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Invited review

Polycystic kidney disease – a truly pediatric problem

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Abstract. Polycystic kidney disease (PKD) represents the most common inherited cause of chronic renal failure. PKD is a relatively uncommon cause of chronic renal failure or mortality in childhood and adolescence, but is nevertheless often responsible for symptoms of renal disease. Current research into the pathogenesis of PKD suggests that disturbance of the normal regulation of growth and development of tubular epithelium is intrinsic to cyst formation and growth. Features of cystic epithelium that are analogous to earlier stages of renal development include altered composition of the extracellular matrix, abnormal cell proliferation, and the persistence of a secretory pattern of fluid and electrolyte transport. The potential for early diagnosis and intervention in PKD makes it an area of great interest to the pediatric nephrologist. Animal and in vitro studies have achieved modification of cyst growth by reduction of dietary protein, use of amiloride and its analogs, antagonism of the epidermal growth factor receptor system, anti-inflammatory therapy, and most recently with the use of taxol, an agent that inhibits microtubule assembly. PKD may represent an area in which childhood diagnosis and intervention will have a significant impact on the prevalence of chronic renal failure in adult life.

Key words: Autosomal dominant polycystic kidney disease – Autosomal recessive polycystic kidney disease

Introduction

Polycystic kidney disease (PKD) is an important cause of chronic renal failure in the adult patient community, with treatment of PKD costing U. S. $750,000,000 in the United States [1]. The impact of PKD in the adult tends to overshadow the importance of PKD as a cause of morbidity in children. This review will focus upon three concepts: that PKD is often symptomatic in childhood, that PKD represents disordered renal development, and that the clinical course of PKD may be ameliorated by early diagnosis and intervention. Consideration will be limited to the entities commonly referred to as infantile or autosomal recessive PKD (ARPKD) and dominant or adult-type PKD (ADPKD). Acquired cystic disease that may develop in kidneys of patients with chronic renal failure due to any cause may be considered polycystic, but the small published experience of this condition in children makes meaningful review difficult.

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PKD: a symptomatic disorder in childhood

In ARPKD, fusiform dilatation of the collecting ducts is invariably associated with abnormal proliferation of the bile ducts and hepatic fibrosis that is distributed in a "bridging" pattern between portal triads [2]. Associated oligohydramnios and pulmonary hypoplasia is commonly lethal in the perinatal period. Inheritance is autosomal recessive with prevalence reported between 1:6,000 and 1:40,000. Gene frequency is thus in a range from 1:40 to 1:100. Although perinatal death is common, a significant number of patients may survive into childhood. Kaplan et al. [3] reported a survival rate of 86% at 3 months of age, which declined to 46% by 15 years of age, in a review of 55 cases collected over 34 years. Blyth and Ockenden [4] noted an inverse relationship between the extent of cystic change in the kidneys and the rate of decline in renal function, which led them to propose four distinct alleles for ARPKD. A number of case reports have described significant variation in expression within a single kindred that has refuted this concept [5, 6]. Children with ARPKD usually have systemic hypertension and develop signs of portal hypertension in adolescence or early adult life, with hypersplenism and increased risk of gastrointestinal hemorrhage from esophageal varices.

In ADPKD, renal architecture is distorted by multiple cysts whose number and size increase with increasing age.

