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Original article

Characterization of patients with Caroli's disease: Systematic review

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Abstract

Caroli's disease (CD) is a rare congenital disease, which presents with multifocal segmental intrahepatic bile duct dilatation. It was first described by Jacques Caroli in 1958 as a saccular or fusiform dilatation of the intrahepatic bile ducts. **Objective:** To characterize the population that has been diagnosed with Caroli's disease. **Materials and methods:** Systematic review. **Results:** 66 articles were analyzed. The age group most affected was children under 10 years old, where a higher prevalence was evidenced in males. This condition was associated with other comorbidities such as polycystic kidney in 20%. The most frequent manifestation was hepatomegaly (44.7%), followed by fever (42.4%), and abdominal pain in the right upper quadrant (41.2%). The most used diagnostic method was magnetic resonance imaging in 73.8% of the sample. The findings showed predominance of intra-hepatic dilatation in 76.5%. The most widely used treatment was antibiotic therapy to treat recurrences due to cholangitis. **Conclusion:** Caroli's disease has an extremely low incidence and occurs more frequently in the American continent, affecting mainly patients in the first decade of life, with a predilection for the male sex. It is characterized by a dilatation of the intrahepatic ducts that can affect other organs such as the kidneys, causing renal cysts.

Keywords

Caroli's disease; Cystic liver disease; Intrahepatic dilatation; Portal hypertension; Hepatomegaly; Cystic dilation; Newborn diseases.

INTRODUCTION

Caroli's disease is a rare congenital disorder, characterized by ectasia and dilatation of the intrahepatic bile ducts, thus altering the biliary tract in its entirety[1]. When bile duct dilation occurs together with liver fibrosis, the condition is called *Caroli syndrome*[2].

Alonso-Lej was the first to classify choledochal cysts, but his classification was later modified by Todani in 1977[3,4]; the latter is described in **Table 1.**

Caroli's disease has a genetic component associated with other liver and kidney diseases, and the relationship with polycystic kidney diseases is of greater interest. Its genetic origin is involved with the mutation of the *PKHD1* gene, which is also responsible for the production of the protein fibrocystin. It is also known that this protein is mainly expressed in the kidney and, in a secondary manner, in the liver and pancreas[1,5].

Most cases involve compound heterozygotes for this gene, which explains why both alleles have 2 different mutations that cause the gene to be defective and lead to an abnormal production of fibrocystin. This reflects the diversity of the background mutational processes experienced by the *PKHD1* gene[1,5].

Furthermore, its presentation is unusual, as it occurs in less than 1 per 1 000 000 inhabitants[5]. Despite all the avai-

lable literature on this condition, it has not been possible to establish the risk factors directly involved in the onset of the disease clearly and concisely[1,5].

Table 1. Todani classification

Type	Description	Frequency
I	Cystic, saccular or fusiform dilatation of the extrahepatic biliary duct	80 %-90 %
II	Saccular diverticulum of of the common bile duct	0 %-2 %
III	Choledochocoele involving intraduodenal portion of the common bile duct	1%
IV	Multiple cystic dilations of the intra- and extra-hepatic bile duct (IVA) or extrahepatic only (IVb)	10 %-15 %
V	Diffuse cystic involvement of the intrahepatic bile duct (Caroli's disease)	20%

Symptoms may be varied; some patients may present with abdominal pain, cholangitis and its consequent fever, jaundice, pancreatitis, weight loss, and asthenia. Its clinical presentation may progress to end-stage liver disease. Diagnostic methods include liver biopsy, nuclear magnetic cholangiography, and abdominal ultrasound[2,5].

Caroli's disease is known to be an aggressive disorder of the intrahepatic bile ducts, so it is common to find sequelae in patients suffering from this condition[6-8]. The outcome of Caroli's disease can be successful or a failure in terms of therapeutic approach, to the point that the last resort to treat a patient is to perform a liver transplant to avoid early mortality; however, in some cases, this method is insufficient or not used, and patients die inevitably[9-11].

The objective of this study is to describe the clinical presentation, diagnosis and treatment of this disease based on a systematic review of the literature.

MATERIALS AND METHODS

Type of study

A systematic literature search was conducted based on the PRISMA 20 statement and the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.022.

