MEDICAL GRAND ROUNDS

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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Autosomal dominant polycystic kidney disease (ADPKD) constitutes the clinically most significant cystic disorder involving the kidney. The prevalence in reported clinical cases varies between 1 in 200 and 1 in 1000, and the incidence rate in the United States is 1.38 in 100,000. Overall, approximately 400,000 to 600,000 U.S. residents have ADPKD, making this disorder more common than either cystic fibrosis or sickle cell anemia (1,2).

Although renal manifestations are most commonly associated with ADPKD, systemic involvement is frequent, and extra-renal manifestations (i.e. hepatic cysts, berry aneurysms) may dominate the clinical picture (3). Since cystic diseases of the kidney were reviewed in this forum (4), important advances have evolved in the understanding of ADPKD. Notably, the genetic locus responsible for the majority of cases has been mapped and the ability to diagnose the disorder prior to the onset of clinical symptoms has been refined. In addition, epidemiological definition of cardiac valvular disorders occurring in ADPKD have emerged and new recommendations regarding the need for screening of cerebral aneurysms have been developed.

SPECTRUM OF CYSTIC DISORDERS INVOLVING THE KIDNEY:

Cyst formation within the adult kidney can arise from a variety of etiologies (5) as listed in Table I.

TABLE I

CLASSIFICATION OF RENAL CYSTS

- Polycystic Disease
  - Adult polycystic disease
  - Infantile polycystic disease
    - Polycystic disease of early infancy
    - Polycystic disease of childhood
    - Congenital hepatic fibrosis
- Renal Dysplasia
  - Multicystic dysplasia
    - Unilateral multicystic kidney
    - Bilateral multicystic dysplasia
  - Focal and segmental cystic dysplasia
  - Cystic dysplasia associated with lower urinary tract obstruction
  - Familial cystic dysplasia
- Renal Cysts in Hereditary Syndromes
  - Meckel syndrome
  - Zellweger cerebrohepatorenal syndrome
  - Jeune asphyxiating thoracic dystrophy
  - Tuberous sclerosis complex and Lindau's disease
  - Cortical cysts in syndromes of multiple malformations
- Renal Cortical Cysts
  - Diffuse glomerular cystic disease
  - Peripheral cortical microcysts
  - Juxtamedullary cortical microcysts
  - Simple cysts, solitary and multiple
- Renal Medullary Cystic Disorders
  - Medullary sponge kidney
  - Medullary cystic disease complex
    - Familial juvenile nephronophthisis
    - Renal-retinal dysplasia
- Miscellaneous Parenchymal Renal Cysts
  - Inflammation and necrosis
    - Medullary necrosis
    - Lithiasis
    - Tuberculosis
    - Echinococcosis
- Neoplasia
  - Cystic degeneration of carcinoma
    - Multilocular cystadenoma
    - Dermoid cyst
  - Endometriosis
  - Traumatic intrarenal hematoma
- Extraparenchymal Renal Cysts
  - Pyelogenic cyst
  - Parapelvic cyst
  - Perinephric cyst

Although the causes of cyst formation are extensive, the definitive diagnosis of ADPKD, at least after the age of 20 years is seldom difficult, and the following criteria (6) serve to discriminate this disorder from cysts arising from other causes:

1. ADPKD seldom becomes clinically manifest before the second decade, although rarely the adult form can be detected in childhood. Very rarely, the infantile (autosomal recessive) form, which is associated with hepatic fibrosis, may be found after the age of 20.
2. ADPKD generally, entails <u>bilateral</u> renal involvement.
3. ADPKD has an autosomal dominant patten of inheritance and thus a family history is often present.
4. By radiographic and sonographic criteria, cysts of widely varying size are scattered throughout the parenchyma of both kidneys.
5. By pathologic examination, the cysts are lined by a monolayer of epithelia and dysplasia is absent.
6. Multisystem involvement with cysts is common.
7. The clinical course is often characterized by a slow, inexorable decline in renal function.

CLINICAL PRESENTATION

The physician is faced with making the diagnosis of ADPKD through two avenues: patients presenting with symptoms or signs of urinary tract involvement or individuals seeking diagnosis because of an affected kindred member. Symptoms of ADPKD are listed in Table II.