Cysts may be seen in the liver, pancreas, and other organs. Approximately 10% of patients develop berry aneurysms of the cerebral circulation [7]. The condition is inherited as an autosomal dominant with new mutations being relatively common. The gene frequency for ADPKD is approximately 1:400 individuals in a population of European extraction. Expression is highly variable, however, and approximately half of carriers may remain asymptomatic. ADPKD is an uncommon cause of renal failure in childhood, but is often symptomatic. Sedman et al. [8] prospectively studied 154 children under 18 years of age who were at risk for ADPKD by means of an affected parent or sibling. Using ultrasound they identified 23 patients using a diagnostic criteria of five or more cysts, 3 of whom progressed to renal failure. Twenty-eight children were considered suspect for ADPKD with fewer than five cysts or an inhomogeneous renal echo pattern, suggestive of small cysts. The ADPKD children had a significantly higher prevalence of gross hematuria, hypertension, palpable abdominal mass, and hernia, with 74% reporting renal symptoms compared with only 34% of unaffected children. Milutinovic et al. [9] reported the detection of liver cysts at 8 months of age and pancreatic cysts by 16 years of age in a child with ADPKD. Fick et al. [10] found that 2 of 11 children who were diagnosed in utero or in the 1st year of life by ultrasound progressed to renal failure in childhood. Zeier et al. [11] were unable to document an increased risk of hypertension in 12 children with ADPKD and normal renal function, although they did note slightly greater left ventricular mass. Twelve patients between 15 and 25 years of age, however, did demonstrate both a significant increase in blood pressure and the development of left ventricular hypertrophy.

Both ADPKD and ARPKD may thus produce end-stage renal disease, hypertension, and renal masses in childhood. As a consequence clinical findings in the absence of a clear family history may therefore be unreliable in distinguishing between the two. Unfortunately, there are also pitfalls in using imaging or laboratory parameters to establish a diagnosis of a specific type of PKD. In younger patients, ultrasound, now the main technique used for the study of renal cystic diseases, may show enlarged hyperechoic kidneys in both forms of the disease [12]. Conversely macroscopic cysts may be detected in older patients with ARPKD. The dilatation of collecting ducts is a relatively constant feature of ARPKD histology; however, significant involvement of the collecting ducts may also be seen in patients with ADPKD [2, 3]. ADPKD may feature the early development of glomerular cysts, but this feature is not specific to ADPKD, and may be seen as a sporadic phenomenon or in association with a number of other inherited diseases [13].

The use of liver biopsy has been proposed as a means of distinguishing between ADPKD and ARPKD [2]. Although a diagnosis of ARPKD can not be supported in the presence of normal liver histology, the presence of hepatic fibrosis does not exclude a diagnosis of ADPKD. Congenital hepatic fibrosis has occurred in association with ADPKD that has been confirmed by imaging studies, histology, and linkage to the PKD-1 gene locus on the short arm of chromosome 16 [14, 15].

Perhaps the single most useful investigation in the evaluation of a child with early onset of cystic renal disease is ultrasound of the parents. Bear et al. [16] reported a false-negative rate of detection of ADPKD of zero in patients greater than 20 years of age. Thus, a negative ultrasound of both parents reduces the probability of a diagnosis of ADPKD to the level of a spontaneous mutation. Genetic linkage studies may be of some value in establishing a diagnosis of ADPKD, but their use is limited to the context of determining carriage of the gene in an individual who is a member of a pedigree in which ADPKD is known to occur, and in which linkage markers segregate in an informative pattern [17].

PKD as a disorder of renal development

In all types of cystic disease, the enlargement of the cyst wall is associated with hyperplasia of renal epithelium [18]. Cystic epithelia in the cpk mouse abnormally express proto-oncogenes, normally down-regulated after early development of the kidney [19–21]. A transgenic mouse that overexpresses the c-*myc* proto-oncogene spontaneously develops PKD [22]. Cysts will continue to enlarge after the loss of connection to a functioning glomerulus, implying net fluid secretion across the cystic epithelium [1]. As neither proliferation, proto-oncogene expression, nor net fluid secretion are functions of mature tubules, the occurrence of these changes implies the presence of a less-differentiated state of epithelium. Rankin et al. [20] have proposed a "maturational arrest" model of PKD. Congenital or early-onset forms of PKD may represent a failure of the epithelium to achieve a terminally differentiated state, whereas diseases associated with cyst formation in a previously mature and functional kidney are associated with a loss of terminal differentiation. Cystic epithelia tend to be simpler in ultrastructural detail than their mature counterparts, consistent with this hypothesis [23]. Genes such as Exo-1 and SGP-2 (clusterin), whose expression is normally a feature of immature epithelium, are expressed in a persistent fashion in cystic epithelia [24, 25].

