Autosomal dominant polycystic kidney disease and pain - a review of the disease from aetiology, evaluation, past surgical treatment options to current practice

Badani KK, Hemal AK, Menon M

ABSTRACT

Autosomal Dominant Polycystic Kidney Disease (ADPKD), often referred to as “adult” polycystic kidney disease, is one of the commonest hereditary disorders. It affects approximately 4 to 6 million individuals worldwide. The disease progresses to end-stage renal disease and it accounts for 10-15% of patients requiring dialysis in the United States. A comprehensive Medline search for aetiology, evaluation, screening, cellular biology, and treatment was utilized to locate, extract, and synthesize relevant data with respect to this topic. Special attention was focused on urologic literature and surgical textbooks regarding operative treatment of pain associated with ADPKD.

Now, patients with ADPKD have more treatment options. More specifically, several therapeutic alternatives are now available for the management of pain in these patients. A recent review of literature supports the performance of open or laparoscopic cyst decortication procedures for control of pain and infection without the worry of causing further renal impairment in those with preserved renal function.

KEY WORDS: Polycystic, pain, laparoscopic, robotic surgery

Autosomal Dominant Polycystic Kidney Disease (ADPKD), also called as “adult” polycystic kidney disease, is one of the commonest hereditary disorders. It affects approximately 4 to 6 million individuals worldwide. The term “adult” used to describe this disorder is a common misnomer as the disease is known to occur in newborns and young children. ADPKD is known to affect 500,000 persons in the US, with an incidence of 1 in 6000. ADPKD ultimately progresses to end-stage renal disease and it accounts for 10-15% of patients requiring dialysis in the United States.

Although cases are diagnosed in children, most patients are identified between the ages of 30 to 50 years. All affected subjects manifest with the disease, if he or she lives long enough. Renal failure in this population is seldom seen prior to age forty. ADPKD patients manifest with several other associated anomalies that include cysts in the liver, pancreas, spleen, and lungs; aneurysms of the circle of Willis, often named “Berry” aneurysms are responsible for death in up to 8 to 11% of patients with ADPKD. Mitral valve prolapse and colonic diverticula are some of the other anomalies seen in these patients.

A comprehensive Medline search regarding etiology, evaluation, screening, cellular biology, and treatment was employed to locate, extract, and synthesize the most up-to-date information regarding this disease. Special attention was focused on the urologic literature, as well as on surgical textbooks, for evaluating operative treatment for pain.

Genetics and Cell Biology

Two genes have been identified: PKD1 and PKD2 have been associated with ADPKD. Some patients with ADPKD do not have either of these genes. Hence, it is postulated that another gene, designated PKD3, that is yet to be characterized, is associated with ADPKD. PKD1 gene is found on the 16p chromosome, and accounts for 85-90% of all cases of ADPKD. The protein product of the PKD1 gene is polycystin-1, a membrane receptor that binds to proteins, carbohydrates and lipids to initiate an intracellular response through phosphorylation pathways. The PKD2 gene is found on chromosome 4, representing 5-10% of cases. The PKD2 protein product is polycystin-2. Both these protein products are thought to be present in the renal tubular epithelia. Families with both PKD1 and PKD2 defects share the same major manifestations, however, PDK2 patients are thought to have a later clinical onset and slower progression of their disease. Therefore, patients with the PKD2 defect have a longer life expectancy (69.1 years) as compared to those with the PKD1 defect (55.0 years). It has also been suggested that the disease is more severe and aggressive when genetically inherited from the mother than from the father. Patients with both genetic defects (PKD1 and PKD2, known as trans-heterozygous) have a more severe clinical course and outcome than patients with a single mutation.
Attention has been focused on the genomic sequence of the PKD1 gene as this gene has a high rate of mutability. Qian et al reported that the mutation analysis of PKD1 has been largely unsuccessful due to its highly repetitive nature. More specifically, approximately 70% of its sequence is replicated in at least three copies on 16p13.1, with the remainder of the gene exhibiting nearly identical sequencing. This unique feature of PKD1 may account for the wide range of phenotypes observed in this clinical condition.

Maintenance of normal renal structure after birth is regulated by a fine balance of cellular proliferation and programmed cell death (apoptosis). In polycystic disease, this process is malfunctional, and apoptosis is abnormally persistent. This can result in the destruction of normal renal parenchyma, while allowing proliferation of cystic epithelium. In these patients, cystic epithelia persist and proliferate throughout life, whereas normal renal tubular epithelial cells cease to proliferate at birth. In addition, cultured epithelial cells from ADPKD patients have an increased ability to proliferate and grow in vitro.