TABLE II

SYMPTOMS OF ADPKD

	NUMBERS	RANGE IN REPORTS	MEAN PERCENTAGE
Flank pain	601/1194	(19–78%)	50
Abdominal pain	114/185	(60–75%)	62
Hematuria	555/1534	(13–57%)	35
Headache	87/317	(15–50%)	27
Gastrointestinal complaints	114/776	–	15
Nocturia	32/223	–	14
Colicky pain	127/993	–	13
Dysuria	20/223	–	9
Frequency	5/59	–	8

TABLE III

ORGAN SYSTEM

ABNORMALITIES ENCOUNTERED IN ADPKD

Genitourinary
- Polycystic kidney
- Ovarian cysts
- Hypernephorma

Gastrointestinal
- Hepatic cysts
- Pancreatic cysts
- Diverticulosis
- Hiatal hernia

Cardiovascular
- Cardiac valvular abnormalities
- Berry aneurysms
- Thoracic and abdominal aortic aneurysms

In retrospect, each may reflect abnormalities of the multiple systems involved in the disease (Table III). Thus pain, hematuria, polyuria, and dysuria can stem from renal involvement, whereas headache and abdominal pain may represent hypertension (and/or cerebral aneurysm) and liver cysts, respectively. Detailed discussion of the approach to the asymptomatic patient who requests evaluation for inheritance of ADPKD is discussed in later sections.

Following is a review of organs and systems which are significantly involved in ADPKD, and discussions of their pathophysiology and management.

KIDNEY

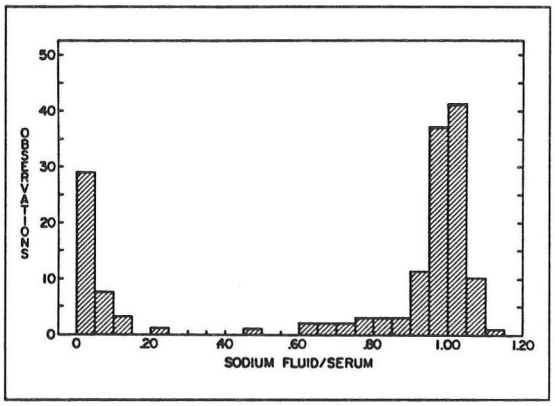
Dalgaard projected that 100% of individuals carrying the gene for ADPKD will manifest renal cysts by the age of 80 (1). There is however, considerable variability in the extent to which the kidney is involved, and indeed, some kindreds have been identified in which clinically significant renal involvement has not occurred (7). Complications of renal involvement in ADPKD include progression to end stage renal disease, calculi, frequent and treatment-refractory infection and a modest loss of urinary concentrating ability. Controversy exists regarding the possibility of renal neoplasms having an increased frequency in ADPKD.

Cystic involvement of the kidney may progress to the point of

extensive architectural distortion and destruction of the renal parenchyma. Renal cysts may originate from any portion of the nephron, including the glomerulus. Attempts have been made to determine by functional analysis, the origin of these cystic dilations. In such studies, Grantham (8-9) examined the sodium content of cysts from patients with ADPKD. Shown in Figure 1 are the results of this analysis.

FIGURE 1

CYST SODIUM CONCENTATIONS FROM ADPKD SPECIMENS



"Proximal cysts" are so named because the intracystic sodium concentration was equal to that of plasma, presumably reflecting the fact that sodium is reabsorbed isotonically within the proximal tubule. In contrast "distal cysts" have a low cyst/plasma sodium concentration ratio, indicative of the fact that the distal nephron (thick ascending limb of Henle and collecting duct) is capable of generating steep lumen to blood sodium gradients. More recently, this issue has been re-examined by Silva (10) through the use of immunocytochemical markers which are specific for the various nephron segments. General agreement exists between the two studies with respect to the percentages of proximal and distal cysts.

