Causes of Death in Autosomal Dominant Polycystic Kidney Disease \(^1,2\)

Godela M. Fick, Ann M. Johnson, William S. Hammond, and Patricia A. Gabow \(^3\)

G.M. Fick, A.M. Johnson, W.S. Hammond, P.A. Gabow, University of Colorado Health Sciences Center, Denver, CO
W.S. Hammond, Department of Veterans Affairs Medical Center, Denver, CO
P.A. Gabow, Denver Health and Hospitals, Denver, CO

(J. Am. Soc. Nephrol. 1995; 5:2048-2056)

**ABSTRACT**

To determine the causes of death in autosomal dominant polycystic kidney disease (ADPKD) patients and to examine whether the extrarenal manifestations of ADPKD influence the causes of death, the medical records of 129 patients who died between 1956 and 1993 were reviewed; 58% of the 129 patients had an autopsy performed. Seventy-seven percent died after reaching ESRD. The mean age at death increased from 51 yr for those who died before 1975 to 59 yr for those who died after 1975, reflecting the introduction of renal replacement therapies. The most common cause of death before 1975 was infection (30%), followed by uremia (28%) and cardiac disease (21%); after 1975, these were cardiac disease (36%) and infection (24%). Infection was equally prevalent before and after 1975, presenting as sepsis in 94% and directly relating to ADPKD in 47% of these patients. Underlying factors for cardiac death were cardiac hypertrophy, seen in 89% of all autopsied patients, and coronary artery disease, seen in 81%. A neurologic event was the cause of death in 12% of patients; these were ruptured intracranial aneurysm in 6%, hypertensive intracranial hemorrhage in 5%, and ischemic stroke in 1%. The mean age of those who died of ruptured intracranial aneurysm was 37 yr. No patient died of renal cancer. Liver cysts were the most common extrarenal manifestation, seen in 70% of the autopsied cases; cysts in other organs were very rare. Colonic diverticula were found in 21%. Thus, the renal and extrarenal manifestations of ADPKD are important contributors to morbidity and mortality.

**Key Words:** Mortality, autopsy, ESRD, kidney transplant, infection

**A**utosomal dominant polycystic kidney disease (ADPKD) is a systemic disorder with various renal and extrarenal manifestations \(1\). Although these manifestations influence morbidity, it is unclear to what extent they contribute to the mortality of the disorder. The renal manifestations include cysts, adenoma, stones, infection, and renal insufficiency \(1\). The most common extrarenal structural abnormality is liver cysts, which occur in up to 75% of patients older than 60 yr \(2-4\); they can become infected and cholangiocarcinoma can occur, contributing to morbidity and mortality in ADPKD dialysis patients \(5\). Mitral valve prolapse was found by two prospective echocardiographic studies to occur in 26% of ADPKD patients, compared with 2% in a control population \(6,7\). Some patients have required valve replacement, and in some, congestive heart failure due to cardiac valve abnormalities was a significant contributor to death \(8\). A retrospective study suggested a higher prevalence of colonic diverticula, with complications including sepsis and death in ADPKD patients \(9\). Finally, after many reports on an association between intracranial aneurysms and ADPKD \(2,10-14\), three recent prospective studies have found an incidence of intracranial aneurysms of 5 to 11% in ADPKD subjects \(15-17\).

Despite this array of abnormalities in ADPKD, there is only limited information relating the renal and extrarenal manifestations to the causes of death. An epidemiologic study by Iglesias et al. \(1\) determined the cause of death in 29 ADPKD patients, 20 of whom had an autopsy performed \(18\); the most common cause of death was cardiovascular. Other studies examined only specific subgroups of ADPKD patients, such as those on dialysis \(19-21\) or with a renal transplant \(22,23\) or those with a specific manifestation \(9,24\), or they do not provide clinical details and autopsy data \(25\). Therefore, the goals of this study were \(1\) to determine the causes of death in a large ADPKD population with and without ESRD; \(2\) to examine whether the extrarenal manifestations of ADPKD influence the causes of death; and \(3\) to further define the spectrum of pathologic findings in ADPKD.