Development and maturation of the kidney is associated with synthesis and incorporation of an increasing amount of heparan sulfate proteoglycan (HPSG) into the tubular basement membranes [26]. There, however, is a significant decrease, due to reduced HPSG synthesis, in the incorporation of radiolabelled sulfate into extracellular matrix secreted by epithelia from ADPKD kidneys in vitro [27]. In a different culture system, however, Wilson et al. [28] demonstrated an increased uptake of radiolabelled sulfate into a structurally very abnormal membrane, which took the form of proteinaceous spheroids rather than a laminated membrane. Both groups propose that disturbed epithelial-extracellular matrix interaction may influence the abnormal epithelial proliferation.

Epithelial proliferation may be mediated by autocrine or paracrine action of peptide growth factors. Epidermal growth factor (EGF) or transforming growth factor-α (TGF-α), which compete for the same tyrosine kinase-dependent receptor, may induce cysts in vitro [29]. EGF-like activity has been isolated from human and murine cyst

fluids [30, 31]. Epithelia cultured from ADPKD kidneys have shown enhanced or normal response to mitogens such as EGF in different culture systems [32, 33]. Abnormal localization of the EGF receptor to the apical surface of cystic epithelia has been identified in murine and in vitro preparations of human PKD [34, 35]. Conversely, Gattone et al. [36] have demonstrated decreased expression of EGF in the cpk mouse model of PKD, and they propose that EGF action is necessary to maintain the terminally differentiated state. We have found that cyst induction in newborn mice by glucocorticoids was associated with increased expression of the fetal renal mitogen TGF-α, but not EGF [37]. Two recent studies in the cpk mouse [38], a model of early-onset recessive PKD, and the Hans:SPRD-cy rat [39], a model of ADPKD, have indicated abnormal metabolism of EGF pro-hormones, producing a different spectrum of biologically active metabolites in the urine of animals with cystic disease. This may reconcile some of the contradictory findings on EGF action in cystic disease. Another growth co-factor implicated in cystic disease is angiotensin-II. Increased activity of the renin-angiotensin system has been documented in human ADPKD [40]. Enhanced expression of renin occurs in cystic epithelia [41]. Angiotensin is a potent potentiator of the action of other mitogens, such as EGF, in the kidney [42]. Angiotensin converting enzyme inhibition has been shown to be effective in the treatment of hypertension in ADPKD, although it may precipitate renal failure in advanced cases [43, 44].

The accumulation of fluid in cystic spaces remains an area of controversy between studies that support sodium-dependent transport from mislocated Na, K-ATPase and those that suggest cyclic AMP-dependent chloride transport may be the dominant process. Apical mislocation of the ubiquitous transport enzyme Na, K-ATPase has been demonstrated in most animal models of PKD [45–47]. Wilson et al. [48] have demonstrated apparent Na, K-ATPase-dependent secretion from the apical surface of cystic epithelia by functional but mislocated Na, K-ATPase. In a series of studies in a model of cyst formation produced by culturing MDCK cells in a collagen gel, transport that could be stimulated by arginine vasopressin and other means of increasing intracellular cyclic AMP was generated [1]. Ye and Grantham [49] recently used a similar system to study individual cysts dissected from ADPKD kidneys. They found that cysts that were allowed to retain the fluid present at their removal continued to secrete fluid in vitro. If this fluid was removed, treatment with forskolin, an agent that increases intracellular cyclic AMP, would also stimulate fluid secretion. Recent studies have demonstrated a potential role for the cyclic AMP-dependent cystic fibrosis transmembrane conductance regulator, a chloride channel, in fluid secretion in cystic epithelia from cpk mice [50]. This is normally expressed on the apical surface of proximal tubular cells and basolateral surface of collecting duct cells, but some cysts of collecting duct origin showed apical expression. It remains to be determined if this is specific to cystic epithelia, represents reversion to a less-differentiated state, or is an epiphenomenon of the disturbed polarity of other membrane proteins seen in this model.

