REVIEW ARTICLE

Current diagnostic evaluation of autosomal dominant polycystic kidney disease

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KEY WORDS

autosomal dominant polycystic kidney disease, chronic kidney disease, Ravine criteria renal cysts, renal ultrasound examination

ABSTRACT

Despite changing epidemiology of chronic kidney disease, autosomal dominant polycystic kidney disease (ADPKD) is one of the most prevalent causes of end stage renal disease. The first symptoms of the disease occur usually in the 3rd or 4th decade of life, however, it can often be diagnosed much earlier. Advances in the understanding of the disease may lead, in the near future, to slowing the progression of ADPKD in asymptomatic individuals. ADPKD is diagnosed on the basis of family history (autosomal dominant inheritance) and radiological imaging. Ultrasound examination (US) of the kidneys is the most important imaging diagnostic method. US is highly sensitive and specific in patients >30 years of age. In US, Ravine criteria are applied and their modifications with other imaging techniques (computed tomography [CT], magnetic resonance [MR]). In all cases, however, there are multiple cysts in both kidneys and, importantly, concomitant renal enlargement can be observed, which is typical of ADPKD. High expectations for early ADPKD diagnosis are risen by genetics and proteomics. However, these methods are not used routinely. The most sensitive parameter in the evaluation of the disease progression is total renal volume. This parameter is presently used in clinical studies, but its utility in monitoring an individual patient has not been fully proven. Unfortunately, MR and CT are expensive and in case of significantly enlarged kidneys US does not yield accurate assessment of their size and is not sensitive enough for monitoring the disease progression. The rate of glomerular filtration rate (GFR) decline is usually constant. Therefore, it is important to monitor GFR in individuals who have developed renal insufficiency. Other tests, including markers of kidney injury, e.g. albuminuria, or vascular flow parameters, are used mainly in clinical studies. Thus, before more efficient therapeutic approaches have been developed, an early diagnosis and prevention of the disease complications are most essential.

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Received: March 17, 2008.
Revision accepted: May 14, 2008.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2008; 118 (12): 767-773
Translated by Iwona Rywczak, MD, PhD

INTRODUCTION Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorders associated with a defect in a single gene and at the same time one of the most common causes of chronic renal failure (CRF). The symptoms are developed usually in one's 30s or 40s, and at the age of 60 approximately 50% of patients require renal replacement therapy.[1] Therefore, ADPKD is commonly encountered in nephrological practice and in outpatient care. The diagnosis of ADPKD is not difficult in most cases, nevertheless, in some patients establishing a diagnosis or excluding the disease may raise doubts. The diagnosis is relevant in respect of prognosis. Until the age of 70, as many as 77% of ADPKD patients will start renal replacement therapy or die, mainly due to cardiovascular complications.[2]

Recently, a considerable progress in the understanding of the background and course of the disease has been made. Thus, an early diagnosis and appropriate care acquire particular significance. The technological development of imaging, genetic and molecular tests have brought new opportunities in the diagnostic evaluation of ADPKD. The objective of this paper is to present which of

TABLE 1 Ravine criteria applied in ultrasound diagnostics of autosomal dominant polycystic kidney disease type 1

Age (years)	Number of cysts	
	Positive family history	Negative family history
<30	at least 2 in 1 or both kidneys	at least 5
30–59	at least 2 in each kidney	at least 5
>60	at least 4 in each kidney	at least 8

TABLE 2 Criteria applied in ultrasound diagnostics of autosomal dominant polycystic kidney disease type 2

Age (years)	Number of cysts
15–19	1 in each kidney or 2 unilaterally
20–29	>3 altogether, at least 1 in each kidney
30–59	at least 2 in each kidney
>60	at least 4 in each kidney

TABLE 3 Diagnostic criteria for autosomal dominant polycystic kidney disease in magnetic resonance

Age (years)	Number of cysts in both kidneys
<30	at least 5
30–44	at least 6
45–59 (females)	>6
45–59 (males)	>9

the numerous tests available are considered the "gold standard" in ADPKD diagnostics and at what stage of the disease they should be performed.

Diagnosis of autosomal dominant polycystic kidney disease The basis for ADPKD diagnosis is family history and imaging studies.