Population

The entire population with a diagnosis of Caroli's disease, which had been treated and whose cases had been published between 1979 and 2019, was included. Sociodemographic, clinical, and therapeutic characteristics and prognosis were analyzed to determine factors associated with the presence of the disease.

Inclusion criteria

Reports, case series, cross-sectional studies, case-control studies, cohorts, and clinical trials with sociodemographic, clinical, imaging, and treatment data related to Caroli's disease (cystic liver disease) were included.

Exclusion criteria

Topic reviews, letters to the editor, and studies that did not involve human subjects were excluded.

Variables

The variables included were sex (M/F); country; year of publication; history (disease [renal agenesis, rheumatoid arthritis, cholangitis, chronic malnutrition, dyspepsia, renal medullary spongiosis, persistent biliary fistula, hepatitis, neonatal jaundice, oligohydramnios, pyelonephritis, esophageal varices, gastric varices, polycystic kidney and liver disease, family history of kidney disease, cirrhosis, chronic kidney disease, portal hypertension, polycystic kidney] surgical [Roux-en-Y choledochojejunostomy, esophageal variceal ligation, laparoscopic cholecystectomy, renal transplantation, laparotomy]), and clinical manifestations (pruritus, pale stools, loss of appetite, weight loss, abdominal distension, epigastralgia, jaundice, splenomegaly, generalized abdominal pain, nausea/vomiting, abdominal pain in the right hypochondrium, fever, hepatomegaly); diagnostic methods (abdominal angiogram, intraoperative cholangiography, choledochography, percutaneous transhepatic cholangiogram, hepatobiliary scintigraphy, upper gastrointestinal endoscopy, scintigraphy, urography, radiography, endoscopic retrograde cholangiopancreatography [ERCP], CT scan, ultrasound, MRI); characteristics of the disease (findings and affected lobe); management; and sequelae.

Literature search strategy

The search was carried out by 3 researchers, who conducted it between September 10 and 28, 2019. The databases used were PubMed/Medline, Scopus, Embase, SciELO and Science Direct. The search was performed using the following key words (DeCS [MeSH]): enfermedad de Caroli (*Caroli's Disease*), dilatación intrahepática (*intrahepatic dilation*), and enfermedad quística del hígado (*cystic liver disease*).

Search restrictions

The search was limited to literature related to studies involving human subjects, published in English and Spanish.

Data extraction

Data were extracted by 3 researchers belonging to the project, who, as a search strategy, identified and detected the literature to be studied. Then, articles were selected based on their titles to choose those that were in line with the proposed objective. Subsequently, the abstracts of the selected articles were evaluated and, finally, the full texts were reviewed to be chosen and included in the present study.

A database was created and registered in Excel 2013 and analyzed using the SPSS statistical package version 22; the univariate analysis was performed by means of descriptive statistics, determining absolute and relative frequencies for the qualitative variables, while measures of central tendency and dispersion were estimated for the quantitative variables.

Biases

There were several biases to control due to this study design. The first was poor selection of participants, which was avoided by establishing inclusion and exclusion criteria. The second was measurement bias, which was corrected by creating a data collection form that was applied by the 3 researchers. The third was the gap bias when recording the information since data were obtained from case report records and published case series, with the possibility that the information collected was incomplete.

RESULTS

Selection of studies

The search strategy allowed finding 854 articles in the databases; then, after applying the search restrictions, 517 studies were removed, yielding a total of 340 articles. Subsequently, titles and abstracts were reviewed, resulting in the elimination of 245 publications, for a total of 95 articles. After the complete review of the manuscripts, 17 were considered not to meet the criteria for responding to the study. 12 of the remaining 78 articles were removed because they were duplicated, resulting in a total of 66 published articles corresponding to reports and case series; however, no articles from cross-sectional studies, case-control studies, cohorts, or clinical trials were found. Therefore, one of the limitations of the present study is the difficulty in making a causal inference.

The following flow chart depicts the study selection process (**Figure 1**), which adhered to the PRISMA statement.

Sociodemographic characteristics of patients

At the time of collecting and analyzing data on the most common age of presentation (**Table 2**), it was found that the disease has the highest prevalence in the age range of 0 to 40 years, with 63 patients reported; in addition, characteristic peaks could be observed at the ages of 0-10 years (32.9 %), 20-30 years (22.4 %), and 30-40 years (14.1 %)[9,12].