**METHODS**

Information was gathered from three major sources: \(1\) 244 pedigrees were reviewed: the closest relatives of any affected family member who had died were contacted and, after explaining the goals of the study, were asked to consent to the release of medical information on their deceased relative. \(2\) Forty-four autopsies, five clinical records, and one death certificate on patients who were part of the initial
University of Colorado database on ADPKD (data before 1985) were reviewed. (3) A newsletter explaining the aims of the study on the causes of death in ADPKD was sent to all patients in the database of our ongoing prospective study on ADPKD. Patients were asked to volunteer information on any relatives with ADPKD who died including when they died, at which hospital, and who the private physician was. If patients answered these questions, we asked them to sign consent forms to release medical information from their medical records or autopsy reports. These data sources resulted in 129 study subjects, 75 with autopsy records and 53 with clinical records. Histologic slides were available for reevaluation from 36 autopsied cases and 2 ESRD patients who had nephrectomies.

The 75 autopsies were reviewed by the clinical investigator and the pathologist according to a formal protocol, and a consensus regarding the cause of death was reached. Special attention was given to heart morphology, arteriosclerosis of the aorta and coronary arteries, intracerebral aneurysms, colonic diverticula, and extrarenal cysts. Because the autopsies had been done for routine clinical purposes, only total heart weights were available. We defined cardiac hypertrophy as a heart weight above the normal range (>350 g in men, >300 g in women) (26). Fifty-three clinical hospital records were reviewed by two clinical investigators, and again, a consensus on the cause of death was reached. For one patient who died in 1964 of uremia, only the death certificate was available.

Causes of death were classified as due to ESRD, infections, cardiac disease (including myocardial infarction, congestive heart failure, sudden death or arrhythmias, and pericarditis), neurologic event (including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage), pulmonary emboli, carcinoma, and other. ESRD was defined as uremic symptoms or complications together with serum creatinine levels ≥10 mg/dL or as the beginning of dialysis or renal transplant. In each case, a primary cause of death and underlying condition(s) were identified. If there were significant contribut ing factors, for instance, severe chronic congestive heart failure in addition to pulmonary emboli or infection, a secondary cause of death and underlying condition were noted. In addition to the patient's age at the time of death and year of death, we recorded whether or not he/she was on renal replacement therapy or had a renal transplant. Because uremia was a frequent cause of death before hemodialysis treatment became generally available and was not observed as the primary cause of death after 1975, we also analyzed causes of death separately for the two time periods before and after 1975, in order to examine whether the institution of renal replacement therapy would significantly alter the most frequent causes of death in ADPKD.

Microscopic slides of the liver from 36 cases (with one to six slides per case) were available for review. When blocks were available, periodic acid-Schiff and Masson's trichrome stains were prepared and examined. Microscopic slides of kidneys were available from 36 patients, of whom 32 had ESRD. Two to 14 histologic sections were available from each patient. Additional sections were taken from paraffin blocks in 14 cases, and periodic acid-Schiff and Masson's trichrome stains were prepared and examined.

RESULTS

There were 129 records (78 men, 51 women) on causes of death from 1956 to 1993. Seventy-five subjects (58%) had an autopsy performed; in 53, information was gathered from clinical records, and one death certificate was included. Ninety-nine deaths occurred after the patient had reached ESRD (77%); 25 patients (19%) had received a renal transplant. The mean age at death was 55 ± 1 yr and was not significantly different between patients with and without ESRD. The mean duration of ESRD was 3.5 ± 0.4 yr. Fifty-seven deaths occurred before 1975; 72 occurred after 1975 (Table 1). The mean age at death for patients with ESRD increased from 49 to 60 yr from before 1975 to after 1975, which in part was because of longer survival with ESRD (1 versus 5.7 yr; Table 1). Also, after 1975, patients entered ESRD at older ages than before 1975 (54 versus 48 yr; P < 0.01).

The frequencies of the primary causes of death before and after 1975 are displayed in Figure 1. The most common cause of death before 1975 was infection (30%; mean age, 48 ± 2 yr), followed by uremia (28%; mean age, 50 ± 2 yr), whereas after 1975, only one 78-yr-old man who was bedridden after an intracranial hemorrhage died of uremia. The most common causes of death after 1975 were cardiac disease (36%; mean age, 59 ± 2 yr) and infection (24%; mean age, 60 ± 2 yr). Infections were equally prevalent before and after 1975 (30 and 24%; P = not significant). The most common form of infection was generalized sepsis (32 of 34 infection patients). Thirty-two of the patients who died of infection had reached ESRD, with 15 having received a renal transplant. Twenty-three of the sepsis cases had an autopsy performed.