PKD: a potentially treatable disorder

Complementing conventional imaging techniques with genetic linkage studies for ADPKD genes may permit identification of the majority of carriers prior to symptom development. This is of limited value unless reproductive counselling or specific treatment can be offered. One study has indicated that genetic counselling in ADPKD has only a slight impact upon reproductive decisions [51].

As yet, there is no specific therapy that is known to ameliorate the progression of PKD in man. Nevertheless, Roscoe et al. [52] have recently noted that the average survival and age of onset of end-stage renal disease in patients with PKD in Toronto is increasing. This may reflect improving general care of patients with renal disease, the impact of an unrecognized beneficial therapy, or perhaps the application of more liberal inclusion criteria for end-stage renal failure programs.

Animal studies have provided some tantalizing evidence that cyst formation may be subject to modification by external forces. Modification of dietary protein has been beneficial in at least two animal models of PKD. In the pcy mouse model of recessive, adult-onset PKD, reduction in dietary protein was associated with a dramatic decrease in the rate of cyst progression and marked improvement in animal survival [53]. A more modest benefit has been demonstrated in the Hans:SPRD-cy rat [54]. The mechanism by which this benefit occurs is not known, but dietary protein modification influences most pathways implicated in renal growth regulation.

Reduced hyperplasia of cystic epithelia in vitro has been achieved with the use of tyrosine kinase inhibitors that block transduction of EGF- or TGF-α-mediated cell growth signals [55]. Woo et al. [56] have recently successfully reduced the rate of cystic change and dramatically increased survival in homozygous cpk mice with taxol, which inhibits microtubule assembly, an integral part of cell division. It proved far more effective at reducing cystic change than other antimitotic drugs. Treated animals, however, showed significant inhibition of somatic growth. The modification of solute transport by amiloride and its analogs or by loop diuretics has reduced cyst expansion in the in vitro MDCK model [57]. Such therapy has not yet been shown beneficial to human or animal in vivo studies.

Cystic change is invariably associated with variable degrees of inflammatory infiltrate, the basis for which is not understood. Pro-inflammatory cytokines have been identified in ADPKD cyst fluid [58]. Bacterial endotoxin is a potent co-factor in cyst induction in nor-dihydroguaretic acid-induced PKD in the rat [59]. Decreased ammonia trapping in the medulla has been proposed to contribute to inflammation and fibrosis in PKD [60]. In the Hans:SPRD-cy rat, treatment with an anti-inflammatory dose of methylprednisolone was associated with a marked reduction in cystic change, implying the inflammatory response may play a role in mediating cyst formation [61].

With the concerted efforts currently being made to map PKD genes, the potential for genetic manipulation must be considered. The most common PKD gene, designated PKD-1, is found on chromosome 16 [17]. The serendipitous occurrence of a translocation in the region 16p13.3 that was

associated with an ADPKD phenotype in two members of a Portuguese family has recently permitted precise localization of the PKD-1 gene by the European Polycystic Kidney Disease Consortium [62]. The translocation breakpoint was contained within a 14-kilobase region which was subsequently found to be the site of different mutations, all of which were deletions, in at least three ADPKD kindreds. The exact extent of the gene is yet to be determined, and the incomplete sequence available at present has not provided any insights into the function of the ADPKD gene product.

Genetic study of PKD is confounded by the existence of at least one other locus that produces a PKD phenotype. A locus has recently been identified on chromosome 4 that segregates with PKD in a number of families that do not demonstrate linkage to the locus on chromosome 16 [63]. The locus for ARPKD has apparently been identified, but this information is being withheld pending peer review publication (L. Guay-Woodford, personal communication). Should these genes be precisely mapped, identification of the gene product may accelerate efforts to identify a critical pathway. The potential for direct genetic modification will rest upon the ability to introduce corrective genes into the cell, which is proving a difficult challenge even in far more accessible tissues, such as the lung and the hematopoietic system.

