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3-1-2010

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Recommended Citation

Yee J. Autosomal Dominant Polycystic Disease: More Than Just Empty Space. *Advances in Chronic Kidney Disease* 2010; 17(2):113-114.

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Autosomal Dominant Polycystic Disease: More Than Just Empty Space

In this issue of *Advances in Chronic Kidney Disease*, we focus on autosomal dominant polycystic kidney disease (ADPKD), the foremost heritable form of kidney failure that eventuates in ESRD and a disorder marked by cysts that are generally “empty” by ultrasonography. Treating ADPKD has always been difficult because sufficient quantitative methods to extrapolate disease prognosis were wanting. Phenotypic variability and the imprecision with which one could predict the onset of ESRD frustrated the clinician. Meanwhile, scientific inquiry into the pathogenesis of ADPKD continued and has recently produced a story that has plausibly reconciled some of the clinical conundra.

ADPKD is caused by dominant genetic transmission of either of 2 defective genes, *PKD1* or *PKD2*. Generally, *PKD1*-responsible disease is more severe than *PKD2*-associated disease; however, there is much phenotypic heterogeneity. In this regard, unusually mild cases of ADPKD may be attributed to the transmission of so-called “hypomorphic” alleles (ie, those that have retained partial activity).

Cystogenesis proceeds consequent to damage of the “good” unaffected copy of the affected gene. Thus, at the genetic locus, the disorder behaves as a recessive disorder consequent to somatic mutation. This “second hit” hypothesis recapitulates the original multimutation conceptualization of cancer generation by Nordling¹ and its subsequent expansion and popularization by Knudson in his work regarding oncogenic transformation in retinoblastoma².

Defects of the polycystin-1 and polycystin-2 gene products of, respectively, ADPKD1 and ADPKD2, both of which localize to the cilium, disrupt normal cation-signaling pathways of the cell. Hence, cyst formation is initiated with inexorable enlargement, but the type 2 genotype generally manifests itself as a less severe phenotype. Indeed, the results from the Consortium of Radiological Imaging Study of ADPKD trial inform us that the larger the cyst mass or renal volume, the worse the prognosis, irrespective of whether the cysts derive from a ADPKD1 or ADPKD2 gene defect, the latter of which showed lesser total and kidney cyst volumes in comparison with their ADPKD1 counterparts. In addition, it is the amount of empty cyst space indicative of the absence of functional renal parenchymal mass that correlates best with prognosis.

ADPKD has induced as much uncertainty and ambiguity of practice than nearly any other kidney disorder. Obfuscation by the presence of 2 genotypes has been profound in terms of capably communicating with afflicted persons their future relationship between ADPKD and progressive CKD. The questions that have been repeatedly brought forth for the past several decades include the following.

1. Screening: Who has the disease and who should be screened within a family?

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1548-5595/10/1702-0001\$36.00/0

doi:10.1053/j.ackd.2009.12.003

What are the most cost-effective screening tests? Should patients be screened for concurrent liver disease, cardiac valvular anomalies, or intracranial aneurysms?

2. Symptoms: Is the back pain from ADPKD? Should a headache in an ADPKD patient immediately prompt suspicion for an intracranial aneurysm? Is bloody urine attributable to cyst rupture and hemorrhage, a urinary tract infection, or a neoplasm? How and when should one limit one's activity profile?
3. Prognostic factors: What influences the worsening of disease? Is the serum creatinine, the blood pressure, or the protein most important? If kidney failure occurs, is the prognosis different in the ADPKD patient?
4. Management: Should intractable pain from enlarging cysts be treated with narcotics? What is the best antibiotic for urinary tract infections in ADPKD? Is the anemia of CKD the same in ADPKD as it is in most other types of CKD? Are radiocontrast procedures or gadolinium-based magnetic resonance imaging studies advisable for more detailed evaluation? Are there evidence-based methods to retard the progression of CKD in ADPKD patients? Is there a more optimal menu of therapeutic agents for ADPKD? Is peritoneal dialysis strictly forbidden?
5. Clinical trials: What investigations are ongoing, and what are the preliminary

results? Are there practical and clinical extensibilities of any of the trials to date?

To resolve these issues, the Guest Editors have compiled a tight package of manuscripts that resolves in part many of the vexing questions that have plagued basic scientists and clinical nephrologists who have investigated and/or treated ADPKD. The materials presented within this brief compendium serve as guideposts for the practitioner who consults upon and manages patients with ADPKD.

To summarize, the cysts of ADPKD are not emblematic of nothingness, but they are dynamic and proliferative structures that we must contend with. They represent much more than just empty space. Perhaps now, given the emergence of salutary therapies, guided by current explorations into the pathobiology of cysts and the results of clinical trials, we can, for the first time, offer a more palatable menu of therapies for ADPKD patients that differs from the expectant strategy to which we had heretofore become accustomed.

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Editor

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