

Antenatally Diagnosed ADPKD



To the Editor: Advances in antenatal ultrasonography have substantially improved the counseling of pregnant women.^{1–4} With this advancement comes a diagnostic dilemma in the approach to antenatal diagnoses of cystic kidney disease. The differential diagnosis of enlarged cystic echogenic kidneys includes autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease, renal cysts and diabetes syndrome, and other syndromic disorders.^{2,3,5}

ADPKD is the most commonly inherited renal disease, occurring in 1 in 400 to 1000 live births.^{1,3,4} Disease progression is marked by growth of renal cysts, nephromegaly, and advancing renal dysfunction, ultimately resulting in end-stage kidney disease in more than 50% of patients in the fifth to sixth decade of life.^{2–4,6–12} Extrarenal manifestations include intracranial aneurysms, cardiac valvular defects, diverticular disease, and cysts in the liver, spleen, and pancreas.^{1,3,4,6,7}

Mutations in 3 genes have been reported: *PKD1* (16p13.3), responsible for 80% to 85% of cases; *PKD2* (4q22.1), responsible for 10% to 15% of cases; and the recently identified *GANAB* (11q12.3).^{1,3,4,5,8–14} Patients with *PKD1* mutations have a poorer prognosis than patients with *PKD2* mutations, on average reaching end-stage kidney disease at 55 versus 70 years, respectively.^{1,5,7,10,14}

ADPKD is an autosomal dominant disorder with 100% penetrance and both intra- and interfamilial variability in disease presentation and phenotype.⁴ A “2-hit” hypothesis postulates that a germline mutation inactivates one *PKD1* allele whereas a subsequent somatic mutation inactivates the other allele, resulting in cyst formation.^{5,12,13} Because a second somatic mutation is not identified in all renal cysts, other genomic and nongenomic cystogenic impacts have been suggested.^{5,12,13,15}

Historically, ADPKD has been recognized as an adult-onset disease; however, symptoms can manifest in early childhood.^{1–3,6} Since the first report of fetal cases in 1971, ADPKD has increasingly been diagnosed *in utero*.^{2,3,6,11} Early diagnosis allows the opportunity for close follow-up and monitoring of disease progression.^{2–4,6,11} Given the increasing diagnosis of ADPKD *in utero*, it is desirable to form an approach so as to better inform clinical practice and to counsel affected families.

The aim of our study was to review our antenatally diagnosed cases of ADPKD and to describe their phenotype during a short-term follow-up.

Full methods are included as supplemental material ([Supplementary Methods](#)).

RESULTS

An overview of our ADPKD cohort is shown in [Table 1](#).

Six children were identified with a presumed diagnosis of ADPKD ([Table 1](#)) and were referred for tertiary pediatric nephrology and genetics input from centers in Queensland (population of 4.97 million).¹⁶ All 6 cases were included in the study based on the antenatal ultrasonography findings of bilateral nephromegaly and echogenic kidneys. Mean age at referral was 22.6 weeks’ gestation (range, 20–33 + 2 weeks). All children were born at term, had no prenatal or postnatal complications, were well with normal growth and development, and had bilaterally enlarged and cystic kidneys (>3 cysts bilaterally) at last follow up. Mean age at last follow-up was 10.6 months (range, 2.5–30 months).

One child had pyelonephritis at 4 months of age requiring i.v. antibiotics. One child had a splenic cyst noted at 4 months of age.

One subject had no known family history of ADPKD (1/6). Parents of this subject had normal renal ultrasound results before the age of 40 years, and thus ADPKD could not be confidently excluded. Genetic testing identified two *PKD1* variants: a *de novo* pathogenic mutation (p.Lys2529Asn) and a paternally inherited “variant of uncertain significance” (VOUS) (p.Ser225Leu).

DISCUSSION

With increasing awareness of ADPKD and advancements in imaging technology, more cases of ADPKD are being diagnosed antenatally.^{2–4} We have experienced an increase in referrals of antenatally diagnosed cases in recent years.

Antenatal cystic kidneys are identified by ultrasound imaging.^{2,4,5,10} Although the differential for echogenic or cystic kidneys *in utero* remains broad, a focused family history is able to delineate these.^{2,3,10} In the absence of a positive family history, the distinction of ADPKD from autosomal recessive polycystic kidney disease may be difficult.^{1,2,5,10} Involvement of a multidisciplinary team is essential for antenatal counseling and for guiding postnatal management.^{12,17} Furthermore, early detection of affected individuals facilitates timely implementation of an anticipatory approach, particularly important with potential emerging disease-modifying therapies.^{2,4,6,11} All children included in this report were appropriately referred to a tertiary center and received timely multidisciplinary team review.