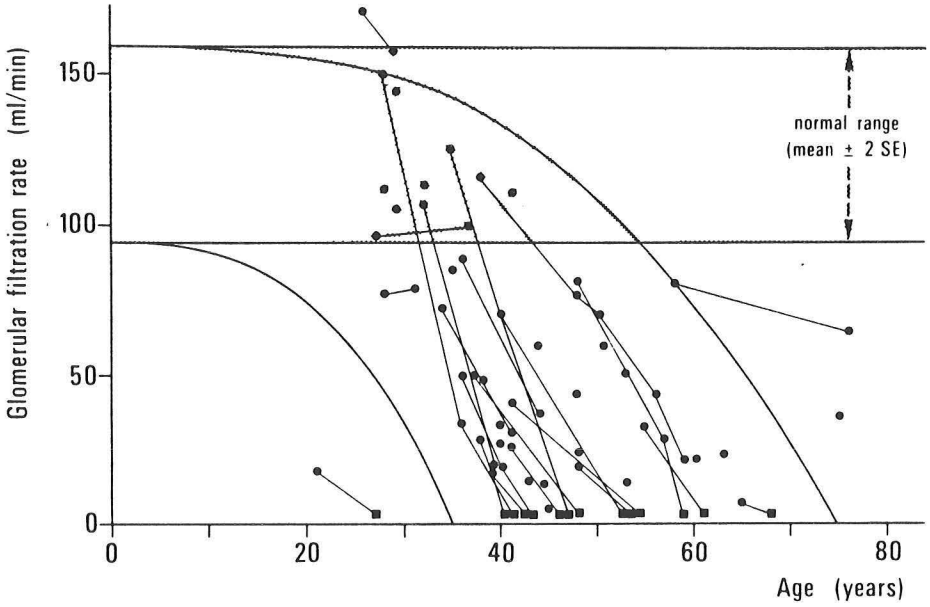
It has been estimated that only 1-2% of all nephrons develop cyst formations (11). The etiology of the development of cysts is ill-understood, reflecting a lack of knowledge of the gene product responsible for the development of ADPKD. Currently, most investigators (3,6) have focused upon a primary defect in the basement membrane of the tubules which accounts for the dilation and cyst formations. In part this is based upon the previous demonstrations that the tubular basement membrane, under normal conditions, limits distension (12) and the fact that only a slight hydrostatic pressure head has been demonstrated in cysts (6). Supportive of this notion is electron micrographic evidence demonstrating expansion and distortion of the basement membrane in kidney tubules from patients with ADPKD (13). At present, the causal relationship between this histologic pattern and the pathogenesis of the disease is not known. In addition, hyperplasia of the epithelial monolayer lining the cysts is evident; however, this is currently discounted as a primary defect.

Attempts have been made to identify environmental factors which might aggravate the underlying genetic predisposition to cyst formation and hence possibly account for the marked variability in the course of the disease. Studies conducted in experimental animals have implicated various toxins and drugs (14-17), and recurrent infections and/or bacterial exposure (18) in provoking an acceleration of cyst formation. The relevance of these observations to the development of cysts in patients with ADPKD, however, is unknown.

Likewise, the probability that a given individual with ADPKD will progress to end stage renal disease has not been determined, although it is clear from recent studies that the prognosis is considerably better than was proposed earlier. It does appear, however, that patients demonstrating a decline in function are predisposed to progress to the point of renal failure (19-20). Shown in Figure 2 are the results of a longitudinal study (19) which indicates that once renal insufficiency ensues, there is a slow progression over a period of about 10 years which ultimately results in uremia.

FIGURE 2

GFR IN RELATION TO AGE IN 38 PATIENTS



The pathogenesis of this progression is not understood; it has been suggested that enlarging cysts compromise functional parenchyma through pressure-induced atrophy (6).

At the present time, there is no medical regimen, other than treatment of hypertension, which is available as therapy. Indeed,

the renal benefit of treatment of hypertension is conjectural and based upon the effects of antihypertensives in the progression of hypertensive nephropathy.

Infections of loculated cysts and the management of urinary tract infection in the patient with ADPKD were discussed previously in this forum (4). The central recommendation that hydrophobic antibiotics such as chloramphenicol be used in refractory cases remains current.

CEREBRAL ANEURYSMS

As shown in Table IV, berry aneurysms have been noted to occur in patients with ADPKD at an incidence ranging from 10-40% (21-22). To date, there has been only one prospective angiographic study of neurologically asymptomatic ADPKD patients and it is perhaps significant that a high incidence of aneurysms (40%) was found in this study, in which 17 individuals from 10 families were noted to have cerebral aneurysms (22). The relationship of the development of cerebral aneurysms to renal tubular cyst formation (and extra-renal manifestations) remains unknown. Proposed mechanisms for the development of aneurysms in patients with ADPKD include loss of, or alteration of, the arterial internal elastic membrane (23). Parallels between the increased incidence of aneurysms in ADPKD and Ehlers-Danlos syndrome and fibromuscular hyperplasia (23) have fostered speculation that a defect in extracellular matrix may result in the development of cerebral aneurysms in patients with

ADPKD (23).