Family history Due to the autosomal dominant type of inheritance, the morbidity risk for siblings and offspring of an ADPKD patient is 50%. Family history should serve to determine the existence or non-existence of that risk. It should be a standard procedure to perform further tests on each person with a 50% risk of developing ADPKD. As a rule, ADPKD is diagnosed in 1 of the parents. If there is no ADPKD patient in a numerous family, the probability of positive diagnosis is markedly lower. The exception is a *de novo* mutation when a patient does not inherit the disease but transmits it. In case of people with no family history, the risk of ADPKD development is the same as in the general population, i.e. 1/1000.[3-5]

Imaging studies The other factor essential in ADPKD diagnosis is an imaging test. Only 20 or so years ago, urography, renal arteriography and scintigraphy were the basis of diagnostic imaging.[6] Urographic tests sometimes wrongly suggested the presence of kidney cancer and, as a consequence, patients were exposed to unnecessary surgery.[6] Currently, due to low costs, reproducibility and availability, ultrasonography is a basic imaging test. The test sensitivity can be illustrated by the data according to which in ultrasonography cysts are found in 89% of ADPKD patients >30 years of age.[7]

It is justified to ask a question as to when the first ultrasound examination (US) should be performed. The answer is not unambiguous. No lower age limit has been determined, however, it is well known that ultrasonography preformed in the first years of life is of little diagnostic significance. Admittedly, cysts may be already present in the first year of life and even in fetal life[8], but the lack of cysts does not necessarily exclude the disease. The relationship between the number and size of cysts and the patient's age causes difficulty in ADPKD diagnosis in children. Certainly, US should be performed between the age of 20 and 30 when the probability of positive diagnosis is accompanied with potential prophylaxis introduction or treatment of the disease complications. Ultrasonography at the age of 30 at the latest should be a standard measure if previously that test has not been performed or to date tests have not shown lesions, and when the disease symptoms have developed.[1,3,4]

Of note, the classic ultrasound criteria for diagnosis of a simple cyst involve a round shape and sharp borders of the lesion, smooth wall without septums or calcification, echo-free interior and acoustic amplification proportional to its size. Single cysts should always be distinguished from hematoma, abscess, or cancer.[7]

Currently, Ravine criteria, presented in TABLE 1, are commonly applied in ADPKD diagnosis.[1,3,9,10] Positive family history remains relevant. Ravine criteria are applicable only to people with ADPKD type 1 family history. For ADPKD type 2, the criteria specified in TABLE 1 are of limited value. Their sensitivity for persons <30 is only 67% (compared with that for ADPKD type 1 of 100%).[3] This group suggested different criteria[11], presented in TABLE 2.

As shown in the table, a diagnosis <14 years of age is unlikely. On the other hand, the applied criteria offer almost 100% certainty of diagnosis in persons >30.[11] Irrespective of a patient's age, the ultrasound criteria and a disease type, it should be kept in mind that except for the presence of cysts, a characteristic feature of ADPKD is renal enlargement.[1]

The diagnosis may also be established based on other imaging techniques, like computed tomography (CT) and magnetic resonance (MR). High costs of these tests limit their application to establishing the diagnosis in unclear cases, e.g. in very young persons. It should be borne in mind that these tests are more sensitive than ultrasonography, thus Ravine criteria cannot be applied. In approximately 17% of healthy persons between 18 and 29, ≥2 cysts are found, usually <1 cm in diameter.[12] If only all the cysts of that size, presented in TABLE 2, were eliminated, Ravine criteria could be used in CT diagnosis. It is worth mentioning that separate MR criteria for persons

TABLE 4 Diseases associated with the presence of renal cysts which might potentially require differentiation from ADPKD

Autosomal recessive polycystic kidney disease
Tuberous sclerosis complex
Von Hippel-Lindau disease
Medullary cystic kidney disease
Oral-facial-digital syndrome
Polycystic dysplastic kidney disease
Medullary sponge kidney
Acquired cystic kidney disease

with positive ADPKD family history (TABLE 3)[12] have been worked out.

Altogether, available data show that no family history and a patient's age are limitations of the ADPKD diagnosis using imaging techniques. If a family history is negative, the diagnosis is uncertain until enlarged kidneys, the presence of numerous cysts in the kidneys and cysts in the liver have been detected.

Genetic tests A mutation of the polycystin 1 or 2 genes accounts for ADPKD. Those genes are located on chromosome 16 and 4, respectively. There are ADPKD type 1 or 2, depending on a mutated gene. Earlier papers suggested the existence of a rare ADPKD type 3, however, no mutation responsible for that type of disease has not been demonstrated to date. Currently, authors much less frequently mention a potential occurrence of ADPKD type 3.[3] Hereditary background of the disease makes its diagnosis based on genetic tests theoretically possible, irrespective of a patient's age. In practice, genetic analysis is not a standard procedure, being labor-consuming and expensive. The tests are performed mainly on young persons if US provides insufficient information and if there are additional recommendations, e.g. a wish to be a kidney donor. The polycystic kidney disease gene size and the number of described mutations hamper genetic evaluation of ADPKD.[5,13,14]

Diagnostic evaluation involves direct or indirect detection of the mutations. The latter uses e.g. DNA linkage analysis technique. The fundamental drawback of this method is a necessity to test at least 4 ADPKD patients and numerous healthy members of the same family. Direct detection techniques of mutation used when only a proband's blood sample is available are free of that limitation. Then, the sensitivity in detection of an individual mutation exceeds 60%. These tests, although expensive, are commercially available.[5,13,14]

To date, >200 mutations of both genes altogether have been described. Their full list is available at http://archive.uwcm.ac.uk/uwcm/mg/hgmd/search.html.

