Polycystic Kidney Disease: Genes, Therapy and a New HBO Hypothesis

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“*The Task of Medicine: Cure Sometimes, Relieve Often, Care Always*”
- Ambroise Pare

**BACKGROUND**
Polycystic Kidney Disease (PCKD) is the most frequent inherited renal cystic disease around the world. PCKD affects 600,000 in the United States and 12.5 million people worldwide. PCKD is a very complex group of disorders characterized by the formation and growth of multiple renal cysts, containing urine-like fluid, which displace renal tubules and frequently leads to end stage renal disease (ESRD). PCKD has two major forms and can be transmitted as autosomal dominant or recessive traits with variable penetrance and expression.  

Major advances have been done towards our understanding of the natural history, PCKD genetics, embryonic and cystogenesis, PCKD genes and proteins, intracellular signaling pathways and biomarkers. At the molecular, cellular and clinical level PCKD is associated with calcium dysregulation, cyclic AMP accumulation, hypoxia, apoptosis, local fluid secretion, impaired transcription and cell-cell/matrix adhesion, increased proliferation, inflammation, impaired circulation, dedifferentiation, disordered cell division, circulatory abnormalities, cyst growth, fibrosis, vascular remodeling, ischemia, activation of the renin angiotensin aldosterone system, hypertension, renal dysfunction and ultimately ESRD.

**INCIDENCE, GENES, POLYCYSTINS AND MUTATIONS**
Autosomal Dominant Polycystic Kidney Disease (ADPKD) occurs with an incidence of 1:1000. ADPKD is typically found in patients 30 to 50 years of age. ADPKD is a systemic disorder that may be associated with cysts in liver, pancreas, spleen, arachnoid membranes; intracranial aneurysms, intestinal diverticuli, cardiac hypertrophy and mitral valve prolapse abnormalities. About 80-85% of ADPKD are caused by mutation in the PKD1 gene, located in the short arm of chromosome 16, which encodes for polycystin-1 (PC-1), a large transmembrane protein that weights 460 kD with 11 transmembrane domains. It is organized into 46 exons encoding a 14kb mRNA. About 333 different PKD1 mutations have been reported. The remaining 10-15% of ADPKD cases are caused by PKD2 gene, located in chromosome 4q21, which encodes for polycystin-2 (PC-2), a protein of 110 kD with six transmembrane domains and 95 different mutations. A third gene may exist and has been noted in certain families that have no linkage to PKD1 or PKD2. Approximately 10-20% of patients do not have a positive family history. Polycystins play a critical role in the function of the primary cilium and in tubular and vascular development. PC-1 functions as a membrane receptor, capable of binding and interacting with many proteins, carbohydrates and lipids; PC-2 act as a calcium permeable channel, which functions at multiple subcellular locations.

Autosomal recessive polycystic kidney disease (ARPKD) is less common and has an incidence of 1 in 20,000 live births. It is caused by mutations of the PKHD1 gene. It typically begins in utero and is expressed at birth. Affected newborns present with a small amount of amniotic fluid, Potter facial phenotype (premature appearance with a large epicantalic fold). It is characterized by pulmonary maldevelopment, cystic kidneys, congenital hepatic fibrosis, portal hypertension and biliary dysgenesis. It has a high mortality, about 30%, in the neonatal period.

**PROGRESS ON THE STUDY AND TREATMENT OF APCKD**
Major advances have been achieved over the past decades in the study of PCKD. However, the fact is that PCKD remains a serious and progressive renal health problem worldwide. In the US alone it is estimated that about 600,000 people has PCKD, many of them are undetected. The prevalence is 1 case in every 500 people. APCKD accounts for 5% of the ESRD populations in the United States. The PCKD foundation estimates that about 1 billion dollar is spent yearly in the care of PCKD patients.

One hundred seventy three years ago, Rayer stated in his French Atlas of the Diseases of the Kidneys: “the cystic degeneration of the kidneys, once it reaches the point where it can be recognized or suspected during life, is an illness without cure.” His comments remain as pertinent now as then. At present there is no definitive treatment available that prevents or slows down PCKD.

A recent 2014 data analysis of 20,596 patients with Adult Polycystic Kidney Disease (APCKD) from the ERA-EDTA

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Registry by Spithoven et al concluded that no effective renoprotective therapies for APCKD have emerged between 1991 to 2010. My nephrological experience over the past 30 years here in El Paso endorse their contention.

MARKERS OF DISEASE PROGRESSION AND THERAPEUTICS
The kidneys in PKD patients may range from normal (240 to 340 grams) to weighing more than 4000 grams or a volume from 300-400 in healthy controls to more than 1500 in APCKD as measured in MRI. Recently, kidney volume has been proposed and used as a surrogate marker of disease progression. In PKD patients kidney volume tend to increase about 5.3% per year and vasopressin V2 receptor antagonists (Tolvaptan) and somatostatin analogs (Octreotide) appear to slow the rate of volume increase but they are not approved yet for clinical use. Sirolimus has also been used in randomized trials but it has not been consistently effective and is also not approved for therapeutic use.

Caffeine stimulates cAMP in vitro and stimulates fluid cyst secretion. Avoiding or limiting caffeinated beverages may prevent cyst growth/formation due to effects on G-coupled proteins.

Proteinuria is a traditional marker of renal dysfunction and disease progression and preliminary studies with Triptolide report a decrease in proteinuria in patients with APCKD. Again this agent is not available either in our PKD therapeutic armamentarium. All in all, more than 20 therapeutic agents have been proposed or studied mostly in experimental studies including metformin, inhibitors of: epidermal growth factor, tyrosine kinase, tumor necrosis factors; cyclooxygenase 2, rapamycin, caspases, etc., but unfortunately no cure has been found yet. The interested reader is referred to recent APCKD therapeutic reviews. Nonetheless, there is an urgent need for innovation and additional interventions or alternative therapies outside the traditional nephrological dogma.

NEW HBO HYPOTHESIS
An area that may merit further experimental and clinical studies is the use of Hyperbaric Oxygen (HBO) therapy in APCKD. The experience gathered from our gastroenterology colleagues suggests that in Pneumatosis Intestinalis HBO may lead to cyst regression on imaging and cysts symptoms resolution. If something similar could occur in APCKD, HBO may be an adjunct to treatment and potentially help with the renal changes and disease progression that occurs in APCKD. It might even postpone the need of renal replacement therapy. In brief, the rationale, uses and side effects of HBO are detailed elsewhere and in the recent review. A research proposal is in preparation to study the effects of HBO on PCKD.

REFERENCES
19. Myint TM, Rangan GK, Webster AC. Treatment to slow progression Continued on page 7
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