The male sex is predominant (48 cases), with a percentage of 56.5 %[13-18]. It was also identified that the country that reported the most cases of this disease was the United States with 17.6 %[12,19,20]. The underlying diseases most frequently associated with the development of this condition, in descending order, are polycystic kidney (17 cases: 20 %), portal hypertension (16 cases: 18.8 %) and CKD (8 cases: 9.4 %)[19,21,22]. Another relevant variable is surgical history, in which no relevant data were obtained since the results were similar, and there was no evidence of a factor with a greater impact on the results. Laparoscopic cholecystectomy, renal transplantation and laparotomy were performed in 3.6 % and Roux-en-Y choledochojejunostomy with esophageal varices ligation in 1.2 %[23-25].

Clinical features

The analysis of the series of clinical cases reviewed by the researchers found that the most frequent manifestations of Caroli's disease were hepatomegaly in 38 patients (44.7 %)[26-30], followed by pain in the right hypochondrium in 35 patients (41.2 %), splenomegaly in 20 patients (23.4 %), and jaundice in 19 cases (22.4 %). Fever was present in 42.4 % of patients, which is a manifestation of cholangitis as a complication of this condition (**Table 3**)[31-36].

According to the clinical cases selected by the research group, it was observed that the 3 diagnostic tools most used at the time of proposing a diagnosis were magnetic resonance imaging (MRI) in 62 patients (73.8 %); followed by ultrasound in 35 patients (41.6 %); CT scan, with a percentage of use of 38.1%; and ERCP, in 28.57 %. Although ultrasound is the second most commonly used diagnostic method, it is useful for screening, but confirmation by cholangiopancreatography is required [37-41].

Caroli's disease is a rare congenital disorder, so the main studies carried out on this condition described important findings (**Table 4**), including intrahepatic dilatation, which occurred in 65 patients with a percentage of 76.5 %, so the choledochus was dilated in 37 patients, with a percentage of 43.5 %. The second most relevant finding was chole-

