Prevalence of Cysts in Seminal Tract and Abnormal Semen Parameters in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background and objectives: Autosomal dominant polycystic kidney disease is a systemic disorder with a wide range of extrarenal involvement. The scope of this study was to analyze the prevalence of seminal cysts and to correlate these findings with the sperm parameters in patients with autosomal dominant polycystic kidney disease.

Design, setting, participants, & measurements: A prospective study enrolled 30 adult men with autosomal dominant polycystic kidney disease. Of these 30 patients, 22 agreed to provide a semen sample for analysis, and 28 of 30 agreed to undergo an ultrasound rectal examination. Data obtained from the semen tests and from the ultrasound study were compared.

Results: Cysts in the seminal tract were present in 10 (43.47%) of 28 individuals. Twenty of 22 patients showed abnormal semen parameters, with asthenozoospermia as the most common finding. No correlation between ultrasound findings and sperm abnormalities was observed.

Conclusions: The presence of cysts in the seminal tract is remarkably high (43.47%); however, this finding does not correlate with sperm abnormalities, which are also a frequent finding, especially asthenozoospermia. This semen abnormality is probably related to the abnormal function of polycystins. More attention should be paid to reproductive aspects in the initial evaluation of patients with autosomal dominant polycystic kidney disease before their ability to conceive is further impaired by uremia.


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utosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders, occurring in approximately one of 1000 individuals in the general population. ADPKD is a genetically heterogeneous disorder caused by mutations in either the PKD1 or the PKD2 gene, which encode for the proteins polycystin-1 and polycystin-2, respectively. Most ADPKD cases (>80%) are due to mutations of the PKD1 gene and are associated with an earlier onset and faster disease progression than the PKD2 phenotype. ADPKD has been widely studied during the past decade, having shed new light on polycystin structure and function. Polycystin-1 and -2 are highly conserved ubiquitous transmembrane proteins that, in the kidney, are located in epithelial cells of renal tubules, in particular in the primary cilia at the luminal side of the tubules, as well as in other areas of the renal cell epithelium. Polycystin-1 is a large protein with a long extracellular N-terminal region, 11 transmembrane domains, and a short intracellular C-terminal tail. Polycystin-2 is structurally related to the transient receptor potential channel family, and it is known to function as a nonselective cation channel permeable to Ca²⁺. Polycystin-1 and -2 form heteromeric complexes and co-localize in the primary cilium of renal epithelial cells. The primary cilium is a long nonmotile tubular structure located in the apical surface of epithelial cells in renal tubules. Its function was unknown for a long time; however, recent studies proposed a role of the primary cilium as a mechanoreceptor that may sense changes in apical fluid flow and may be able to transduce them into an intracellular Ca²⁺ signaling response (1). This model involves the participation of polycystin-1 as a mechanical sensor of ciliary bending induced by luminal fluid flow. Bending of the cilium would cause a conformational change in polycystin-1 that would in turn activate polycystin-2–associated Ca²⁺ channel, increasing the intracellular Ca²⁺ concentration and triggering intracellular signaling pathways leading to normal kidney development.

Many extrarenal features are well known in ADPKD. Hepatic cysts are the most common extrarenal manifestation of ADPKD. More than 75% of individuals who have ADPKD and are older than 60 yr have hepatic cysts (2). The prevalence of intracranial aneurysms is approximately 10%, and the prevalence of pancreatic cysts is 6 to 9%; however, other extrarenal organ involvement, such as aortic abdominal aneurysms, colonic diverticulae, and cardiac valve abnormalities, has been questioned for ADPKD. Other rare associations have been reported, but their prevalence remains unknown. This could be the case for thoracic aortic aneurysm, hernias, and seminal tract cysts.

There have been several case reports on cysts in epididymis, seminal vesicles, prostate, and testes in patients with ADPKD. Also some cases of infertility have been reported. Even a structural
abnormality in the sperm from some patients with ADPKD has been reported; however, ADPKD is not a disease that is considered to cause infertility. Fewer than 10% of cases are sporadic, and in the remaining 90%, the disease has been inherited independently from the mother or the father. Moreover, large pedigrees are frequent. The aim of this study was to determine the prevalence of cysts in the seminal tract and to correlate it with sperm parameters.