Another justification for vigorously attempting to identify individuals with PKD would be the treatment of preventable non-renal complications. The occurrence of ruptured cerebral aneurysm is perhaps the most catastrophic of these. Risk factors for this complication are incompletely determined, although there is some suggestion that certain pedigrees may be more prone to aneurysm than others [64]. One of the difficulties with this particular complication has been that detection rests upon a highly invasive angiographic procedure. Recent studies have shown that magnetic resonance imaging may prove a sensitive and specific tool for identifying early stages of these aneurysms [65].

Conclusion

The current gap between our ability to diagnose PKD and our ability to treat these conditions creates serious philosophical dilemmas for both families that carry these genotypes and physicians who care for them. Because of rapid developments both in the area of early diagnosis and preventable complication, and possible therapies that ameliorate cyst formation, this author feels that it is generally advantageous that patients have the best possible information about their individual risk of PKD. The argument that identification of pre-symptomatic cases may prejudice individuals with respect to career choice and insurability holds little credence. In fact, the converse argument can be made that aggressive use of imaging and molecular biological techniques to exclude carriage of PKD may be advantageous to an individual.

The need for involvement of pediatric nephrologists in PKD programs is a reflection of the politics and economics of health care. Pediatric nephrologists, like all pediatricians, are in the best position in the health care system to practice preventative medicine relevant to their specialty. Reduction or delay of renal failure in the adult population is an excellent justification for strong pediatric nephrology programs. PKD may represent an excellent opportunity to achieve such a goal.

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Literature abstracts

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A monoclonal antibody marker for Alport syndrome identifies the Alport antigen as the α5 chain of type IV collagen

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The nephropathy of Alport syndrome is associated with unique abnormalities of glomerular basement membranes and is caused in many families by mutations in the X-chromosomal gene COL4A5, which encodes the α5 chain of type IV collagen. We have previously reported that Alport epidermal and glomerular basement membranes fail to bind a monoclonal antibody, Mab A7, that reacts with normal epidermal and glomerular basement membranes, and that this abnormality is unique to Alport syndrome. The molecule in normal tissues that reacts with Mab A7 was termed the "Alport antigen." In the present study we used recombinant carboxyterminal noncollagenous (NCl) domains of the α1, α2, α3, α4 and α5 chains of type IV collagen to determine the molecular identity of the Alport antigen. Mab A7 was found to bind specifically to the NCI domain of the α5 chain of type IV collagen, by ELISA and immunoblotting studies. This finding provides a molecular explanation for the utility of Mab A7 as a marker for the Alport basement membrane defect. Mab A7 can identify the Alport basement membrane defect in those patients in whom COL4A5 mutations prevent incorporation of α5 (IV) into basement membranes.

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COL4A5 gene deletion and production of post-transplant anti-α3 (IV) collagen alloantibodies in Alport syndrome

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Mutations in the COL4A5 gene encoding the α5(IV) chain of type IV collagen have been implicated as the primary defect in X-linked Alport syndrome. Several kinds of mutations have been reported so far, spanning point mutations to complete gene deletions. About 5% of Alport patients, who undergo renal transplantation, develop anti-glomerular basement membrane (GM) nephritis, causing loss of allograft function. In one such patient, COL4A5 gene deletion was recently identified. In the present study, the GBM constituent, targeted by the anti-GBM alloantibodies from the patient who had complete COL4A5 gene deletion was identified. Its identity was determined on the basis of circulating antibody binding to various GBM constituents, domains of bovine type IV collagen and recombinant NCl domain of human type IV collagen. These results establish, for the first time, the absence of the α5(IV) chain in Alport GBM and, in the same patient, the production of an alloantibody that is targeted to a different chain of type IV collagen, the α3(IV) chain. These findings provide further support for the hypothesis that: (1) anti-α3(IV) collagen alloantibodies mediate the allograft glomerulonephritis: and (2) COL4A5 gene mutations cause defective assembly of the α3(IV) chain in Alport GBM, as reflected by the production of anti-α3(IV) alloantibodies.