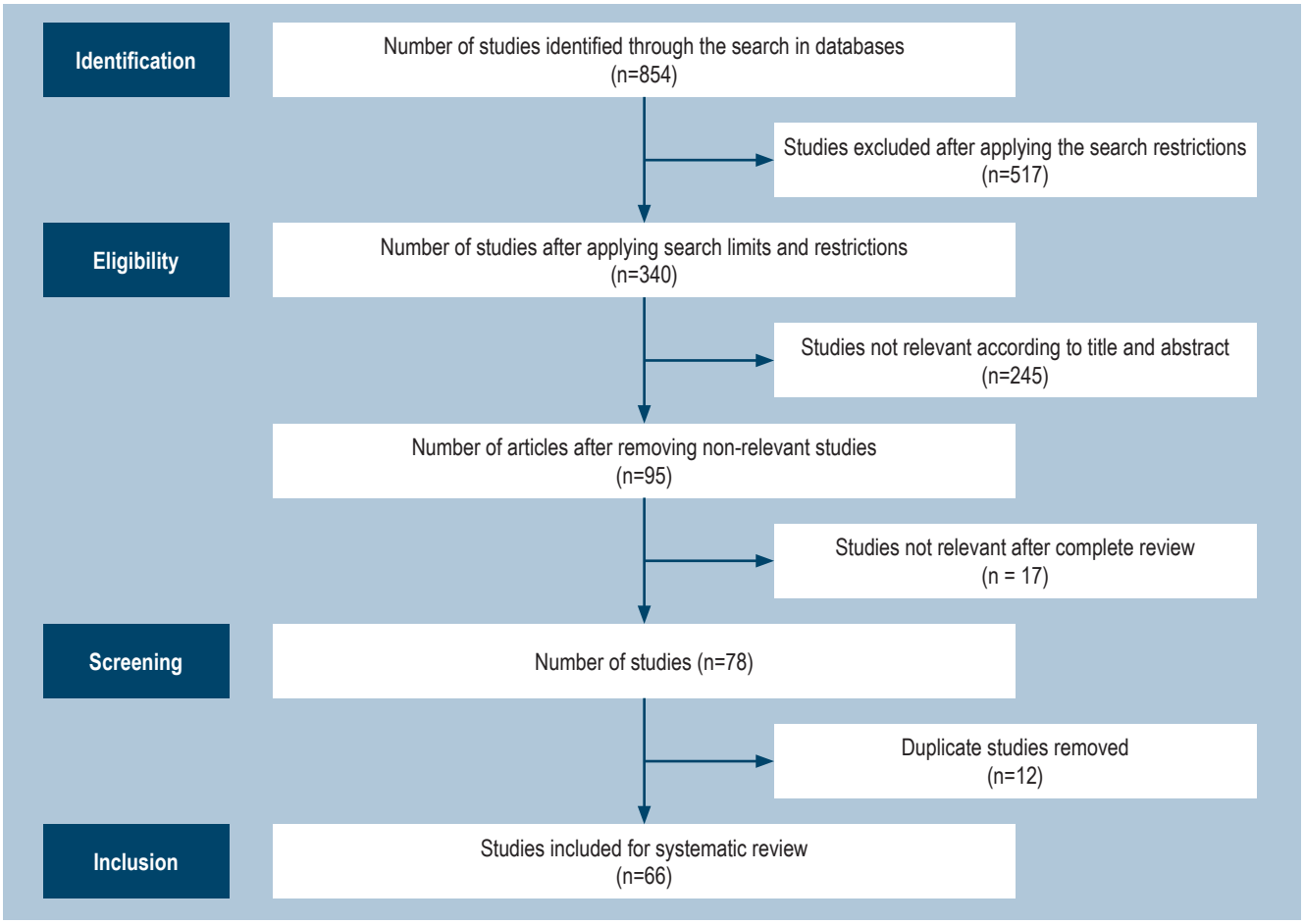

Figure 1. PRISMA flowchart for study selection.

lithiasis in 26 patients, with a percentage of 30.6 %, which caused renal cysts in 17 patients, equivalent to 20.0 %[42-45].

According to the pathophysiology of Caroli's disease, it can be located unilaterally or bilaterally; in the present analysis, there was a trend toward a bilateral location in 48 cases (56.5 %), followed by the right lobe in 22 cases (25.9 %), and the left lobe with 15 cases (17.6 %)[6,10,46-48].

Therapeutic characteristics and prognosis

Regarding the therapeutic approaches that can be used for Caroli's disease (**Table 4**), the most commonly used was antibiotic therapy in 40 cases (47.1 %), followed by ERCP in 35 cases (41.2 %), ursodeoxycholic acid in 9 cases (10.6 %), and transplantation in 14 cases (16.5 %)[12,15,49-56].

The most frequent complication was recurrent cholangitis (6 cases), representing 7.1 % of the total number of cases (6-8). In this study, 8 cases resulted in death, accounting for 9.4 % of all cases[9-11].

DISCUSSION

In the past, access to imaging studies was limited, so they were not used frequently when providing care to these patients; with this in mind, it was concluded that Caroli's disease was most likely underdiagnosed[57]. Therefore, one of the objectives of this review was to characterize patients presenting with this disease since it is a rare disorder comprising various abnormalities, including intrahepatic saccular dilatation, cholecodal dilatation, formation of stones, and cholangitis[19].

On the one hand, case reports on this disease are scarce; however, it was evident that the most frequent age of presentation was 0-10 years of age (32.9 %), followed by 20-30 years (22.4 %), and 30-40 years (14.1 %). On the other hand, the age range of 0 to 40 years was prevalent in 63 patients, implying that Caroli's disease occurs more frequently in young and middle-aged adults, as stated by Saracíbar[58] and Shenoy[59].