Materials and Methods

A prospective study was designed to evaluate the prevalence of epididymal, seminal vesicle, prostatic, and testicular cysts in patients with ADPKD and correlate these findings with the semen parameters.

Patients

A total of 30 adult male patients were asked to participate in the study. Informed consent was signed in all cases. The study was approved by the ethical committee of the hospital. We did not study patients who were younger than 18 yr, because we considered that it was not ethical to request a transrectal ultrasound and sperm analysis for research purposes. All patients were sequentially recruited from the outpatient clinic of inherited kidney diseases. The inclusion criteria were the following: ADPKD diagnosed on the basis of Ravine's criteria (3), age between 18 and 50, and estimated GFR (as estimated by the Modification of Diet in Renal Disease [MDRD] formula) >60 ml/min (stages 1 and 2 of kidney failure). The limits on age were proposed to avoid infertility bias as a result of increased age; stages 3, 4, and 5 of chronic kidney disease were also discarded for the same reason.

All patients underwent a complete screening of renal function by blood and urine test and were interviewed about their marital status and any history of infertility. Each patient underwent a formal review, physical examination, semen analysis, and abdominal and transrectal ultrasound.

Ultrasound Studies

Ultrasound was performed using Acuson Sequoia 512, 3.5-MHz convex probes (Acuson, Mountain View, CA) for abdominal and testicular examinations, and 10-MHz linear probes for transrectal examination. Epididymal cysts were defined as well-defined anechoic areas with no internal echoes and with posterior acoustic enhancement. Seminal vesicle cysts were defined as discrete anechoic areas (simple cysts) or hypoechoic areas containing internal echoes (hypoechoic cysts) >5 mm in diameter. The differentiation between seminal vesicle cysts and dilation of seminal vesicles was made by the presence of isolated anechoic and isoechoic areas, a normal appearance of the remaining parts, and the absence of asymmetric or bilateral enlargement of the seminal vesicles. Prostate cysts were defined as discrete anechoic areas characteristically thin walled, well defined, homogeneous, and with posterior acoustic enhancement.

Semen Collection and Assessment of Semen Function

Semen samples were produced by masturbation, collected into sterile containers, and immediately transported to the laboratory. Semen analyses were performed after total liquefaction. A conventional semen profile was obtained for each sample using the procedures described by the World Health Organization (4). Twenty-two patients agreed to undergo a semen examination. Hypospermia was defined as volume <2 ml, oligozoospermia as sperm concentration <20 x 10⁶/ml, asthenozoospermia as <50% of spermatozoa with forward motility (a+b), and teratozoospermia as <15% of normal forms.

Statistical Analyses

Continuous data were expressed as means and SD of the mean and assessed with the two-tailed t test for unpaired data. All comparisons between groups were performed by χ² tests. Significance was established for P < 0.05.

Results

Thirty patients were invited to participate in this study. Two of them refused to collaborate. The mean age of the 28 who agreed to participate in the study was 37.1 yr (SD 5.3).

Twenty-eight of the 30 agreed to undergo a transrectal ultrasound examination. Cysts in the seminal tract were present in 10 (43.47%). Curiously, none of the patients had cysts in more than one location: Six in seminal vesicles, one in the prostate, and three in the epididymis (Table 1). Twenty-two of 30 patients agreed to undergo a semen analysis. Two of them were normozoospermic, and 20 were abnormal. Nine of those showed an abnormal ultrasound. The correlation between sperm abnormalities and ultrasound findings can be seen in Table 2. The differences in ultrasound findings between patients with abnormal semen and normal parameters were not statistically significant. No patient with normal semen parameters showed cysts in the seminal tract. The most frequent seminal abnormality was asthenozoospermia followed by teratozoospermia. Seminal volume was decreased (<1 ml) in 30% of patients.