The expansion of renal cysts is mediated by epidermal growth factor (EGF), and patients with ADPKD are unusually responsive to the proliferative stimulus of EGF. In addition, mitogenic concentrations of EGF has been found in the cyst fluid of these patients in large enough amounts to stimulate proliferation. Recently, researchers have focused their attention on the inhibition of the receptor for EGF on the cystic epithelium, more specifically, the EGF-receptor tyrosine kinase. In an experimental rodent model, these inhibitors have been found to reduce the number of cysts and extend the lifespan of mice with polycystic kidney disease. These inhibitors of tyrosine kinase are now under investigation in Phase I and II clinical trials for determining their efficacy in slowing down the progression of cyst formation and preserving renal function in adults with ADPKD.

**Aetiology**

Several theories have been proposed to explain the aetiology of ADPKD. One theory attempts to explain the occurrence of the disease on the basis of a defect in the basement membrane of the renal tubules. Abnormalities have been documented in the basement membrane structure as well as in the expression of integrin receptors in polycystic kidney patients. Genetic experiments have shown that alterations in matrix adhesion proteins, and their subsequent complexes, can lead to cyst formation. It is postulated that the presence of these abnormal antigens increases compliance leading to outpouching of the tubules. Another theory, which relates to the previous theory, postulates that a defect in the proteins of the supportive extracellular connective tissue matrix could be responsible for the manifestations of the disease. This theory can help explain the occurrence of basement membrane abnormalities, cysts in the kidneys as well as in other organs of the body. The third theory states that epithelial hyperplasia leads to obstruction and weakening of the tubular wall. This has been supported by the frequency of hyperplasia and adenomas that are seen in up to 91% of specimens. Finally, abnormal location of the Na-K ATPase in the cyst epithelium in an apical position, rather than in a basolateral orientation, results in fluid entering the cyst lumen instead of leaving it. The net reabsorption of fluid in normal kidneys is mediated by the sodium pump (Na-K-ATPase) resulting in a sodium gradient. Patients with polycystic kidneys have this pump in the aforementioned apical position (luminal) within the cell membrane of tubular epithelia. There is also another channel named the Na/K/2Cl symporter that is displaced to the basal surface of the epithelial cell.

Several other mechanisms have been proposed that may contribute to the overall process of cyst formation. One involves malfunction of intracellular signal-transduction pathways that regulate cell proliferation, migration, and differentiation. Another is an abnormality in the ciliary structure or function. The renal collecting tubule cells have a solitary central cilium whose function is not well described. Mutant mouse strains with polycystic kidney disease have been shown to have abnormal cilium structure resulting in cyst formation.

**Presentation and Symptoms**

Symptoms typically begin between 30 and 50 years of age. The most common symptoms include microscopic and gross haematuria, flank pain, gastrointestinal symptoms and renal colic. Hypertension is the commonest clinical manifestation, with some series reporting its presence in up to 80% of patients. Thirty to sixty per cent of ADPKD patients with hypertension have normal creatinine levels. Early blood pressure control has improved the outcome of patients with ADPKD, especially those related to subarachnoid haemorrhage from intracranial aneurysms. Some authors have postulated that the hypertension associated with this disease is renin mediated. The renal cysts stretch renal tubules, resulting in ischaemia of the distal portions of the renal parenchyma. This stimulates renin release, which is supposedly responsible for the high-renin hypertension seen in these patients.

Microscopic or gross haematuria is reported in up to 50% of these patients. It is the presenting sign in 19 to 35% of ADPKD patients, with the first episode occurring at a mean age of 30 years. Urolithiasis occurs in 20 to 30% of patients. Most of these cases have been treated conservatively with alkalisation of urine and hydration therapy. Extracorporeal shockwave lithotripsy is the mainstay of treatment for renal calculi in these patients. Severe, often debilitating, flank, back, and/or abdominal pain has an incidence quoted as high as that of hypertension approximating 60% of patients. Up to 45% of ADPKD patients develop end-stage renal disease by age 60 years.

Manifestations related to other organ-systems also occur. Hepatic cysts occur in up to 60% of adults, and usually occur after the development of renal cyst. In addition, hepatic cysts are found more commonly in adults versus children, as well as in females versus males. Berry aneurysms can occur in up to 40% of patients, and there is an approximately 9% mortality rate from subsequent subarachnoid haemorrhage. There also
appears to be a strong association of aneurysm rupture with hypertension in these patients. Other associated anomalies commonly seen in this condition include pancreatic cysts, mitral valve prolapse and colonic diverticula.