Table 2. Sociodemographic characteristics

Variable	Prevalence	n	%	95%CI	
Age	0-10	28	32.9	22.95	42.93
	10-20	4	4.7	0.2043	9.207
	20-30	19	22.4	13.5	31.21
	30-40	12	14.1	6.716	21.52
	40-50	8	9.4	3.205	15.62
	50-60	7	8.2	2.392	14.08
	60-70	6	7.1	1.614	12.5
	> 70	1	1.2	0.0	3.469
Sex	Female	37	43.5	32.99	54.07
	Male	48	56.5	45.93	67.01
History of disease	Renal agenesis	1	1.2	0.0	3.469
	Rheumatoid arthritis	1	1.2	0.0	3.469
	Cholangitis	1	1.2	0.0	3.469
	Chronic malnutrition	1	1.2	0.0	3.469
	Dyspepsia	1	1.2	0.0	3.469
	Renal medullary spongiosis	1	1.2	0.0	3.469
	Persistent biliary fistula	1	1.2	0.0	3.469
	Hepatitis	1	1.2	0.0	3.469
	Neonatal jaundice	1	1.2	0.0	3.469
	Oligohydramnios	1	1.2	0.0	3.469
	Pyelonephritis	1	1.2	0.0	3.469
	Esophageal varices	1	1.2	0.0	3.469
	Gastric varices	1	1.2	0.0	3.469
	Polycystic kidney and liver disease	2	2.4	0.0	5.575
	Family history of kidney disease	3	3.5	0.0	7.452
	Cirrhosis	5	5.9	0.8806	10.88
	CKD	8	9.4	3.205	15.62
	Polycystic kidney	17	20	11.5	28.5
	Roux-en-Y choledochojejunostomy	1	1.2	0.0	3.469
Surgical history	Ligation of esophageal varices	1	1.2	0.0	3.469
	Laparoscopic cholecystectomy	3	3.6	0.0	7.452
	Kidney transplant	3	3.6	0.0	7.452
	Laparotomy	3	3.6	0.0	7.452

CKD: Chronic kidney disease; CI: Confidence interval.

The sex with the greatest predisposition for this disorder has been determined to be male (56.5 %), although there is a study suggests that the female sex is the most affected, with a male:female ratio of 1:1.8[1].

Polycystic kidney, which was found in 20% of the sample, may be regarded as a predisposing factor and had the greatest impact; this fact supports the reports of other authors, who also state that polycystic kidney is frequently found in these patients[49,59-63].

The clinical manifestations of this disease are varied and can be mistaken for other abdominal conditions; however, there is trend toward 3 main manifestations, namely hepatomegaly (44.7 %), fever (42.4 %) and pain in the right hypochondrium (41.2 %), which is similar to the reports of

Table 3. Clinical features

Variable	Prevalence	n	%	95%CI	
Clinical manifestations	Pruritus	3	3.5	0.0	7.452
	Acholic feces	4	4.7	0.2043	9.207
	Loss of appetite	8	9.4	3.205	15.62
	Weight loss	8	9.4	3.205	15.62
	Abdominal distension	13	15.3	7.643	22.95
	Epigastric pain	17	20	11.5	28.5
	Jaundice	19	22.4	13.5	31.21
	Splenomegaly	20	23.52	14.51	32.55
	Generalized abdominal pain	29	34.1	24.04	44.2
	Nausea/vomiting	32	37.6	27.35	47.95
	Abdominal pain in the right hypochondrium	35	41.2	30.71	51.64
	Fever	36	42.4	31.85	52.86
	Hepatomegaly	38	44.7	34.14	55.27
Studies performed	Abdominal angiogram	2	2.38	0.0	5.575
	Intraoperative cholangiogram	2	2.38	0.0	5.575
	Choledochography	2	2.38	0.0	5.575
	Transhepatic percutaneous cholangiogram	3	3.57	0.0	7.452
	Hepatobiliary scintigraphy	4	4.76	0.2043	9.207
	Upper GI endoscopy	5	5.95	0.8806	10.88
	Scintigraphy	6	7.14	1.614	12.5
	Urography	7	8.33	2.392	14.08
	X-ray	8	9.52	3.205	15.62
	ERCP	24	28.57	18.67	37.8
	Tomography	32	38.1	27.35	47.95
	Ultrasound	35	41.67	30.71	51.64
	Resonance	62	73.81	63.5	82.39

Carrera[60] and Ahmed[59]. Therefore, the use of diagnostic aids is essential to correctly identify this disease[64].

It was observed that most articles published in the 1990s reported that the best diagnostic methods for this disease were ultrasound and tomography, based on Sood[13], Kaiser[19] and Sans[65]. However, this was variable because other authors also mentioned ERCP as the most effective method because it showed the anatomy of the biliary system more precisely[16]. It can be inferred that the most commonly used diagnostic method currently, according to the case reports reviewed by the researchers, is magnetic resonance imaging (73.81 %) because of its non-invasive nature and its excellent ability to show the biliary system and the possible association with portal hypertension and cholangiocarcinoma[62,64,66].

