreased ECM integrity in the setting of mildly increased abdominal distension.

The presence of abdominal wall hernias is significant for two reasons. First, the higher prevalence of hernias in the ADPKD population suggests increased complications from abdominal hernias, mainly intestinal incarceration or strangulation leading to significant morbidity. Second, hernias can influence the modality of renal replacement therapy for an ESRD ADPKD patient. In a study of 75 dialysis units in the United States, 1864 peritoneal dialysis patients (PD) were
evaluated for anatomic complications. Out of this cohort, 200 patients experienced complications with hernias comprising 60.4% of all complications. Cystic disease was the only predictor of peritoneal complications (ORR 2.55, CI 1.87–3.67 and P < 0.001) [66]. In a recent study of 42 ADPKD patients and 84 matched non-diabetic controls on PD, overall mortality, technique survival and peritonitis infection rates were similar in both the groups, but the ADPKD cohort had a 33.3% incidence of hernia versus a 7.1% incidence in controls (P < 0.001) [67]. Out of those patients with hernias, 4.7% of the ADPKD patients required emergent surgery for bowel strangulation versus 1.1% of the controls. However, surgical intervention was successful in all cases and did not lead to permanent transition to hemodialysis.

Currently, there are no recommendations for hernia screening in the ADPKD population. A physical examination should be performed to evaluate for abdominal or inguinal hernias. Surgical interventions tend to be provider-dependent or patient-driven and largely based on aesthetics, complications or preparation for peritoneal dialysis or transplant.

**BRONCHIECTASIS**

Polycystin-1 expression has been localized to bronchial epithelium [68]. Expression has been demonstrated by gene expression with a real-time PCR in human and mouse airway epithelia cells. In addition, autopsy findings demonstrated changes consistent with bronchiectasis in one of five patients with ADPKD. Retrospective radiographic analysis using chest CT in 95 patients with known ADPKD demonstrated a prevalence of 37%, significantly higher than patients with non-ADPKD CKD (13%). Bronchiectasis tended to be mild in patients with a predominance of lower lobe involvement. The clinical significance and impact of bronchiectasis in ADPKD patients are unfortunately not known. Given the mild nature of the radiographic finding, routine screening is not recommended. Imaging should be guided by symptoms.

**FERTILITY**

ADPKD affects male fertility through direct effects on the seminal vesicles. Seminal vesicle cysts have been found through CT, MR or ultrasonography in ADPKD patients with a prevalence of 39–60% [69–71]. Worsening renal function and presence of hepatic cysts correlated positively with seminal vesicle cyst prevalence [70]. Apart from cysts, seminal vesicles may also demonstrate dilation [72]. A retrospective study looking at 68 patients with ADPKD, without evidence of seminal vesicle cysts, compared with 68 aged-matched non-ADPKD controls demonstrated increased seminal vesicle size on CT [73]. The cause of this dilation is not known, but may be due to obstruction secondary to immotile sperm through the ejaculatory duct. The presence of seminal vesicle abnormalities and cysts has not been correlated with infertility. However, case reports of patients with seminal vesicle cysts with subsequent ejaculatory duct cystic resection have shown variable results from restoration of fertility to no change in fertility outcomes [72, 74].

Decreased sperm motility (asthenozoospermia) has been reported in a high percentage of patients with ADPKD. In one study, 20 of 22 patients who had semen analysis had abnormal sperm, with asthenozoospermia being the most common finding [71]. In *Drosophila* and sea urchin, polycystins are required for normal spermatogenesis and function [75]. No clear association between polycystins and spermatogenesis has been identified in humans. Male ADPKD patients with infertility should undergo semen analysis and ultrasound evaluation for structural abnormalities.

In contrast, female ADPKD patients do not have any direct fertility issues; cysts do not directly impair the normal female reproductive tract and cysts do not form in ovaries at rates different than the general population. Likewise, fertility does not seem to be different in ADPKD non-dialysis-dependent patients than the general population [76]. However, females with ADPKD who become pregnant have higher morbidity than non-ADPKD females. In a study looking at 235 ADPKD patients and 108 unaffected family members, maternal complications were higher in the former with preexisting hypertension being the most significant risk for developing complications [77]. Fetal complications were similar between the two groups. In this study, preeclampsia was more likely to occur in hypertensive ADPKD patients than in normotensive ADPKD patients and renal function was worse in ADPKD patients with more than three pregnancies.