The source of sepsis was directly related to ADPKD manifestations in 15 patients (47%) (Figure 2). Seven of them had renal cyst infection (confirmed by autopsy in five), and two had an underlying urinary tract infection (with autopsy confirmation in one). One patient died of sepsis due to a liver cyst infection (confirmed by autopsy), and another patient was found to have infected liver cysts on autopsy. One dialysis patient died at age 39 of supplicative cholangitis; on autopsy, the liver and spleen were enlarged, with microscopic findings consistent with congenital he-

TABLE 1. Comparison of deaths before and after 1975 in 129 ADPKD patients (1956-1993)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deaths before 1975</th>
<th>Deaths after 1975</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>57</td>
<td>72</td>
</tr>
<tr>
<td>Male</td>
<td>34 (60%)</td>
<td>44 (61%)</td>
</tr>
<tr>
<td>Mean Age (yr)</td>
<td>51 ± 1</td>
<td>59 ± 2</td>
</tr>
<tr>
<td>Deaths With ESRD</td>
<td>46 (81%)</td>
<td>53 (74%)</td>
</tr>
<tr>
<td>Mean Death Age With ESRD (yr)</td>
<td>49 ± 1</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Mean Death Age Without ESRD (yr)</td>
<td>55 ± 5</td>
<td>55 ± 4</td>
</tr>
<tr>
<td>Mean Duration of RRT (yr)</td>
<td>1.0 ± 0.2</td>
<td>5.7 ± 0.7</td>
</tr>
</tbody>
</table>

P < 0.001 after 1975 versus before 1975.

RRT, renal replacement therapy.
Seven of the 18 patients with a cardiac primary cause of death and an autopsy performed had increased heart weights (range, 390 to 680 g). Sixteen had coronary artery disease that was classified as severe in 12, moderate in 1, and mild in 3. In addition to these patients, severe congestive heart failure was a significant contributing factor to death in seven subjects. All four who had an autopsy performed had cardiac hypertrophy (range, 500 to 650 g), and coronary artery disease was present in two.

Increased heart weights (range, 320 to 630 g) occurred in 37 of the 53 patients who did not die of cardiac disease (primary or secondary) and who had an autopsy performed. In nine people, this information was not available, and only seven patients had normal heart weights. Also, 33 of these 53 subjects had coronary artery disease, classified as severe in 7, moderate in 16, and mild in 10; 7 had old myocardial infarctions, and 8 had diffuse or localized myocardial fibrosis. No myxomatous heart valves or chordae tendineae were described in any autopsy report.

Sixteen patients (12%) died of a neurologic event. Ischemic stroke occurred in 2 patients, and intracranial hemorrhage was the cause of death in 14 patients. Eight of them died of a ruptured intracranial aneurysm at a mean age of 37 ± 3 yr, only one of them after reaching ESRD. Six patients died of presumably hypertensive intracerebral hemorrhages at a mean age of 51 ± 3 yr, with autopsy confirmation in three; three had ESRD. Persons who died of a neurologic event were significantly younger than those patients who died of other causes (47 ± 4 versus 56 ± 1 yr; P < 0.01).

Seven patients died of pulmonary emboli; this diagnosis was established by autopsy in all cases. No underlying vena cava or renal vein thromboses were found. There were four cancer deaths—two colon cancers and two breast cancers. No patient died of renal cancer, and only one patient carried a diagnosis of renal cell carcinoma; he died at age 73 of cardiac disease.

Thirteen patients died of "other" causes. These were gastrointestinal bleeding in two, acute pancreatitis in two, renal cyst hemorrhage and uremia in two, withdrawal from dialysis in two (one 79-yr-old woman after 1.5 yr of hemodialysis and one 64-yr-old woman after 12.5 yr of dialysis), acute renal failure as the result of angiotensin-converting enzyme inhibitors in one, hypercalcaemia in one, and car accident in one. Acute dissection of the ascending aorta was the cause of death in one 67-yr-old patient, and rupture of an atherosclerotic abdominal aortic aneurysm was the cause of death in one 56-yr-old patient; both diagnoses were established by autopsy.