**Incidence of Renal Cell Cancer**

After ADPKD patients have progressed to end-stage renal disease, the incidence of benign renal adenomas in these patients approximates 1 out of 4 or 5 patients. This is almost equal to that in patients with acquired renal cystic disease as a result of end-stage renal disease. Recent studies have demonstrated that patients with ADPKD do not have an increased incidence of renal cell cancer as compared to the general population. In other words, these patients should not be subjected to intensive screening protocols for detection of renal cell cancer. Some authors have observed that when renal cell cancer occurs in ADPKD patients, it is often bilateral (12% vs. 1-5%), multicentric (28% vs. 6%), and has sarcomatoid histology (33% vs. 1-5%) in comparison to the general population.

**Evaluation and Screening**

Evaluation of these patients should include a elicitation of three-generation span of family history for polycystic kidney disease. Without a family history, a presumptive diagnosis can be made with evidence of bilateral renal cysts, and two of the following criteria: bilateral renal enlargement, greater than two hepatic cysts, cerebral aneurysm, solitary cyst of the arachnoid, pineal gland, pancreas, or spleen. The number of simple cysts increases with age, and Ravine et al reported that the presence of only two cysts (unilateral or bilateral) is required to make the diagnosis in patients aged 30 years or younger without a family history. Patients aged 31-59 years require the presence of at least two cysts bilaterally, and subjects over the age of 60 years require the presence of at least four cysts bilaterally for making the diagnosis of ADPKD. All the offspring should be screened with ultrasound regardless of the presence or otherwise of symptoms. Bear et al reported that even asymptomatic relatives with a negative ultrasound have a 28% chance of developing ADPKD if they are 10 to 19 years of age, and carry a 14% risk if they are 20 to 29 years of age. Other reports state that the rate of ADPKD ranges from 32% to 50% in siblings and children younger than 20 years.

**Treatment - History and Current Options**

Current recommendations for surgical interventions for management of polycystic kidney disease have evolved from a controversial and interesting history. There are a few clear indications for the treatment of polycystic kidneys. These include uncontrollable hypertension, severe back and loin pain, abdominal fullness, renal deterioration due to enlarging cysts, haematuria/haemorrhage, and recurrent infections. As mentioned previously, 50 to 70% of ADPKD patients have severe back, flank, or abdominal pain that is refractory to oral analgesics. Pain can result from several processes. One hypothesis is that the renal cysts can cause pain directly from stretching, rupture, or mass effect of the entire kidney (Figure 1). The cysts can become infected leading to abscess causing significant pain along with systemic illness. These patients can also form renal calculi leading to urinary obstruction. Finally, haemorrhage within the cyst has been shown to be a cause of pain and morbidity. The scope for using NSAIDS is limited in patients with ADPKD, as their use is associated with a risk of worsening renal function. In cases of non-responsiveness to analgesics, one can opt for surgical nephrectomy, mostly reserved for those with renal failure or cyst decortication, reserved for those with preserved renal function.

**Surgery for management of pain and preservation of renal function**

In 1911, Rovsing described an operation where he surgically unroofed cysts to relieve pain in three patients. All three patients had improvement in their pain, however, serious questions were raised about this approach in view of deteriorating renal function in patients undergoing surgical treatment. There was a lack of enthusiasm for further research in this area until 1951, when Goldstein et al and Dalgaard et al reported a series of 16 and 119 patients, respectively, undergoing surgical interventions for treatment of pain. Overall, their results indicated that cyst decortication resulted in considerable pain relief, but unfortunately, their work was disregarded in most scientific circles for not adhering to scientific rigor. In 1957, Bricker et al reported two patients with mild renal insufficiency preoperatively, and both patients had worsening renal function after cyst decortication for pain. The procedure of surgical cyst decortication was discredited for nearly 20 years after this report was published in the New England Journal of Medicine.

In 1986, Ye et al, in China, resurrected surgical decortication of cysts. This series, updated in 1997, showed pain relief at 1 and 5 years to be 92% and 81% respectively in a series of 260 patients with a total of 324 open procedures. They also reported no decline in renal function. Several subsequent reports confirmed these findings, and in 1993 Elzinga et al proposed laparoscopic unroofing procedures as an alternative to open surgery. They reported 32 cyst decortication procedures (39 renal units) with 80% patients becoming pain-free at 12 months, and 62% having sustained pain relief at 24 months.
months. In those whose pain recurred, it was found to be less intense, and required less analgesics than preoperatively. Importantly, these authors showed that the overall decline in renal function in ADPKD patients was unaffected by the operation. In other words, surgical procedures did not hasten or retard the rate of natural decline in renal function. Within two years of Elzinga’s report, several new studies were published supporting laparoscopic cyst surgery.41,43