Proteomics At least several dozens of proteins obtained from the biological material from ADPKD patients (serum, urine, liquid obtained from the cysts) are overexpressed. This observation enables to seek a marker useful in the diagnosis and monitoring of the disease. Among those proteins, the following have been identified: growth factors, apoptosis regulators, transporting proteins, receptor proteins, signal proteins, enzymes, transcription factors, and others. Currently, those proteins are not used in routine practice.[13]

Other symptoms In most ADPKD patients, the diagnosis is currently established in the asymptomatic period during screening of the patient's kindred or by chance. Nevertheless, ADPKD is a disease of variable symptomatology and some symptoms may encourage to broaden diagnostic evaluation. The first and common symptom, although usually unnoticed, is urine condensation disorders and associated with slight polyuria. It is estimated that even 60% of children with ADPKD do not condensate urine when desmopressin is administered.[3,15] Other common clinical symptoms and lesions found by chance during control tests are as follows: hypertension (in later stages of the disease: 100% of patients), acute or chronic pain: 60%, hematuria: 50%, urinary tract infection: 20% in males and 60% in females, lithiasis: 20%. Cysts in the liver are found in 80% of 60-year-old patients, other lesions include mitral valve prolapse: 20–25%, brain artery aneurysms: 8%, pancreatic cysts: 9%, hernias: 20%, and intestinal diverticulosis.[3,4]

Differential diagnosis In most cases, ADPKD diagnosis leaves no doubt. Mistakes are predominantly caused by inexperience of the examiner. The diagnosis is handicapped by the fact that numerous diseases to be differentiated from ADPKD are relatively infrequent (TABLE 4). The decisive factor is usually the size of kidneys and presence of cysts in the liver.

In patients without family history, it is essential to differentiate from autosomal recessive polycystic kidney disease. It is manifested by clinically advanced renal insufficiency present already in childhood or early youth. The lack of typical family history may hinder the diagnosis, therefore, dubious cases should be evaluated by liver biopsy where fibrosis is present.

Cysts in the kidneys are found in 20% of patients with tuberous sclerosis complex. The disease is associated with characteristic skin and neurological symptoms. The concomitance of kidney cancer and polycystic kidney disease requires to exclude von Hippel-Lindau disease. Another genetically determined disease is medullary cystic kidney disease which most commonly occurs as juvenile nephronophtisis and is associated with CRF in childhood. Differentiation from ADPKD may constitute a problem in case of autosomal dominant inherited medullary cystic

kidney disease, in which the first symptoms are present usually in adults in their thirties. A rare X-linked disease is oral-facial-digital syndrome with characteristic lesions in the oral cavity, face dysmorphia, developmental hand and finger disorders and mental retardation.

Multicystic renal dysplasia in adults is usually a unilateral disorder. It is distinguished by frequent presence of calcification in the cyst walls and abnormal structure of parenchyma between the cysts visible on US. Another congenital, but not genetically determined disease is medullary sponge kidney in the course of which lithiasis and nephrocalcinosis is commonly observed.[1,5,13,18,19]

Differentiation from acquired cystic kidney disease usually is easy, given negative family history, a small size of kidneys and lack of cysts located outside the kidneys. Acquired cysts are found in a large number of patients – approximately 50%.[16,17]

Diagnostics of ADPKD progression Half of ADPKD type 1 patients require renal replacement therapy at the age of 54, and half of ADPKD type 2 patients at the age of 73.[20] However, ADPKD is characterized by high variability of the disease progression and definite CRF may even be detected in a 2-year-old child.[21] In the light of available data, proper assessment of the stage of the disease advancement and the disease progression is of crucial importance in the diagnostic process.

Glomerular filtration rate From the tests carried out among ADPKD patients, it is well known that in case of CRF the disease progression is constant, similar in most patients; glomerular filtration rate (GFR) decreases approximately 4–5 ml/min/year.[1] Therefore, in CRF patients, the calculation of GFR should be a standard, preferably according to Modification of Diet in Renal Disease formula. In patients without CRF, changes in creatinine levels are very slow, hence the calculated GFR may be distinguished by their low dynamics. An average decrease in GFR in patients without hypertension and CRF ranges from 2 to 3 ml/min/year.[22]