Table 1. Semen parameter abnormalities in patients with ADPKD

<table>
<thead>
<tr>
<th>Location of Cysts</th>
<th>Semen Abnormality</th>
</tr>
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<tbody>
<tr>
<td>Seminal vesicles</td>
<td>Hypospermia/severe asthenozoospermia</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>Severe asthenozoospermia</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>Mild asthenozoospermia</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>Hypospermia/mild asthenozoospermia</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>Mild teratozoospermia</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>Normal</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Mild asthenozoospermia</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Mild asthenozoospermia/severe teratozoospermia</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Moderate oligozoospermia/severe teratozoospermia</td>
</tr>
<tr>
<td>Prostate</td>
<td>Mild asthenozoospermia/mild teratozoospermia</td>
</tr>
</tbody>
</table>

*ADPKD, autosomal dominant polycystic kidney disease.
abnormalities in patients with ADPKD because large families with ADPKD are very frequent. Fang et al. (5–11) have published this is a disorder that prevents men from having children, though several reports on infertility in ADPKD have been published. In general, nephrologists do not have the impression of cranial aneurysms. Patients with ADPKD are usually fertile, although many different organs may be involved, and hence the prevalence finding in patients with ADPKD.

Eight of 28 patients had complained of infertility, and one of them had a normal semen analysis. It does not mean that the rest were infertile or even that these eight patients were infertile as a result of a male factor. Among the other patients, some had offspring, but others had never tried to have children.

Discussion

ADPKD is a systemic disorder with a preferential renal involvement; however, many different organs may be involved, and some of them may cause a high morbidity among these patients, for example massive polycystic liver disease and rupture of intracranial aneurysms. Patients with ADPKD are usually fertile, although several reports on infertility in ADPKD have been published (5–11). In general, nephrologists do not have the impression that this is a disorder that prevents men from having children, because large families with ADPKD are very frequent. Fang et al. (12) in a retrospective study reported six patients with ADPKD among 4108 infertile individuals. They concluded that the prevalence of ADPKD among these infertile patients was higher than expected. If we take into account that the prevalence that they used for ADPKD is unacceptably low (one in 2000), then the number of individuals with ADPKD among these infertile individuals is as expected; however, ADPKD could be underdiagnosed in this series, because an abdominal ultrasound was not routinely performed. Belet et al. (13) in a prospective study of 104 patients with ADPKD reported 5% prevalence of infertility on the basis of an interview about their history of infertility.

Table 2. Ultrasound findings and semen parameter abnormalities in patients with ADPKD

<table>
<thead>
<tr>
<th>Ultrasound Findings</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

These results were compared with our population of semen donors ($n = 207$; mean age 24.8; SD 53; Table 3). The only significant difference between both populations was the percentage of progressive motile ($a + b$) forms ($P < 0.0001$). This result is in accordance with the fact that asthenozoospermia is the most frequent finding in patients with ADPKD.

Among the patients studied, 28.5% complained of infertility, which is a higher rate than expected for couples who are not affected by ADPKD and live in the same region. In Western countries, it is estimated that 15% of couples and 7% of men are infertile. In seven of eight cases in which the patients complained about infertility, a relationship with abnormal semen parameters was seen, although female infertility was not assessed. There is no report in the literature of systematic semen analyses in nonuremic men with ADPKD. The study presented here is the first to perform ultrasound studies at the same time as semen analyses.

The rate of abnormal semen analyses was higher than expected, especially regarding asthenozoospermia. Asthenozoospermia means reduced sperm motility. It is the most frequent seminal abnormality found in men and may cause infertility; however, sperm in these patients keeps some fertilizing capacity and therefore there is sometimes an incidental finding in a fertile man.

The semen test results were compared with those obtained from semen donors at our institution. There was a significant difference in the rate of progressive motile spermatozoa ($a + b$ forms). Patients with ADPKD showed a lower rate of $a + b$ forms, which is in line with the predominant semen alteration in these patients (i.e., asthenozoospermia). We ruled out other factors associated with asthenozoospermia, such as urogenital infection or inflammation and heavy smoking. On the basis of this study, there is no significant relationship between seminal tract cysts and semen abnormality. These cysts could result in azoospermia, but this was not a frequent finding in the ADPKD population. Asthenozoospermia is not related to obstruction but more likely to abnormal spermatozoa development. Because the flagella and cilia of the spermatozoa possess the same ultrastructure, the location of polycystin-1 and 2 in the primary cilia and its defect in ADPKD may be related to the abnormal spermatozoan structure. Perhaps certain mutations in the PKD genes are responsible for the difficulty in constructing the central microtubules of the flagella. Watnick et al. (15) found that PKD2 was localized at the distal tip of the sperm flagella in Drosophila melanogaster, and a targeted mutation in this gene caused nearly complete male sterility. Whether polycystin-2 plays a role in mammalian sperm development and function remains an open question, although the evidence in Drosophila together with the location of polycystin-2–related proteins in a broad array of ciliary structures and the finding of sperm test alterations in patients with ADPKD suggest that some relationship between mutations in the PKD genes and abnormal spermatogenesis is present (16). Also, mice with autosomal recessive PKD (Tg737) have defects in sperm tail development. PKD2 mutant

