Cent. Eur. J. Med. • 8(3) • 2013 • 335-338
DOI: 10.2478/s11536-012-0064-2

VERSITA

Central European Journal of **Medicine**

Impact of liver cysts in progression of polycystic kidney disease

Research Article

Alma Idrizi[1]*, Myftar Barbullushi[1], Arben Beqiri[2], Liri Hoxha[3], Alketa Koroshi[1], Nereida Spahia[1], Margarita Gjata[4], Xhoana Xhaferri[1], Valbona Bajrami[1], Nestor Thereska[1]

1 Service of Nephrology, UHC Mother Teresa, Tirana, Albania

2 Service of Surgery UHC Mother Teresa, Tirana, Albania

3 Service of Gastrohepatology UHC Mother Teresa, Tirana, Albania

4 Service of Internal Medicine UHC Mother Teresa, Tirana, Albania

Received 15 April 2012; Accepted 29 June 2012

Abstract: Introduction. Liver involvement is the most frequent extrarenal manifestation in autosomal dominant polycystic kidney disease (ADPKD). We studied the impact of liver cysts on renal function in our patients with ADPKD. Methods. a retrospective observational from January 2002 to January 2009 e divided 138 patients with ADPKD into two groups: one group of 68 patients without liver cysts and another group of 70 patients with liver cysts. Renal function was considered to be impaired when the creatinine clearance was less than 60 ml/min. Differences were considered significant at the $P<0.05$ level. Results. The liver cysts were more frequent in female patients. No renal failure survival difference was found between patients in both groups ($P=0.05$). Female patients with liver cysts and three or more pregnancies had a worse survival rate than female patients with liver cysts with fewer than three or no pregnancies ($P<0.01$). Conclusion. Our study showed that there was no renal failure survival difference between patients with liver cysts compared with those without liver cysts. Female patients with liver cysts and three or more pregnancies had a greater risk of developing end stage renal disease when compared with patients with liver cysts and fewer than three or no pregnancies.

Keywords: *Autosomal dominant polycystic kidney disease • Liver cysts • Pregnancies • Renal failure survival*

1. Introduction

Liver involvement is the most frequent extrarenal manifestation in autosomal dominant polycystic kidney disease (ADPKD). Liver cysts are responsible for most hepatic complications, but other liver changes may occasionally be encountered, including congenital hepatic fibrosis and segmental dilatation of the biliary tract [1]. Although liver cysts are very rare in persons younger than 20 years, their prevalence increases from 20% in the third decade to 70% in the seventh decade of life, reaching a plateau beyond this threshold [2]. The aim of this study was to evaluate the impact of liver cysts on renal function in our patients with ADPKD.

2. Patients and Methods

In a retrospective observational study from January 2002 to January 2009, we divided 138 patients with ADPKD into two groups: one group of 68 patients without liver cysts and another group of 70 patients with liver cysts. Both groups were matched in regard to age, gender, smoking, renal function, blood pressure, proteinuria,

* *E-mail: alma_idrizi@yahoo.com*

uric acid, lipidic profile, renal volume, gross hematuria, renal stones, and extrarenal complications that included pancreatic cysts, cardiac valvular abnormalities, and colonic diverticula (excepting liver cysts). Patients were subjected to biochemical evaluation every 3 months. The median follow-up time was 4.8±2.6 years.

None of the female patients in our study had previously used estrogen-containing contraceptives. Impairment of renal function was considered the clearance of creatinine (ClCr) of less than 60 ml/min. Loss of function or renal death was determined by the onset of renal replacement therapy or the time of creatinine clearance being less than 15 ml/min. Survival times were calculated as the time to dialysis, transplantation, or death, whichever came first. Kaplan-Meier product-limit survival curves were constructed, and median survival times were calculated using SAS PROC LIFETEST [3]. The median survival time is the time at which half of the subjects reached end-stage renal failure (ESRF) or death. The log rank test was used to compare survival curves. Differences were considered significant at the P<0.05. Risk ratios (RR) were calculated with the Cox proportional hazards model [4].