Atherosclerotic disease of the aorta was present in 57 of the 75 autopsies; in 17 subjects, it was described as severe (mean age, 61 yr), in 17 as moderate (mean age, 55 yr), and in 23 as mild (mean age, 49 yr). In only four subjects was the aorta described as normal (mean age, 40 yr).
Analysis of causes of death in ADPKD patients with and without ESRD (Figure 3) shows that subjects with ESRD were significantly more likely to die from an infection than subjects without ESRD (32 versus 7%; P < 0.01), whereas neurologic events caused death significantly more often in patients without ESRD (38 versus 5%; P < 0.001). None of the cancer deaths occurred in patients with ESRD. Gender differences were observed for cardiac disease, which was significantly more common in men than in women (54 versus 20%; P < 0.05).

Of the 25 transplanted patients, 60% died of infection, compared with 18% of all other patients (P < 0.001). Twenty-four of the transplant recipients died of cardiac disease, which is not different from 31% of all other patients. Four percent died of a neurologic event, 8% died of pulmonary emboli, and 4% died of other causes (Figure 4).

The frequencies of extrarenal manifestations in ADPKD were also reviewed. In 4 of the 75 autopsies, data on liver cysts were missing. Thirty-seven of the remaining 71 subjects had multiple macroscopic liver cysts (52%), 9 had few (13%), and 25 had no liver cysts macroscopically (35%), but 4 of these had microscopic liver cysts. Eighty-three percent of the women had microscopic liver cysts in comparison to only 55% of the men (P < 0.05). Mean ages at death were not different for men or women with or without liver cysts.

Of the 36 cases with available microscopic slides, liver cysts were grossly apparent in 24 and apparent only on microscopic examination in 3. Microscopically, smaller liver cysts had a flattened cuboidal epithelial cell lining, whereas larger cysts had a fibrous wall beneath the epithelial layer. Proliferation of the epithelial lining cells was seen in only a few cysts. Von Meyenburg complexes (VMC) (in the liver parenchyma, often adjacent to portal tracts and liver cysts [Figure 5]) were present in 31 of 36 cases with available microscopic slides. In only one case were cysts present in the absence of VMC; VMC were found in five cases in the absence of cysts.

Hepatic fibrosis was found in 19 cases. In 14, this was mild periportal and occasionally bridging fibrosis, which was often accentuated adjacent to cysts and VMC (Figure 6). Four patients had portal cirrhosis, three of them were known to be infected with the hepatitis B virus; cirrhosis was accompanied by chronic active hepatitis in two cases.

Pancreatic cysts were found on autopsy in 6 (9%) of 67 patients with data on the pancreas. All of these cysts were small, the largest measuring 8 mm; all other cysts were only seen on microscopic examination (Figure 7). Ovarian cysts were also rare; of 18 women with reports on their ovaries, 2 had macroscopic cysts and 1 had a single microscopic ovarian cyst.

In 16 patients, colonic diverticula were described in the autopsy report, which gives a prevalence of 21% if no mention of diverticula were interpreted as no diverticula seen (47 patients had no diverticula; 12 were missing data). The mean age of those with diverticula was 58 ± 2 yr, which is older than those without diverticula (47 patients; mean age, 51 ± 2 yr; P < 0.05). Twelve (80%) of the 16 subjects with diverticula had ESRD.
Sixteen intracranial aneurysms were detected on autopsy in 10 patients, and another one was suspected because of a large subarachnoid hemorrhage in the posterior fossa. Seven of the aneurysms were ruptured and were the cause of death in six patients. One patient had survived a subarachnoid hemorrhage and had a ligated left common carotid artery. In addition, nine unruptured aneurysms were found—six in patients with another ruptured aneurysm and three in patients without rupture. The most frequent location of the aneurysms was the middle cerebral artery; the sizes were not available for most aneurysms, but there was one giant aneurysm measuring 2 × 1.5 cm that had been clipped 5 yr before the patient’s death.