TABLE IV

PREVALENCE OF ANEURYSMS AND SUBARACHNOID HEMORRHAGE IN ADPKD

Author	Total SAH or Aneurysms	Prevalence of Aneurysms or SAH
Suter (1949)	2	2/5
Brown (1951)	8	8/16
Bigelow (1953)	3	3/6
Poutasse (1954)	3	3/3
Melnick (1955)	4	-
Dalgaard (1957)	8	-
Ditlefson (1960)	2	-
Lazarus (1971)	0	0/14
Hatfield (1972)	7	-
TOTAL	37	16/44 (36%)

The clinical approach to ADPKD patients with cerebral aneurysms is in evolution. Most clinical studies indicate that the aneurysms of ADPKD are not different from idiopathic aneurysms with regard to their propensity to result in subarachnoid hemorrhage (21,22,24), as shown in Table IV. Likewise, clinical evidence indicates that treatment of hypertension, which frequently accompanies ADPKD, is beneficial in forestalling catastrophic hemorrhage. There is thus fair agreement that any individual with ADPKD with neurological

signs and/or symptoms should undergo definitive evaluation for the presence of cerebral aneurysms. The central question regarding cerebral aneurysms in this disease is whether neurologically asymptomatic individuals with APDKD should undergo evaluation and repair of aneurysms.

The most quoted study regarding this issue, by Levey, Parker and Kassirer (21), contends that routine screening by cerebral angiography of such individuals with ADPKD is neither clinically justifiable nor cost effective. This study utilized "decision analysis" based upon published data on the prevalence of cerebral aneurysms in patients with ADPKD, the annual rate of aneurysmal rupture, the risk of grave complications of rupture, and the risks of grave complications of angiography and prophylactic surgery, to determine outcome as a function of years of survival. It was concluded that "arteriography should not be carried out routinely because its benefit exceeds one year [gain in survival] only if the presence of aneurysm exceeds 30 percent, if the surgical complication rate is 1% or less, and if the patient is under 25 years of age." In arriving at this conclusion, the authors arbitrarily used 1 year of added survival as a minimum criterion for benefit.

Less quoted is a rebuttal to this paper. Oken (25) noted that the study by Levey, et al (21) used a probability of 37% of grave outcome following rupture of a berry aneurysm, a value derived from a study which did not exclusively assess the probability of grave

outcome from an acute hemorrhage, but rather included some patients who survived to be transferred to a referral hospital (26). In fact, the Mayo Clinic Group, in analyzing all patients from the onset of hemorrhage, found a 58% probability of grave outcome subsequent to a subarachnoid hemorrhage (27). By using this higher mortality rate, Oken concluded that "a patient with polycystic kidney disease may be almost 35 years old and still, on the average, gain a year of survival by choosing arteriography and surgery". In addition, the study by Levey, et al, used a probability of aneurysms in patients with ADPKD of 30%, which is less than the 40% value of the only prospective study relevant to this issue (22). Finally, as Levy, et al noted, their analysis was based upon the use of the cerebral arteriogram as a screening procedure, and explicitly note that "if newer, non-invasive tests, such as digital-subtraction angiography, prove to identify patients who are likely to have a cerebral aneurysm, routine screening with these tests will be warranted in patients with polycystic kidney disease" (21).

Studies now indicate that CT scanning (28) and, perhaps, magnetic resonance imaging (29) provide sufficient resolution to determine whether a patient has a clinically significant aneurysm. In one study, 76 verified cerebral aneurysms were studied with high resolution computed tomography with contrast. Of these, 97.4% were detected, with a lower detection limit of 3mm in aneurysmal diameter.

Consideration of these issues has led to a reassessment of the need to perform screening tests on neurologically asymptomatic patients with ADPKD. Gabow, et al, in conjunction with the Polycystic Kidney Research Foundation, has concluded that it now seems appropriate to screen individuals whose families have a high incidence of berry aneurysms as well as individuals whose activities (piloting airplanes) place them at high risk in the event of a cerebral hemorrhage (3). The former condition is based upon a study (presented in abstract form) indicating that there is variability in the incidence of subarachnoid hemorrhage from kindred to kindred, and that entire kindreds appear to be spared from berry aneurysms, or at least subarachnoid hemorrhages (29). Thus it seems that at present there is emerging agreement that at least a portion of neurologically asymptomatic individuals with ADPKD should be assessed for the presence of berry aneurysms and if clinically appropriate, prophylactic repair should be effected. Is such a conclusion appropriate, or should all theoretical exclusion criteria be dropped, and thus should all clinically operable patients undergo screening and aneurysm repair? In view of (1) the fact that a family history of ADPKD can be elicited in only 50% of clinical cases; (2) the consideration that a family history of subarachnoid hemorrhage is a rather insensitive assay for the presence of berry aneurysms and (3) the demonstration that magnetic resonance imaging and CT scanning are highly sensitive, low risk, means of assessing the presence of aneurysms, my conclusion is that all potentially operative patients with ADPKD should undergo non-invasive screening for the presence of cerebral aneurysms. If

suggestive findings are noted, then arteriography and (if appropriate) repair should follow.