3. Results

Demographic data of patients are presented in Table 1. Liver cysts predominated in female patients in the second group. Also, in this group more patients had a ClCr less than 60 ml/min. The majority of our patients with liver cysts presented with hepatomegaly (62%). Most of them remained asymptomatic, with normal liver function tests. The most common symptoms we encountered in decreasing order were pain (41%), nausea (37%), vomiting (28%) and abdominal mass (25%). Pain was treated with acetaminophen and occasionally with more potent analgesics such as tramadol. Also, in patients with normal renal function, short-term use of non-steroidal anti-inflammatory drugs was employed with the aim of possibly avoiding opioid use. Table 2 shows the distribution of liver cysts in the second group with regard to age group and sex. Liver cysts were more frequent in patients between the ages of 21 and 50 years. Comparison of renal failure survival rates showed no difference between patients with and without liver cysts (median survival 43 years vs. 46 years, P=0.05) (Figure 1). When renal failure survival was compared in female patients in the two groups, no difference was found (44 vs. 46 years, P=0.5) (Figure 2). In the second group, we compared the renal failure survival rate in female patients with liver cysts with three or more pregnancies and those with liver cysts and fewer than three or no

Table 1. Demographic and clinical data of patients

Demographic variable	Patients without liver cysts	Patients with liver cysts	P value
Number of patients	68	70	NS
Gender (M/F)	32/36	30/40	NS
Age (years)	46.4±4.7	45.2±5.1	NS
Renal function ClCr > 60 ml/min/ClCr < 60 ml/min	37/31 patients	32/38	NS
Liver enzymes AST ALT	 23±9.8 25±8.5	 29±11.8 28±12.4	 NS NS
Mean blood pressure values (mmHg) Mean systolic pressure Mean diastolic pressure	 142.5±3.2 90.7±4.7	 137.2±6.3 88.4±5.8	 NS NS
Proteinuria (g/24-hours)	0.7	0.5	NS
Mean renal volume	380±43 cm^3	375±45 cm^3	NS
Gross hematuria			NS
Total cholesterol (mg/dl)	201±13.7	199±15.8	NS
Tryglicerides	164±10.5	159±15.2	NS
Cardiac valvular abnormalities (%)	9%	11%	NS
Smoking (Yes/No)	25/43	23/47	
Body weight (kg)	71.2±5.8	78.6±6.3	<0.05
Body height (cm)	162.8±9.1	163.6±9.2	NS

AST – aspartate aminotransferase,
ALT – alanine aminotransferase,
ClCr – clearance of creatinine,
NS – not significant

Table 2. Distribution of liver cysts with regard to age-group and sex in the second group

Group age (years)	15-20		21-30		31-40		41-50		51-60		>61	
Gender	F	M	F	M	F	M	F	M	F	M	F	M
Number of patients	2	1	8	6	15	11	8	6	4	4	3	2
Total (70 pts)	3		14		26		14		8		5	
			(1%)		(7%)		(14%)		(12%)		(2%)	

Table 3. Loss of function or renal death in female patients with liver cysts

Number of pregnancies	< 3	≥ 3	No pregnancies
Number of female patients with liver cysts (40)	12 (1 renal loss)	22 (7 renal loss)	6 (0 renal loss)