Regarding the findings established by means of diagnostic aids, it was possible to demonstrate intrahepatic dilatation in 76.5 % of the cases; the literature also supports this position since intrahepatic dilatation is a fundamental pillar in Caroli's disease[12,67].

In short, it could be deduced that Caroli's disease has predilection for both hepatic lobes, contrary to Murcia[68] and Sinha[69], who state that the involvement is primarily unilateral in nature with a preference for the left lobe.

There is currently no specific treatment for Caroli's disease because of its low prevalence and unknown pathophysiology mechanisms. Therefore, treatment focuses on preventing complications that may arise during the course of the disease, such as cholangitis, which is managed with antibiotics; however, it should be noted that the their use

Table 4. Therapeutic findings and characteristics

Variable	Prevalence	n	%	95%CI	
Pathognomonic findings	Liver tumor	7	8.2	2.392	14.08
	Tubule dilation	8	9.4	3.205	15.62
	Extrahepatic dilatation	10	11.8	4.916	18.61
	Renal cysts	17	20	11.5	28.5
	Cholelithiasis	26	30.6	20.79	40.38
	Dilated choledochus	37	43.5	32.99	54.07
	Intrahepatic dilatation	65	76.5	67.45	85.49
Affected lobe	Left	15	17.6	9.543	25.75
	Right	22	25.9	16.57	35.19
	Both	48	56.5	45.93	67.01
Therapeutic characteristics	Nephrectomy	2	2.4	0.0	5.575
	Biliary reconstruction	3	3.5	0.0	7.452
	Immunomodulators (cyclosporine, tacrolimus, OKT3)	4	4.7	0.2043	9.207
	Corticosteroids	6	7.1	1.614	12.5
	Cholecystectomy	6	7.1	1.614	12.5
	Segmental liver resection	7	8.2	2.392	14.08
	Ursodeoxycholic acid	9	10.6	4.048	17.13
	Transplant	14	16.5	8.586	24.36
	Sphincterotomy	35	41.2	30.71	51.64
	Antibiotic therapy (fluoroquinolones, beta-lactams)	40	47.1	36.45	57.67
Sequelae	Pyelocaliectasis	1	1.2	0.0	3.469
	Psoriasis	1	1.2	0.0	3.469
	Splenomegaly	2	2.4	0.0	5.575
	Irreversible liver injury	2	2.4	0.0	5.575
	Recurrent cholangitis	6	7.1	1.614	12.5
Mortality		8	9.4	3.205	15.62

OKT3: muromonab-CD3.

does not prevent recurrences. Other possible complications include kidney cysts and chronic kidney failure, which must be treated by nephrologists and depends on the stage of the disease[70]. Finally, liver cirrhosis may occur in advanced stages of the disease, in which other therapeutic measures such as lobectomy and liver transplantation can be used[71,72]. In this regard, timely medical intervention is critical for a good prognosis and avoiding mortality as much as possible; in the present study, Caroli's disease was the cause of death in 8 cases, accounting for 9.4% of all cases[57, 71].

The limitations of the present research are explained by the low number of clinical research studies, leading to the inclusion of reports and case series only, which does not allow for the establishment of causal inference for this disease, but do allow for the adequate characterization of these patients worldwide. Nevertheless, this limitation encourages further research of greater hierarchy in order to better understand risk factors, associations, and novel therapeutic approaches.

Finally, it was concluded that this disease has a low prevalence and occurs more frequently in developed countries, particularly the United States, which has a higher incidence of the disease because more epidemiological studies have been conducted there. This is contrary to what happens in developing countries, where epidemiological studies des-

cribing the presence of this disease are scarce. Furthermore, it was determined that involvement occurs mainly in the first decade of life; however, as was observed in the present study, Caroli's disease can occur at any stage of life, with a predominance in the male sex. Finally, the prevalence of intrahepatic duct dilatation in this disease was confirmed, as well as the possible involvement of adjacent organs, such as the kidneys, thus leading to renal cysts.

Conflicts of interest

None declared by the authors.

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