In addition, of course, aggressive treatment of co-existent hypertension is essential, as hypertension clearly increases the chance of a subarachnoid hemorrhage in ADPKD patients with aneurysms.

HYPERTENSION

Hypertension is a common accompaniment of renal insufficiency of any etiology; however, in patients with ADPKD, elevated blood pressure is found in 60% of individuals prior to the onset of significant renal insufficiency, leading to the proposal that the structural abnormalities (i.e. cysts) are somehow relevant to the pathogenesis of hypertension (30). Supportive of this notion is the finding that the degree of structural destruction (prior to significant loss of clearance) roughly correlates with the incidence of high blood pressure. Thus, in patients with ADPKD older than 18 years of age, with serum creatinine concentrations less than 1.5 mg/dl, renal length and volume are greater than in those with hypertension. In addition, renal cysts in such patients are greater in number, and larger in size than in kidneys of patients with ADPKD who do not have hypertension (31). Further evidence for the interplay of the gross architectural distortion found in polycystic kidneys and the pathogenesis of hypertension comes from two studies which demonstrated that direct surgical

excision of cysts, or thin needle aspiration of cysts, resulted in a remission of hypertension in almost all patients so treated (32,33).

Possible etiologies of the hypertension relevant to these findings are (1) increased tortuosity of the renal arteries (34) (possibly mimicking renal artery stenosis) and/or (2) more primary alterations in the renin-angiotensin-aldosterone axis. With respect to the former, however, it has been found that patients with hypertension and ADPKD do not have a hypotensive response to saralasin, as is the case with classic renal artery stenosis (35). In investigation of the later possibility, pathologic examination of polycystic kidneys has revealed that there is frequent hyperplasia of juxta-glomerular apparatus renin-containing cells. Perhaps more importantly, it was found that renin containing cells were abnormally distributed in such patients; instead of predominant localization of renin to the JGA cells, 50% of the renin-containing cells were localized in the walls of small arterioles. The latter finding has led to speculation that these cells may respond to different stimuli than those normally situated, and thus an aberrantly-triggered release of renin might be related to the hypertension found in patients with ADPKD (36). Some functional data tend to support this view. Although no differences were observed in plasma renin or aldosterone levels in ADPKD patients on either high or low salt diets, angiotensin converting enzyme inhibitors result in a greater rise in renin in hypertensive than in non-hypertensive patients with ADPKD (37).

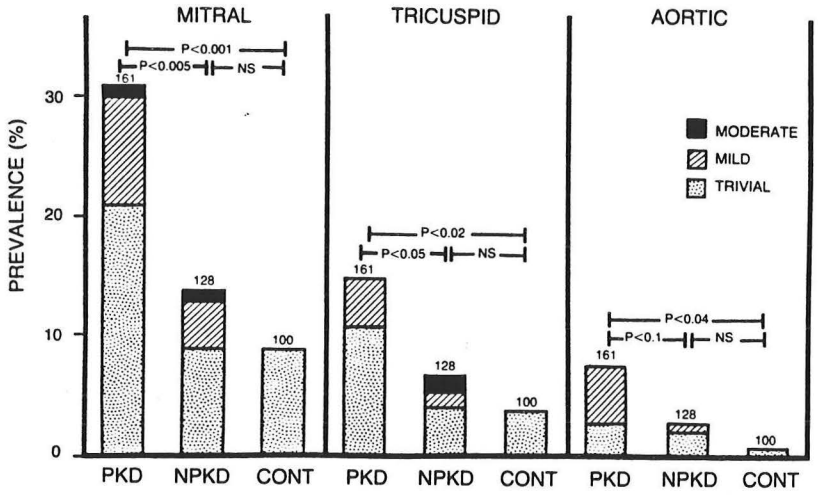
Irrespective of the etiology of hypertension, therapy requires no specialized form in patients with ADPKD, and despite earlier reservations regarding the use of diuretics (6), standard antihypertensive agents have been used successfully to treat the majority of individuals.