Renal histologic findings were similar to those described by other investigators. Most small cysts were lined by cuboidal epithelia, had a delicate basement membrane, and did not have a fibrous wall or capsule. In contrast, larger cysts had flattened epithelia and a fibrous wall that blended into adjacent fibrotic and atrophic renal parenchyma. Within the cyst walls and adjacent parenchyma, there were often strands and bundles of smooth muscle cells separated by collagen fibers (Figure 8).

**DISCUSSION**

Examination of the causes of death of ADPKD patients is essential in order to heighten the clinicians’ awareness of potential complications. It is particularly important to understand how the extrarenal manifestations affect the natural history of the disease because caregivers may tend to focus only on the renal manifestations. Because ESRD is such an important part of ADPKD, it is also useful to know how the advent of dialysis and transplantation altered mortality, and whether the major causes of death are simply a consequence of ESRD or if they are directly related to ADPKD.

The most common causes of death in ADPKD in this series of 129 subjects were infection (30%) and uremia (28%) before 1975 and cardiac disease (36%) followed by infection (24%) after 1975. It is of note that other smaller studies (18) as well as studies that focused on patients on renal replacement therapy (19,20,22) demonstrated a similar prominence of infection and cardiac disease as causes of death (23). The most recent and largest study of ADPKD patients with ESRD found cardiac disease to be the most frequent cause of death (34%), followed by infections (20.4%), which is very similar to our results after 1975 (25).

This high incidence of infections as a primary cause of death in ADPKD patients contrasts with findings in the general ESRD population. The largest databases such as the EDTA Registry and the USRDS Annual Data Report show a much higher death rate due to cardiac disease than due to infections (26–28). Moreover, recent clinical studies examining the incidence of serious infections in dialysis patients show that they are uncommon, and if they occur, they are mostly related to dialysis access (29,30). In contrast, of our 34 patients who died from an infection, in only 3 was the infection caused by their dialysis access; in 47%, the underlying source of sepsis was a manifestation of ADPKD. This direct relation to ADPKD has not been described previously but is of substantial importance to clinicians caring for ADPKD-ESRD patients.

The high incidence of cardiac cause of death in ADPKD patients is also important. A recent examination of graft and patient survival in a large population of ADPKD and nondiabetic transplant patients showed an increased age-adjusted risk for cardiovascular events and mortality in ADPKD patients (23). Although this in part could reflect the sequela of hypertension with LVH and/or of the lipid abnormalities that are common in all ESRD patients (31–34), in the study of Florijn et al., classic cardiac risk factors could not fully explain the increased cardiac risk seen in ADPKD patients (23). Nonetheless, 77% of our
Figure 8. A bundle of smooth muscle cells lies in a septum between two adjacent renal cysts. Hematoxylin and eosin, original magnification, x 125.

patients had ESRD, and cardiac disease is the most common cause of death in ESRD patients, whether the underlying disease is diabetes mellitus or glomerulonephritis (26–28,32–34). However, the presence of ESRD is not the sole factor accounting for the frequency of cardiac deaths because, in our series, the frequency of a cardiac cause of death was not different in subjects with or without ESRD (29 and 31%). Moreover, 21% of the ADPKD patients with increased heart weight reported here did not have ESRD. The early onset and long duration of hypertension in ADPKD is likely to be an important contributor to cardiac disease. Although exact information on hypertension was not available in the study patients, 16 to 33% of ADPKD children (35,36) and 60% of ADPKD subjects have hypertension before impairment of renal function (37–39), and increases in left ventricular mass may begin in childhood (40). Prospective studies on the prevalence of LVH using echocardiographic criteria found LVH in 18 to 24% of ADPKD subjects with a mean age of 40 yr (6,7), increasing to 35% over a 10-yr follow-up period (7). However, in a study of ADPKD and nondiabetic dialysis patients, it was found that left ventricular mass was significantly greater than in nondiabetic patients only in ADPKD patients with cardiac valve abnormalities (21). In our study, 89% of the autopsied patients had cardiac hypertrophy, which is a known independent risk factor for cardiac mortality (41,42). Because hypertension often goes undetected and untreated in subjects with undiagnosed ADPKD (43), a case might be made for early diagnosis or at least early blood pressure checks in at-risk children in order to prevent treatable complications of this disease.