In 2001, Dunn et al published a series of 15 patients who underwent laparoscopic cyst decortication surgery.44 These authors were more aggresive in their treatment approach with up to 600 cysts marsupialized with operative time ranging up to 6 hours. Their results showed that at 26-month follow-up, 62% patients had relief from pain based on their pain analogue scale. Again, there was no significant change in renal function in these patients after the operation. Lee et al in 2003 published a series of 20 ADPKD patients over a mean follow-up period of 32.3 months with a total of 35 laparoscopic cyst decortication procedures.45 Every detectable cyst within 2 mm of the surface of the kidney was treated. They reported a mean operative time of 4.9 hours, and 220 cysts treated per patient. Their results showed that 73%, 52%, and 81% patients reported more than 50% improvement in pain at 12, 24 and 36 months, respectively. The improvement in creatinine clearance at 12, 24, and 36 months was +4%, +7%, and -2%, respectively. This further reinforces the fact that this operation did not affect overall renal function at 3 years.

The current data supports the conclusion that surgical cyst decortication is safe and feasible, and can help control pain in patients with ADPKD without hastening deterioration of renal function (Figures 1 and 2). These procedures, however, have not been proven to prevent renal failure or to prolong current renal function. In asymptomatic patients, cyst decortication is not indicated to prolong renal function and should not be performed for that purpose.

**Surgery for Renal Cell Carcinoma**

Several studies have shown that renal cell carcinoma (RCC) is not more common in ADPKD patients as compared to the general population. However, when RCC does occur, it tends to be bilateral and multi-centric and therefore warrants aggressive treatment. Radical nephrectomy is the cornerstone of treatment in these patients, and aggressive surveillance protocols should be initiated to monitor the contralateral kidney.

**Current and Future Prospects**

Robotic surgery performed laparoscopically is increasingly becoming a popular minimally invasive treatment option in several retroperitoneal operations such as simple and radical nephrectomy, pyeloplasty, and adrenal surgery. There are several advantages of robotic surgery that may aid in further development of surgical treatment for pain in ADPKD. These advantages include wristed movement of the instruments, three-dimensional vision, reduced hand tremor, and precision of movements. Laparoscopic surgery has become the standard of treatment for cyst decortication procedures, and has proven to be safe and efficacious; robotic surgery may further improve the operation to allow precise movement around the renal hilum to treat peri-pelvic cysts that may be difficult to gain access to using traditional laparoscopic equipment. The wristed movement and three-dimensional view would not only facilitate decortication of superficial cysts, but may also allow accurate manipulation of parenchymal cysts. These hypotheses seem promising, however, as yet, have not been studied.

There are several emerging medical treatment options under investigation at this time. The tyrosine kinase inhibitors have been shown to improve histopathological abnormalities and prolong survival in a murine model. This experience has promising implications in human polycystic kidney disease.13 The efficacy of chemotherapeutic agents has also been studied. Since cellular proliferation is thought to be the driving force behind disease progression, some authors have proposed that treatment of ADPKD should be targeted towards inhibition of renal cell proliferation alike to a neoplastic process with the use of chemotherapeutic agents.46 Paclitaxel has been shown to extend life in a murine model by decreasing the rampant growth of tubular cells, thereby preserving renal parenchymal architecture. In a similar, though more rapidly progressive murine model, paclitaxel caused premature death in all the animals studied.47 The use of chemotherapeutic agents, therefore, remains shrouded in controversy, as benefits are seen only in highly specific animal models. Further research is required for developing and testing less toxic derivatives of these drugs.

**Summary**

Patients with autosomal dominant polycystic kidney disease currently have more treatment options than what were available in the past. Several factors contribute to the occurrence of pain in these patients. And fortunately, multiple treatment options are also available. A recent review of the literature supports the performance of open or laparoscopic cyst decortication procedures for control of pain and infection without the worry of causing further renal impairment in those with comparably well-preserved renal function. Laparoscopic decortication has been shown to be safe and efficacious in the treatment of these patients. In patients with end-stage renal disease, nephrectomy still remains the operation of choice after the options of analgesics have been exhausted. Advances in molecular and cell biology will potentially bring promising therapeutic options, the most compelling example being the EGF-receptor tyrosine kinase inhibitors.

Figure 2: Indications for surgical intervention and treatment in ADPKD

![Figure 2: Indications for surgical intervention and treatment in ADPKD](Image)
References

46. Grantham JJ. Time to treat polycystic kidney diseases like the neoplastic disorders they are. (Editorial) Kidney Int 2000;57:539-40.