CARDIAC MANIFESTATIONS

Although clinically significant cardiac involvement is rarely the dominant management problem in patients with ADPKD, emerging evidence indicates that several valvular disorders occur at a much greater frequency in such patients than the general population. In 1984, it was reported that patients with ADPKD had a greater incidence of systolic ejection murmurs (in the absence of hypertension) than did normal age-matched controls (30). Further definition of this issue emerged through studies in which the nature of the valvular defects in these patients were studied. Echocardiography, including Doppler analysis was performed in 163 patients with ADPKD, 130 unaffected family members and 100 control individuals. It was found that mitral valve prolapse occurred at over 4 times the incidence in normal, control subjects (Figure 3), a finding in accord with the previous finding that patients with ADPKD have an increased incidence of palpitations, atypical chest pain, and auscultatory clicks than normal individuals. In addition to mitral valve purpose, aortic insufficiency and tricuspid valve prolapse occur at a higher frequency in patients with ADPKD (38).

FIGURE 3

PREVALENCE OF REGURGITANT VALVES IN ADPKD



At present, the natural history of these valvular disorders in polycystic kidney disease patients has not been defined, and it is not known whether these patients are at a lower or higher risk for complications and progression of these defects. Prophylactic antibiotic therapy is thus based upon standard criteria. Cost-benefit analysis of routine screening of patients with ADPKD for valvular defects has not been performed. However, as approximately 2/3 of the abnormalities can be detected by physical examination (38), and as cardiac complications by natural history studies have not identified such defects as a major clinical problem, evaluation by echocardiography seems best justified only in patients where symptoms and/or physical findings suggest further evaluation.

Cardiac involvement in ADPKD further underscores the systemic nature of the disease and has served to support speculation that the primary defect in the disease owes to disordered synthesis of extracellular matrix leading to a connective tissue defect, as is

the case with Marfan's syndrome and Ehler-Danlos syndrome which are due to Type III collagen deficiency (39).

HEPATIC/GASTROINTESTINAL INVOLVEMENT

Gastrointestinal complications such as diverticula (40), and more commonly, hepatic and pancreatic cysts (41,42), are not infrequent findings in patients with ADPKD. Complications of the former (diverticular perforation) are occasional (40), whereas hepatic cysts are found in 40-75% of patients (42,43). In several reported cases, massive hepatic involvement emerged as the dominant clinical problem. Spontaneous infections of hepatic (and pancreatic) cysts is an uncommon problem which is generally managed non-invasively with systemic antibiotics. More importantly, massive hepatic cyst formation with gross abdominal distension, early satiety and cachexia can present a most difficult complication (42).

The extent of hepatic cyst development is perhaps the most suggestive example of the interplay of genetic and extragenetic factors in the development of phenotype in ADPKD. It has been found that in general, patients with hepatic cysts are older (Table V) than ADPKD patients without cysts and more informatively, hepatic cysts occur at a greater frequency in women, particularly those under the age of 50 (Table VI). (After the age of 50, the incidence of hepatic cysts occurs at similar rates in men and women). In addition, female ADPKD patients have more cysts than do male patients (42,43). Supportive of the notion that hepatic cyst

TABLE V

AGE AND PREVALENCE OF LIVER CYSTS IN ADPKD

Age (yr)	Patients with PKD: Tested (no)	Liver Cysts: No	Liver Cysts: %
10–19	12	0	0
20–29	47	5	11
30–39	31	10	32
40–49	30	11	37
50–59	25	10	40
>60	13	10	77
10–>60	158	46	29

TABLE VI

PREVALENCE OF LIVER CYSTS: FEMALE VS MALE

Patients	Age (YR)*	LC +	% LC	
Females (n=68)	45.3± 14.3	50	73	} NS
Males (n=52)	44.7± 15.0	23	44	

*Means ± 1 SD.

formation is in part under hormonal control stems from the observation that women with liver cysts had more pregnancies than did women without liver cysts (3). Isolated case reports of extreme hepatic cyst development are largely confined to women who have had multiple pregnancies. In this regard, the trophic effects of estrogens in the development of several proliferative lesions of the liver have been noted previously (43). Thus several lines of evidence suggest that estrogens may play a role in the aggravation of hepatic cyst formation in ADPKD patients who are so predisposed. Issues of genetic counseling aside, ADPKD is not a contraindication to pregnancy and indeed, because of the relatively late onset of significant renal insufficiency, there is little genetic lethality imparted by the responsible gene. Nonetheless, consideration of the potential effect of pregnancy upon patients with pre-existent, significant hepatic involvement should be given in counseling individual patients and it may be advisable to consider performing abdominal ultrasonography in women with ADPKD prior to institution of estrogen therapy in order to establish a baseline against which progression of cyst development can be gauged.