Figure 1. Renal survival in patients with and without liver cysts

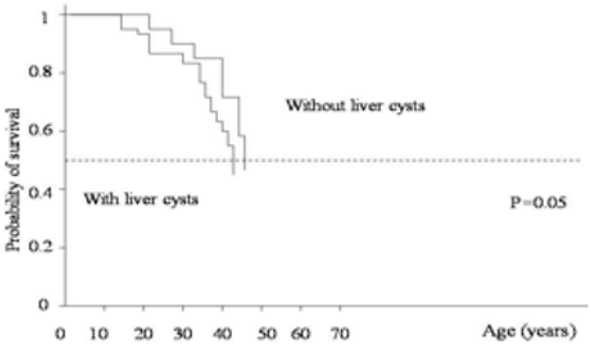


Figure 2. Renal survival in female patients with and without liver cysts

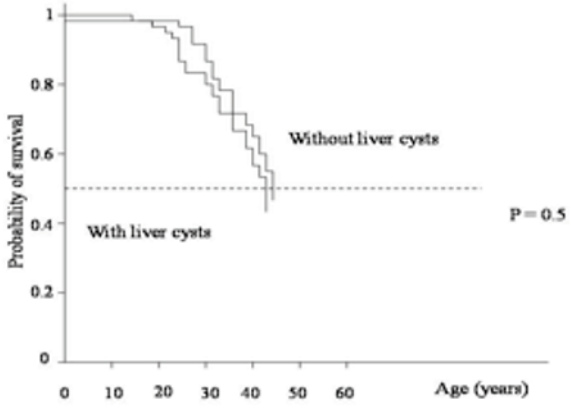
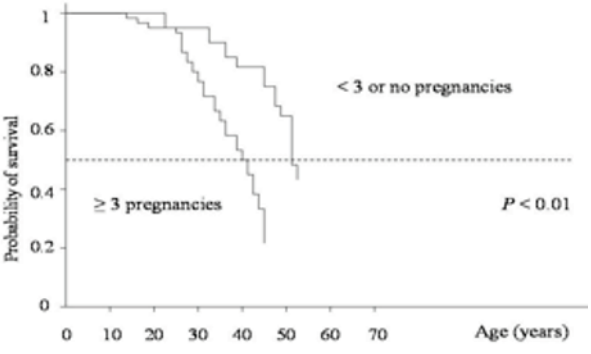


Figure 3. Renal survival in female patients with three or more pregnancies and those with less than three or no pregnancies



pregnancies. Twenty-two female patients with liver cysts had three or more pregnancies, 12 had less than three pregnancies and 6 had never been pregnant (Table 3). The renal failure survival was worse in female patients with three or more pregnancies (median survival, 40 years vs. 52 years, P<0.01, RR=2.6) (Figure 3).

The number of hepatic cysts increased with patient age until it plateaued at 50 years (r=0.52; P<0.01). In patients above this age, the number of liver cysts decreased. In females who had been pregnant, liver cysts were larger and more numerous when compared to those who had never been pregnant (r=0.61; P<0.05).

In three patients with massively enlarged liver cysts who presented with jaundice related to biliary compression by cysts and impaired hepatic function, percutaneous aspiration with sclerotherapy with alcohol was performed, with improvement of symptoms in all three patients.

4. Discussion

Liver cysts are the most frequent extrarenal manifestations of ADPKD. The prevalence of liver cysts among patients with ADPKD is between 75 and 90% (5-10). The occurrence of hepatic cysts in female patients ranges from 58% to 75%, while among male subjects the prevalence ranges from 42 to 62%. In our study, female patients were more prone to hepatic cystic involvement than their male counterparts (63% vs. 37%). Liver cysts appear in patients at a later age than renal cysts but are more extensive in patients with worse renal function and more severe renal cystic disease [6]. Our patients with lower creatinine clearance presented with more involvement of liver cysts. In our study, there was no renal failure survival difference between patients with and without liver cysts, suggesting that liver cysts do not directly influence the deterioration of renal function. Although the development of liver failure in ADPKD is unusual, cystic liver disease is responsible for marked morbidity and accounts for 10% of deaths of patients with ADPKD on dialysis [11]. Liver cysts are not only recognized earlier but also are more numerous and larger in females than in males. In our patients, the frequency of liver cysts was related to decreased creatinine clearance and increased patient age until the frequency reached a plateau at 50 years. The number and size of hepatic cysts in female patients correlated with the occurrence of pregnancy, increased age and decreased creatinine clearance.