Table 3. Comparison of semen parameters between patients with ADPKD and the semen donor population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Semen Donors (Mean [SD])</th>
<th>ADPKD Population (Mean [SD])</th>
</tr>
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<tr>
<td>$n$</td>
<td>207</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.85 (5.36)</td>
<td>37.59 (5.38)</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>3.19 (1.47)</td>
<td>3.35 (1.80)</td>
</tr>
<tr>
<td>Concentration (10^6/ml)</td>
<td>69.22 (46.17)</td>
<td>50.20 (36.77)</td>
</tr>
<tr>
<td>$a + b$ (%)</td>
<td>48.43 (18.51)</td>
<td>29.00 (18.48)</td>
</tr>
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<td>Normal forms (%)</td>
<td>20.15 (10.50)</td>
<td>19.86 (14.84)</td>
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Four different reasons may explain the reported cases of infertility in ADPKD:

1. Cysts in the distal seminal tract may cause obstructive azoospermia or partial obstruction with severe oligozoospermia.
2. Abnormal semen production as a result of abnormal polycystins.
3. Uremia may lead to infertility.
4. Immotile cilia syndrome has been described in some patients who have ADPKD and lack the two central tubules of the tail (9 + 0) (14).

Among the patients studied, 28.5% complained of infertility, which is a higher rate than expected for couples who are not affected by ADPKD and live in the same region. In Western countries, it is estimated that 15% of couples and 7% of men are infertile. In seven of eight cases in which the patients complained about infertility, a relationship with abnormal semen parameters was seen, although female infertility was not assessed. There is no report in the literature of systematic semen analyses in nonuremic men with ADPKD. The study presented here is the first to perform ultrasound studies at the same time as semen analyses.

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mice retain cilia, whereas polaris mutants (Tg737) lack cilia and sperm tails, demonstrating a role for these proteins in ciliogenesis and sperm axoneme development (17). This is also supported by the fact that polycystins seem to play a role in sea urchin fertilization, facilitating the acrosome reaction (18).

The ultrasound findings found in this study support the figures mentioned in the literature. Belet et al. (13) found a prevalence of 18% for epididymal cysts, 39% for seminal vesicle cysts, and 7% for prostate cysts in a study of 104 male patients. Danaci et al. (19) found a prevalence of 60% in seminal vesicle cysts (27 of 45) and 11% for prostate cysts. These figures are definitively higher than the 5.2% prevalence of such cysts in patients without ADPKD (20). Because seminal vesicles are the major contributors to the volume of the ejaculate, a distal obstruction will not allow the passage of most of their fluid into the prostatic urethra, and a low-volume ejaculate occurs; however, the high rate of seminal tract cysts, its poor correlation with semen abnormalities, and the relatively low frequency of infertility expected among patients with ADPKD make the presence of seminal tract cysts common but with mild, if any, clinical consequences.

Several theories explain the process of cystogenesis in ADPKD. A major explanation for this phenomenon is that there is an imbalance between cell growth/proliferation inhibitors and stimulators. The same primary cell abnormalities found in kidney involve cysts and sperm test abnormalities, more attention should be paid to the reproductive aspects in the initial evaluation of these patients before their ability to conceive is further impaired by uremia.

Conclusions
On the basis of this work and assuming the limitations of the sample size, we conclude that although seminal tract cysts are common among patients with ADPKD, they are not responsible for infertility, which is not a common trait among patients with ADPKD; however, asthenozoospermia is a common finding in this population, which may be explained by abnormal spermatozoa development. Because of the high prevalence of seminal tract cysts and sperm test abnormalities, more attention should be paid to the reproductive aspects in the initial evaluation of these patients before their ability to conceive is further impaired by uremia.

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Disclosures
None.

References