In addition to cardiac hypertrophy, coronary artery disease was also very common, occurring in 81% of 63 subjects in whom this information was available from the autopsy report (mean age, 55 ± 1 yr). This is somewhat higher than the 67% found in another autopsy study of ADPKD patients and the 61% found in 54 men and 40 women (mean age, 59 yr) with ESRD without ADPKD (21,44). Moderate to severe arteriosclerotic disease of the aorta was also common in our study, similar to the findings of Iglesias et al. and Ritz et al. (18,21).

Cardiac valvular abnormalities did not seem to contribute significantly to cardiac death in this study. Although mitral valve prolapse has been found in two studies to occur in 26% of ADPKD patients (6,7), the natural history of these lesions is unknown. Over a 10-yr follow-up period in the study of Timio et al., 24 of 228 patients with ADPKD died, but only 1 of them died of a cardiac valvular cause, endocarditis; whether this patient had underlying mitral valve prolapse was not stated (7). Despite the fact that other retrospective studies have demonstrated the contribution of valvular abnormalities to mortality (8), this was not demonstrated in our autopsy data.

Of 16 neurologic deaths in our study, 6 (37.5%) were due to intracerebral hemorrhage unrelated to an aneurysm. This is a lower percentage of nonaneurysmal neurologic deaths than has been reported by others (45,46). The neurologic deaths accounted for 5% of the deaths of the total study population, whereas in Dalgaard's earlier study, 11% of 173 autopsied cases died of cerebral hemorrhage, not including those who died of subarachnoid hemorrhage (2). Similarly, an 11-fold increased risk for cerebral hemorrhage in dialysis patients compared with the general population of the same age and sex has been reported in a prospective study from Japan (47). However, in our study, only half of the patients who died from intracerebral hemorrhage had ESRD; therefore, this was not solely a consequence of ESRD. Another study found that intracerebral hemorrhage occurred in 8% of 96 consecutive ADPKD patients with or without ESRD, most of whom had insufficiently treated hypertension (46). Intracerebral hemorrhage in the ADPKD population may reflect early and sustained hypertension (46), an abnormal central nervous system vasculature (15), or both.
The prevalence of intracranial aneurysms in ADPKD patients without central nervous system symptoms has recently been examined prospectively in three large studies and was found to be 5 to 12% (15-17). This retrospective study found that 6% of deaths were caused by a ruptured intracranial aneurysm, and these deaths occurred in young people (mean age, 37 yr). This young age is in agreement with other studies that have suggested that aneurysmal rupture occurs at a younger age in ADPKD patients than in the general population (24,48). Because ruptured aneurysms tend to cluster in families (49), the life expectancy for subjects from unaffected families may actually be better than the mean age at death in this study, particularly for subjects without ESRD. In order to prevent this mortality at a young age, it is necessary to identify risk factors for ruptured aneurysms, because the screening of all ADPKD patients is not reasonable (50,51).

Macroscopic liver cysts were found in 65% of the autopsied cases (mean age, 54 ± 2 yr), which is similar to the prevalence seen in clinical studies using ultrasound (4) or computed tomography (52). The gender difference (more women with liver cysts than men) has also been observed previously in clinical studies (4,5). Microscopically, liver cysts were associated with VMC in 26 of 27 patients with liver cysts. This is in agreement with a previous study that found a strong correlation between the density of biliary microhamartomas and the stage of polycystic liver disease, thus suggesting that liver cysts arise from progressive dilatation of these microhamartomas (53). Intracystic epithelial proliferation was rare in our samples, similar to the study by Ramos et al. (53). Varying degrees of hepatic fibrosis were found in 53% of liver specimens in our study. One patient had microscopic findings consistent with congenital hepatic fibrosis, and 14 had mild portal fibrosis that was not clearly infectious and may represent mild degrees of congenital hepatic fibrosis. The occurrence of congenital hepatic fibrosis in ADPKD patients with linkage to chromosome 16 has been described previously (54). Although a high prevalence of biliary fibroadenomatosis in ADPKD patients with liver cysts has also been observed by Grünfeld et al. in 11 of 17 patients with liver cysts (5), the pathogenesis of this fibrosis has not been determined.