Estrogens are not only essential for the female reproductive system, but they also control fundamental functions in other tissues including the cardiovascular system, bone, brain and liver. The use of estrogens was identified as a risk factor for harboring liver cysts. In the United States, it has been found that the number of pregnancies correlates with the number of hepatic cysts. A case-control study documented that estrogen treatment of postmenopausal females with ADPKD is associated with selective liver enlargement and abdominal symptoms in such patients may occur because of extensive hepatic cystic disease [12]. When female patients with liver cysts and three or more pregnancies

in the second group were compared to those with liver cysts and fewer than three or no pregnancies in regard to renal failure survival, significant differences resulted, suggesting not only the influence of pregnancy but also, more importantly, the number of pregnancies in the deterioration of renal function. A high frequency of liver cysts in our female patients of reproductive age (21-50 years) favors the role of estrogens in the genesis of these cysts, whereas the low number of female patients with liver cysts more than 51 years of age is probably related to misuse of postmenopausal estrogen-containing contraceptives. Epidemiologic evidence suggests that a specific mutation is not implicated in the liver phenotype in most cases but that the phenotype is strongly influenced by the hormonal environment [1].

Despite the fact that the majority of our patients with liver cysts presented with hepatomegaly, most of them remained asymptomatic, with normal liver function tests. Among those with symptoms, abdominal mass, pain, nausea and vomiting were the most common complaints. Rarely, clinically significant liver disease produces enough symptoms to call for surgical attention. These symptoms range from simple compression to fatal liver failure [10]. Maybe the percutaneous aspiration should be combined with sclerotherapy that uses alcohol or minocycline to minimize the recurrence of symptoms resulting from fluid secretion by the cyst wall after simple emptying.

In conclusion, we found that liver cysts were more frequent in female than male patients. We found no difference in renal failure survival between patients with liver cysts and those without such cysts. Female patients with liver cysts and three or more pregnancies had a greater risk of the development of end-stage renal disease than those with liver cysts and fewer than three or no pregnancies. Women with ADPKD and liver cysts must receive pre-pregnancy counseling. Our findings need to be followed by further studies to explore other possible risk factors for liver cysts in ADPKD patients to effectively prevent well known complications in time.

References

[1] Chauveau D., Fakhouri F., Grünfeld JP. Liver Involvement in Autosomal Dominant Polycystic Kidney Disease–Therapeutic Dilemma. J Am Soc Nephrol 2000; 11:1767-1775

[2] Pirson Y, Chauveau D, Grünfeld JP: Autosomal-dominant polycystic kidney disease. In: Oxford Textbook of Clinical Nephrology, edited by Davison AM, Cameron JS, Grünfeld JP, Kerr DNS, Ritz E, Winearls CG, Oxford, Oxford University Press, 1998, 2393-2415

[3] Statistical Analysis System, Cary, NC, SAS Institute Inc., 1996

[4] Cox DR. Regression models and life tables. J R Stat Soc B34 1972; 187-220

[5] Milutinovic J, Fialkow PJ, Rudd TG, et al. Liver cysts in patients with autosomal dominant polycystic kidney disease. Am J Med. 1980; 68:741-744

[6] Gabow PA, Johnson AM, Kaehny WD, et al. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. Hepatology. 1990; 11:1033-1037

[7] D'Agata ID, Jonas MM, Perez-Atayde AR, et al. Combined cystic disease of the liver and kidney. Semin Liver Dis. 1994; 14:215-228

[8] Que F, Nagorney DM, Gross JB, Jr, et al. Liver resection and cyst fenestration in the treatment of severe polycystic liver disease. Gastroenterology. 1995; 108:487-494

[9] Everson GT. Hepatic cysts in autosomal dominant polycystic kidney disease. Mayo Clin Proc. 1990; 65:1020-1025

[10] Sulikowski T, Kaminski M, Rozanski J, et al. Laparoscopic removal of renal cysts in patients with ADPKD as an alternative method of treatment and patient preparation for kidney transplantation: preliminary results. Transplant Proc. 2006; 38:23-27

[11] Grunfeld JP, Albouze G, Jungers P, et al. Liver changes and complications in adult polycystic kidney disease. Adv Nephrol Necker Hosp. 1985; 14:1-20

[12] Sherstha R, McKinley C, Russ P, Scherzinger A, Bronner T, Showalter R, Everson GT: Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in females with autosomal dominant polycystic kidney disease. Hepatology 1997; 26:1282-1286