**PAIN AND QUALITY OF LIFE**

Pain is present in upwards of 60% of patients with ADPKD, with lower back (71%), abdomen (61%), head (49%), chest (30%) and leg (27%) pain comprising the major sites [78]. Pain can be either acute, as experienced with cyst rupture or hemorrhage, infection, nephrolithiasis or a complication from abdominal hernias. Chronic pain is usually the result of increased distension or impingement. Pain is often debilitating leading to worsening quality of life and limited social interactions in ADPKD patients [79]. However, other studies have shown quality of life of ADPKD patients similar to the general population [80]. Management of pain is often not addressed by healthcare providers and when pain medication is prescribed, analgesia is often suboptimal [79]. In addition to pain, depression has also been found to be extremely prevalent in ADPKD patients. The use of the Beck Depression Inventory scale found depression in 60% of patients with ADPKD in one study [81]. Routine questions regarding the presence of pain and relief with analgesia in addition to routine depression screening should be obtained on each office visit for the ADPKD patient [82].

**SUMMARY OF SCREENING RECOMMENDATIONS**

Table 2 summarizes the major extra-renal manifestations of ADPKD and the associated screening recommendations.
Table 2. Extra-renal manifestations of ADPKD with prevalence and screening recommendations for specific populations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Prevalence</th>
<th>Recommendation</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic cysts</td>
<td>&gt;90%</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>HTN</td>
<td>Up to 70%</td>
<td>Routine BP</td>
<td>All patients routinely</td>
</tr>
<tr>
<td>LVHI</td>
<td>Up to 50%</td>
<td>HTN control</td>
<td>All patients routinely</td>
</tr>
</tbody>
</table>
| Valvar
abnormalities | Up to 30% | Echocardiography | Patients with murmur |
| ICA           | 6–20%      | MRA            | Patients with family history/prior ICA rupture |
| AAA           | 5–10%      | Abdominal U/S  | Males 65–75 with smoking history/>60 with family history |
| Diverticula   | Up to 40%  | None           | N/A        |
| Hernias       | Up to 45%  | Physical Exam  | All patients with high cyst burden |
| Bronchiectasis| Up to 37%  | None           | N/A        |
| GU cysts      | 39–60%     | None           | N/A        |
| Depression    | Up to 60%  | Depression screen† | All patients yearly |
| Pain          | Up to 60%  | QOL Screen     | All patients yearly |

Likelihood ratio (95% CI): positive test 2.9 (2.5 to 3.4); negative test 0.05 (0.01 to 0.35) [82].

†The following two-question screen is recommended: 1. During the past month have you often been bothered by feeling down, depressed or hopeless? 2. During the past month have you often been bothered by little interest or pleasure in doing things?; sensitivity % (95% CI): 97 (83–99); specificity % (95% CI): 67 (62–72).

Table 3. Discussion points during routine office visits

- Dietary advice: limit caffeine, low salt (<2 g/day) diet. Good fluid intake (~3 L a day unless patient has Stage 4–5 CKD). Discuss DASH diet.
- Lifestyle modification: no smoking, moderate alcohol intake, appropriate, regular, low impact physical activity.
- Volumetric MRI to establish kidney size and prognosis. Consider repeating every 5 years.
- If kidney stones or nephrocalcinosis present: 24 h urine to evaluate for metabolic risk factors, with treatment of any metabolic abnormalities detected.
- Counsel regarding family planning: d/c ACEI or ARB prior to conception, discuss pre-implantation genetic diagnosis.
- Minimize estrogen exposure (OCPs in younger women, HRT in older women).
- Discuss participation in ongoing clinical trials.
- Discuss a screening renal ultrasound for at-risk family members.

Although extra-renal manifestations are quite common in the ADPKD patients, the benefits of screening for a particular complication need to be weighed. Rationale for screening has been established since World Health Organization Guidelines for disease screening in 1968 [83]. As with all screening interventions, the particular disease should pose significant morbidity or mortality risks on the patients with an acceptable intervention that can reduce these complications and improve patients’ outcomes. Cardiovascular abnormalities, mainly hypertension, LVH and valvular abnormalities, pose significant morbidity and mortality in ADPKD patients and screening should focus on strict blood pressure measurements and echocardiography in the setting of murmurs. ICA screening is recommended for ADPKD patients with a family history of ICAs. This will allow for detection in patients at the highest risk, without exposing low-risk patients to unnecessary screening procedures. Screening for AAAs is no different than the general unaffected population. Screening for hepatic cysts is usually not necessary as renal imaging most often includes lower hepatic lobes. There are currently no direct guidelines for screening for diverticular disease or male infertility. Finally, the impact of ADPKD on the quality of life in terms of pain-control and depression should be routinely assessed to ensure that these often overlooked symptoms are being addressed adequately.

In addition to addressing extra-renal manifestation screening with ADPKD patients, our practice is also to incorporate discussion of general health management focusing on preventative strategies and healthy lifestyle choices at routine office visits (see Table 3).

CONFLICT OF INTEREST STATEMENT

Dr. N.K. Dahl reports serving as a consultant and as an investigator for Otsuka.

REFERENCES


Received for publication: 29.4.2013; Accepted in revised form: 10.9.2013