As noted previously, the most difficult management problem in ADPKD patients with hepatic cysts relates to a very small subset of individuals with extensive hepatic involvement. Knowledge of the natural course in these patients is not available and thus it is difficult to formulate firm directives for management. To the extent that liver cyst enlargement is under trophic, hormonal control, long-term, conservative follow of the post menopausal

patient is possible. In several studies of extremely severe liver involvement (and continued progression of cyst formation) radical surgical intervention with debulking of the liver and unroofing and fenestration of large cysts has met with success (42,43). This approach, by its nature, should be a therapy of last resort.

DIAGNOSIS

As noted previously, definitive diagnosis of ADPKD in individuals over the age of 20 with bilateral multicystic kidneys is seldom problematic particularly when these patients are identified on the basis of renal signs and/or symptoms. There is generally agreement that ultrasonography is the initial screening test of choice, although CT scanning affords greater sensitivity and is less user-dependent with respect to the quality of image (3,6). Problems in diagnosing ADPKD, however, arise in two settings: in prenatal diagnosis, and in children, adolescents and young adults, who are undergoing evaluation because of a positive family history for ADPDK.

The wide variability in the age at which renal cysts become detectable by ultrasonography has been defined by several studies (44,45). ADPKD has been diagnosed both *in utero* and in neonates by sonography, where the most common findings were renal enlargement (85%) and/or renal cysts (50%). In 13 individuals so diagnosed, all were prospectively (5/13) or retrospectively (8/31) found to

have affected family members. Diagnosis by ultrasonography in this age group is in fact felt to be dependent upon corroborative demonstration of an affected kindred because a number of disorders have similar ultrasonographic findings; these include: ADPKD, autosomal recessive PKD, trisomy syndromes, Sturge-Weber Syndrome, Zellweger Syndrome, Lawrence-Moon-Biedl Syndrome, tuberous sclerosis and Jeunes Syndrome. Lastly, it should be noted that it is extremely difficult to diagnose ADPKD in vitro before the third trimester, which greatly complicates the issue of therapeutic abortion (45).

Bear, et al (44), evaluated ultrasonography as a diagnostic test for detection of ADPKD in all age groups. Although the differential diagnosis of cystic kidneys becomes more limited in later childhood and adolescence than with neonates, the variability in development of ultrasonographically-detectable cysts becomes limiting. As shown in Figure 4, ultrasonography is a more sensitive test than clinical signs and symptoms in detecting ADPKD in patients at 50% risk of developing the disease. However, before age 30-40, significant numbers of individuals carrying the gene for ADPKD cannot be detected by either means. This assumes great importance in genetic counseling in that a sizable portion of individuals who carry the gene for ADPKD cannot be identified during peak reproductive years.

Lastly, is should be noted that the differential diagnosis of ADPKD versus acquired cystic disease of dialysis is seldom problematic.

FIGURE 4

SENSITIVITY OF ULTASONOGRAPHY AND CLINICAL EVALUATION IN DETECTION OF RENAL CYSTS

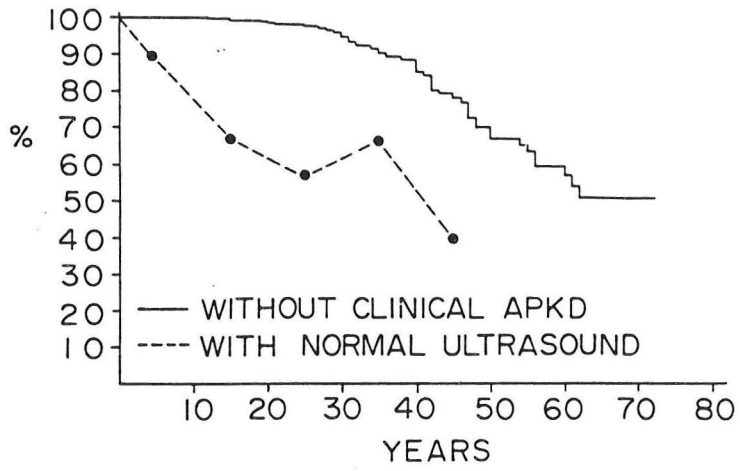


Fig. 1. Survival curves showing the probability of not having clinically apparent APKD with increasing age (—) and the probability of not having ultrasonographically detectable APKD with increasing age (---) among all those at risk of APKD by virtue of having an affected first degree relative. The expected probability of being affected is 0.50.

The former, if progression has ensued to the point of end-stage renal disease, is characterized by large (800g average) polycystic kidneys whereas the latter results in small (200g average) shrunken, polycystic kidneys. Moreover, extra-renal involvement with cysts is absent in acquired polycystic disease (6).