Table 1. Clinical characteristics of children with antenatally diagnosed ADPKD

Clinical features	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	
	F		M		F		M		M		M	
Sex	At diagnosis	At last follow-up	At diagnosis	At last follow-up	At diagnosis	At last follow-up	At diagnosis	At last follow-up	At diagnosis	At last follow-up	At last follow-up	
Age	20 wk GA	30 mo	20 wk GA	4 mo	20 wk GA	4 mo	20 wk GA	13 mo	33+2 wk GA	2 mo	33+5 wk GA	2 mo
Ultrasound findings												
Cystic kidneys	-	+	+	+	-	+	+	+	-	+	+	+
Number of cysts	N/A	>3	>3	>3	>3	>3	>3	>3	N/A	>3	1	>3
Echogenic kidneys	+	+	+	+	+	+	+	+	+	+	+	+
Other anomalies	-	-	-	-	-	-	-	-	-	-	-	-
Kidney length												
Left (centile)	85	>95	>95	>95	>95	>95	70	>95	50	>95	50	>95
Right (centile)	>95	>95	>95	>95	>95	>95	85	>95	50	>95	50	>95
Genetic testing	+		N/A		N/A		N/A		N/A		N/A	
Urological complications	-		-		-		+		+		-	
Systemic features	-		-		+ ^a		-		-		-	
Hypertension	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-
Creatinine (μmol/l)	N/A	<30	N/A	<30	N/A	<30	N/A	<30	N/A	<30	N/A	<30
Family history	-		+		+		+		+		+	
Number of first-degree affected relatives	0		2		1		1		1		1	
Number of second-degree affected relatives	0		2		2		1		4		1	

F, female; GA, gestational age; M, male; N/A, not applicable; +, present; -, absent.
^aSplenic cyst.

The current pediatric approach to the management of cystic kidneys includes annual clinical reviews and intermittent ultrasonography.^{2,4,5,10} Once renal function declines, irreversible structural damage has already been established.^{3-6,10} Regular screening of affected individuals allows early diagnosis and treatment of hypertension, review for potential systemic complications, and enrollment into potential future clinical trials of disease-modifying treatments.^{3,4,6,11} Gimpel *et al.* published recommendations on the diagnosis, management, and follow-up of perinatal cystic kidneys. They recommended phenotype-specific timing of renal ultrasounds postnatally, and a referral to clinical genetics for diagnostic counseling and possible genetic testing.¹⁷ They found that fetuses with bilateral hyperechogenic cystic kidneys, such as in our cohort, have a good prognosis but significant risk of long-term renal disease.¹⁷ To add further to the recommendations from Gimpel *et al.*, our approach is to refer the parents of affected children to an adult nephrologist (Figure 1).

The natural history of ADPKD is characterized by a slow growth of the kidney cysts with few renal or systemic complications until adulthood.^{1,3,6,9,10} Kidney function and blood pressure usually remain normal during childhood and adolescence,^{1-5,10} as in the case of our cohort.

Previous studies have documented that patients detected with ADPKD *in utero* or less than 18 months of age have earlier progression to end-stage kidney

disease.^{1,9} On the other hand, Boyer *et al.* observed a favorable long-term prognosis in prenatally diagnosed ADPKD cases, at least until adolescence.¹ Long-term follow-up of our cohort is required to determine outcomes.

Given the degree of phenotypic variability of ADPKD, counseling of patients and parents can present challenges.^{4,11-14} Genetic testing is not routinely performed. It is costly, time consuming, and not universally available.^{3,4,7,11,12,14} Furthermore, legal and regulatory frameworks guiding the use of genetic information for insurance and employment remain undefined in some jurisdictions.^{3,7,12} De Rechter *et al.* reported that 37.1% of nephrologists advise against genetic testing in childhood because of the adult onset of ADPKD complications, fear of psychological stress, and the lack of effective treatment.¹¹ However, genetic testing can assist in pediatric ADPKD cases with no family history.^{4,12,14} A confirmed genetic diagnosis can allow more targeted management and accurate genetic counseling for parents and other relatives.^{4,12,14}

One of our subjects presented without a family history of ADPKD, prompting diagnostic genetic testing. This identified a *de novo* pathogenic mutation and a paternally inherited VOUS in *PKD1* gene.¹⁸ The VOUS has been classified as such due to the following: conflicting *in silico* predictions; a case report of an ADPKD case stating it as "likely pathogenic"^{19,20}; and the variant co-occurring with another pathogenic