Pancreatic cysts were rare and small; they did not appear to contribute to morbidity or mortality. Ovarian cysts were also seen, but not more frequently than in postmenopausal women of the general population, in whom simple adnexal cysts have been found in 15% by transabdominal and/or transvaginal ultrasound (55). Dalgaard also reported few pancreatic or ovarian cysts (2).

Previously, a high incidence (83%) of colonic diverticula was observed in a small retrospective series of ADPKD patients with ESRD (9), and moreover, they had a high rupture rate (4 of 10). Incidence and rupture rates were higher than in an age-matched dialysis population without ADPKD and an age-matched general population (9). There are several case reports on diverticulitis and colonic perforation in ESRD patients, among whom ADPKD patients seem to be overrepresented (1,56-58). In this autopsy series of 75 patients, colonic diverticula were described in 21% (mean patient age, 58 yr). Two previous prospective pathologic studies on the prevalence of diverticula in the general population have shown about a 40% prevalence by age 60 (59,60); therefore, colonic diverticula do not seem to be more common in ADPKD. However, in the prospective pathologic studies, colons were examined very carefully, which was not the case in some of our autopsy reports. Therefore, our study may underestimate the true prevalence in ADPKD patients.

Among the 129 deceased subjects, there were four cancer deaths, none of them due to renal cancer. Only one patient was known to have had renal cancer, but he died of cardiac disease. Although there has been a suggestion of an association between ADPKD and renal cancer (61,62), our low incidence of renal cancer is in agreement with other studies that show that the incidence is not higher than by the chance coincidence of two common disorders alone (21,45,63-66). Likewise, Dalgaard found only one hypernephroma among his 173 autopsies (2), and of 241 patients either autopsied or monitored for outcome determinations in four other studies, there were only two renal cancers (18-20,22). Thus, although increased proliferation is a characteristic of ADPKD epithelia, this proliferation does not lead to malignancy in ADPKD as it does in von Hippel-Lindau disease (67-69) or acquired cystic disease (70-73). One unexpected finding in our histologic review of kidneys was marked proliferation of smooth muscle cells in cyst walls and adjacent parenchyma, which has not been described previously (2,61,74,75), possibly because special staining for actin is required. The interpretation of this finding remains to be elucidated. The occurrence of only one patient with acute thoracic aortic dissection and one patient with rupture of an abdominal aortic aneurysm does not suggest an association of ADPKD with these vascular events, as has been suggested in previous case reports (76,77).

Thus, in ADPKD patients, the cystic and noncystic renal and extrarenal manifestations contribute not only to disease morbidity but also to disease mortality. One limitation of the study was that we do not know how many patients were of the ADPKD1 versus the ADPKD2 genotype. Because ADPKD2 patients have milder renal disease (25,78,79), the degree to which they are included in the study population may influence the data. However, in our total study population in whom gene analysis has been done, only a single ADPKD2 family has been identified (80). In a similar vein, the nature of the study design excluded patients with oligosymptomatic ADPKD who were not diagnosed with ADPKD before death. Although the numbers of such cases are not large, they do occur (81),
and had they been included, the overall age of death and causes of death may have been altered.

The age at death for all patients increased only by 8 yr (51 to 59) from the period before 1975 to the period from 1975 to 1993, mainly because of the longer survival of ESRD patients as the result of the introduction of renal replacement therapies. This is in agreement with the 4- to 6-yr remaining life expectancy of all ESRD patients at age 50 to 54 yr reported recently (28). Therefore, the largest potential to increase the lifespan of ADPKD patients seems to lie in the prevention of ESRD, but also in attention to cardiac disease prevention and a suspicion for infectious complications. Awareness of this information should permit an improved survival for patients with ADPKD.

ACKNOWLEDGMENTS

This research was supported by Grant 5 P01 DK34039. Human Polycystic Kidney Disease, awarded by the Department of Health and Human Services, Public Health Service, NIDDK. G.M. Fick is supported by a grant from the DAAD (Deutscher Akademischer Austausch-dienst) by a special program to support studies in epidemiology.

REFERENCES