GENETICS

ADPKD, as the name implies, follows a classic Mendelian autosomal dominant inheritance pattern. The disease is characterized by considerable variability in the age of presentation and extent of disease development, but the gene is completely penetrant. It has been estimated that 100 % of individuals carrying the gene for ADPKD will manifest some aspect of the disease (typically renal cysts) by the age of 80 (1). The vast majority of clinically

apparent cases of ADPKD are the result of inheritance of the mutant gene(s); the spontaneous mutation rate has been estimated to be $6.5\text{-}12X10^{-5}$. However, a positive family history is found in only about 50% of cases of ADPKD, owing in part to the extreme variability in the age of onset of clinically apparent disease and the marked spectrum of the severity of the disease (3).

At the present time, the gene(s) responsible for the development of ADPKD has not been identified, and there is no convincing insight from a biochemical standpoint as to the nature of the gene product responsible for the syndrome. However, the gene locus which accounts for the majority of cases of ADPKD has been mapped (46,47) and this bears the greatest promise for provision of a definitive screening test, as well as identification of the molecular basis of the disease process itself.

In 1985, Reeders, et al (46) succeeded in identifying a linkage marker for ADPCK in studies conducted in 9 kindreds from the United Kingdom and the Netherlands. In these studies, it was determined that the ADPKD locus was closely linked to the alpha globin gene cluster of the short arm of human chromosome number 16. The utility of this marker for diagnosis of ADPKD was somewhat diminished by the fact that restriction fragment length polymorphism (RFLP) analysis of kindreds allowed for only 96% accuracy in determining whether a given individual within an affected family would carry the mutant gene. Further resolution derived from the subsequent definition of a second flanking DNA

marker. In 1987, Breuning, et al (47), determined that an additional polymorphic DNA marker, 24-1, was flanking to the ADPKD locus on the side opposite to the alpha globin locus on the short area of choromosome 16. Coincidentally, this marker mapped to a distance from the ADPKD which was nearly equal to that of the distance of the α globin locus from the mutant gene; thus this second marker also allowed for RFLP analysis of kindreds with a 96% accuracy in predicting whether a given individual carries the gene for ADPKD (48). Importantly, combined use of the two markers allows for a predictive accuracy of 99.84%, a figure well within acceptance range for pre and ante natal diagnosis upon which intervention measures might be based. It of course should be noted that, by nature of RFLP analysis, there is no universal probe which can be utilized to screen any given individual. Rather, the analysis must be performed within the context of a given kindred, requiring that DNA from a number of family members be analyzed. Consequently, this test is not generally available and RFLP analysis for the ADPKD gene of chromosome 16 can be obtained at present only by personal arrangement within Reeders.

The utility of these flanking markers in predicting whether a given individual carries the ADPKD gene is in part dependent upon the demonstration that the mutant gene is linked to the α globin and 24-1 loci in all kindreds. This has been found to be the general case (49). But, it is important to note that at least 3 exceptions have, to date, been identified in which an ADPKD gene is <u>not</u> linked to these markers (50,51). Three kindreds from Sicily, Italy and

Denmark have been identified in which it has been clearly shown that the gene locus for ADPKD does not map to the short arm chromosome 16. In all of these instances, the clinical manifestations of the affected individuals were indistinguishable from those in which the gene was localized to chromosome 16, proving that ADPKD is truly a genetically heterogeneous disease and implying that two different gene products can result in the same phenotype.

Although only limited data are available regarding the relative prevalence of the two genetic forms, at present it appears that the form localized to chromosome 16 is more common. The locus for the second genetic form of ADPKD has not been defined, and DNA markers flanking to this second locus are not available. As a result, not all kindreds can be successfully analyzed to determine whether a given individual carries a gene for ADPKD.

CONCLUSION

Autosomal dominant polycystic kidney disease, characterized genetically by high penetrance and variable expressivity, is a heterogeneous disease involving multiple systems. At present it is not known whether the variability in expression is related to multiple genetic forms of the disorder, and the gene product(s) responsible for ADPKD has not been identified. A direct genetic approach holds the greatest promise of resolving both of these

issues, as well as for the development of a widely available screening tests which should prove useful for genetic counseling and disease diagnosis.

A growing appreciation of the multisystemic nature of ADPKD indicates that the physician's approach to affected individuals should involve evaluations of the possibility of cardiac valvular defects, extent of liver involvement prior to institution of estrogen therapy and/or pregnancy and most importantly, screening for operable cerebral aneurysms. The mainstay of therapy remains aggressive treatment of hypertension.

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