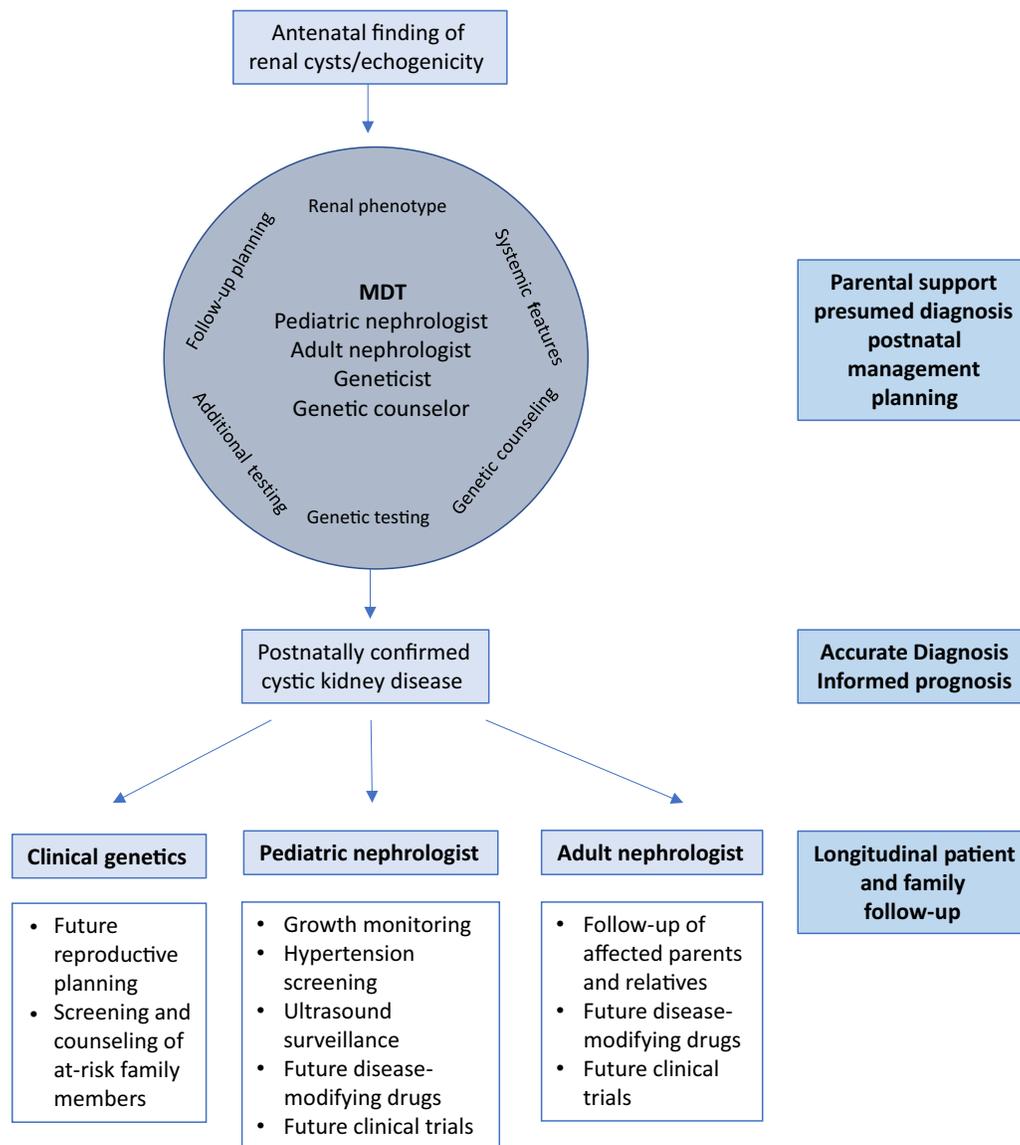


Figure 1. Our approach to antenatally diagnosed autosomal dominant polycystic kidney disease (ADPKD). MDT, multidisciplinary team.

mutation in another patient. Therefore, the VOUS could be a benign finding or could suggest that the father is also at risk for developing ADPKD. If this is a functionally significant variant, it may explain the more severe and earlier onset phenotype in the child due to a 2-mutation hypothesis.^{12–14}

Pharmacological management of ADPKD is rapidly evolving. Phase III clinical trials on the long-term safety of tolvaptan in children with ADPKD have commenced. Adult studies have demonstrated delayed decline of kidney function in patients with rapidly progressing ADPKD on tolvaptan.^{8,18} Early treatment with angiotensin inhibitors to control hypertension might minimize cardiovascular morbidity in ADPKD patients.^{3,4} These emerging treatments may offer early intervention to pediatric high-risk cases or those found to have early disease progression.^{3,4,8} Furthermore, they may alter the approach to antenatally diagnosed

ADPKD and improve the prognosis of affected families.^{3,4,8}

In conclusion, ADPKD has become acknowledged as a pediatric condition, with advancements in ultrasonography resulting in increased diagnosis. With this early recognition, clinicians and families alike are faced with an uncertain future and prognosis, requiring regular reviews for disease progression. Psychosocial outcomes including significant treatment burden, fear of end-stage kidney disease, and variable familial presentation are all realistic concerns that affected individuals and families face. Here we have presented a multidisciplinary approach to and clinical progress of a cohort of antenatally diagnosed cases of ADPKD. Emerging disease-modifying medications may improve the prognosis for these individuals and ultimately reduce the disease burden in adulthood.

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DISCLOSURE

AM has been a member of the tolvaptan Medical Advisory Board for Otsuka Australia Pharmaceutical Pty Ltd. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary Methods.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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The Role of Oxidative Stress and Inflammation in Acute Oxalate Nephropathy Associated With Ethylene Glycol Intoxication



To the Editor: Calcium oxalate crystal (CaOx) deposition within the renal parenchyma is well described as