Renal volume The number and volume of cysts enable ADPKD diagnosis but they also show the disease advancement. Using those indications is difficult, labor-intensive and burdened with low reproducibility of results. What weighs against that solution is the fact that only part of the cyst is visible in imaging tests. Cysts are formed in 5% of nephrones, thus a measurement of even several dozens of cysts will be the measurement of only a small portion of all lesions. It is obvious from histological examinations that cysts are found also in renal parenchyma unaltered in imaging tests. According to the recent data, the most objective test to assess the disease progression and to monitor it is MR-based estimation of total renal volume. Renal volume closely correlates with cyst volume and is easier to estimate.[23] An error in renal volume estimated using MR is <5%.[21] Both total renal volume and the volume of cysts and parenchyma could be precisely estimated by CT.[20] The consortium of Radiologic Imaging Studies to Assess the Progression of Polycystic Kidney Disease demonstrated that renal volume exceeding 1500 ml is associated with a decrease in GFR and rapid progression of the disease.[3,22-24] High total renal volume in imaging tests is also a risk factor for hypertension.[25] Renal volume estimation does not require the use of contrast medium.

It is known that in ADPKD patients the volume of a single kidney increases by approximately 50–70 ml per year. However, there is a large difference among patients with regard to cyst growth speed.[23,25] In children, there is possibility to roughly estimate renal volume by means of ultrasonography.[26]

To summarize, assessment of total renal volume in sensitive imaging tests (mainly MR) performed according to approved and reliable standards is the best method to evaluate disease progression, particularly in patients without renal insufficiency. This test is currently a standard measure in the assessment of ADPKD progression in clinical trials (Tempo, HALT-PKD).[22] A role of US in the assessment of the disease progression is limited.

Renal flow studies Renal flow parameters, resistive index and pulsation index, assessed in Doppler ultrasound test correlate with renal impairment, the risk of hypertension development and its magnitude.[27-29] MR may also be used for renal flow assessment.[30] These tests are of low utility in clinical practice and are used mainly in scientific research.

Markers of kidney damage The assessment of ADPKD progression based on markers of kidney damage also seems to be of low significance. It is known that albuminuria, present also in subjects without hypertension, increases with the disease progression.[31] Novel markers of kidney injury, e.g. NGAL (neutrophil gelatinase-associated lipocalin), L-FABP (liver-fatty acid binding protein), β-N-acetylhexosaminidase (isoenzyme Hex B) have been described.[32-34] Their results, however, could not modify the diagnostic procedures and treatment of ADPKD patients in any way.

Other prognostic factors Although the course of ADPKD depends on numerous factors, studies on larger groups of patients have shown that prognosis is worse in patients with ADPKD type 1, hypertension diagnosed prior to the age of 35, essential hypertension in a family history, massive hematuria prior to the age of 30, liver cysts in females with the disease diagnosed prior to the age of 30, and males (mainly ADPKD type 1).[2,8,34] It is unimportant whether the disease is inherited from one's mother or father.[2]

Obviously, the course of the disease is determined predominantly by its type. Patients with ADPKD type 1 have worse prognoses because complications and CRF develop earlier.[2,36] Perhaps in the future, available, inexpensive and quick genetic tests will allow routine identification of patients with two types of ADPKD having slightly different prognosis.

To sum up, only GFR and total renal volume possess sufficient accuracy and reproducibility to be used for assessment of the disease progression rate. While GFR value is a standard measure in clinical practice, estimation of total renal volume becomes standard in clinical trials.

Diagnostics of complications There exists a range of complications in ADPKD associated with urinary tract, including infections, bleeding, lithiasis, tubulopathies. Early diagnosis of hypertension is most important in terms of the prevention of cardiovascular complications. In order to dispel doubts, a 24-hour blood pressure measurement should be performed. Currently, it is not clear what values of blood pressure entitle to antihypertensive treatment in ADPKD patients. An answer to this question may probably be given by the ongoing HALT-PKD study.[22] Until the doubts have been removed, the commonly approved criteria applied in hypertension therapy should be followed. It is well known that aneurisms represent one of serious cardiovascular complications of ADPKD. They may be present in virtually all arteries; however, the greatest concern is associated with those located intracranially. Imaging examination of the brain vessels should be performed in a person with neurological symptoms, brain aneurisms or subarachnoid hemorrhage in family history, and in case of increased anxiety of the patient.[1] The most common extrarenal complication of ADPKD is liver cysts found in sensitive tests almost in all elderly patients.

CONCLUSIONS

In diagnostic evaluation of ADPKD, precise family history and US are most important. In each person diagnosed with the disease it is essential to monitor the presence of urinary tract and cardiovascular complications. An early diagnosis of hypertension is of great significance. The disease progression is assessed mainly by repeated measurements of GFR. Scientific research uses another, more sensitive index, i.e. the estimation of total renal volume. Progress in ADPKD treatment will certainly serve as a stimulus for establishing reliable and inexpensive methods for early detection of the disease which will enable its treatment before hypertension and renal insufficiency have developed. Presumably, on the basis of current clinical studies, methods that evaluate the disease progression based on the measurements of levels of individual markers of kidney damage in the patients' urine and blood will be developed.

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