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REVIEW

Parapelvic Cysts: An Imaging Marker of Kidney Disease Potentially Leading to the Diagnosis of Treatable Rare Genetic Disorders? A Narrative Review of the Literature

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Abstract
Simple renal cysts are a common finding during abdominal imaging assessment. The incidence increases with age and it is higher in male gender. Parapelvic cysts are a subset of simple cysts that arise within the renal parenchyma, adjacent to the renal sinus, characterized by being generally single, larger, and incompletely surrounded by renal parenchyma. Noteworthy, parapelvic cysts are a rare and understudied condition which, although considered clinically insignificant due to the absence of influence on renal function, still have a controversial aetiopathogenesis. On the other hand, urological management and differential diagnosis have been thoroughly investigated. The aim of our review is to provide an overall vision on this rare condition, usually misdiagnosed and underestimated, on the basis of more recent data. An accurate differential diagnosis of parapelvic cysts can lead to the identification of treatable conditions such as Fabry disease, autosomal dominant polycystic kidney disease, polycystic liver disease and tuberous sclerosis complex disease.

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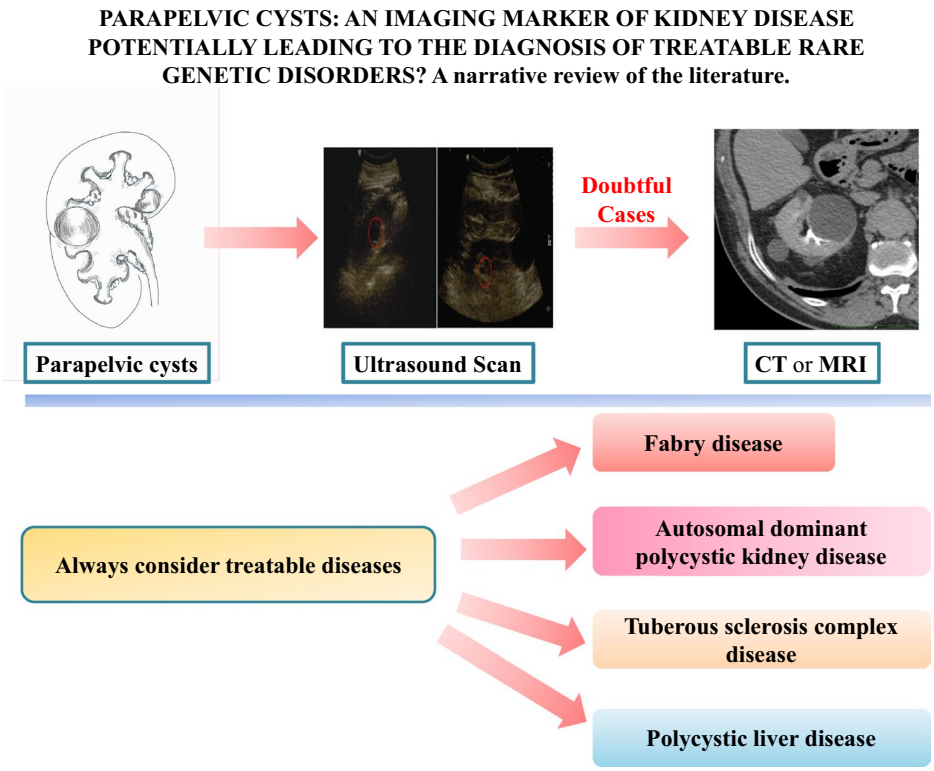
Graphical abstract



Keywords Simple renal cyst · Bosniak classification · Parapelvic cyst · Kidney injury · ADPKD · PLD · TSC · Fabry disease

Introduction

Simple renal cysts are the most common renal lesions incidentally diagnosed during abdominal imaging evaluations; on the contrary, the occurrence of parapelvic cysts, a subset of simple renal cysts, is a rare event. While urological management of parapelvic cysts has been widely investigated in recent years, only poor and outdated data are available about their clinical significance. The presence of renal cysts needs to be related to other signs and symptoms in order to identify treatable conditions (e.g. autosomal dominant polycystic kidney disease, ADPKD; tuberous sclerosis complex, TSC; polycystic liver disease, PLD). Furthermore, recent findings showed that parapelvic cysts could represent an imaging marker of Fabry disease which is a rare condition with a specific treatment. A simple renal cyst is defined as an anechoic mass with fluid content characterized by a thin and well-defined wall, in absence of *septa* or soft-tissue nodules at conventional ultrasound examination. It is known that the incidence of simple renal cysts increases with age, ranging from 0.22 to 0.55% in children up to 36% in the eighth decade. The aetiology of these lesions is unclear; they are assumed to derive from the *diverticula* of the convoluted tubules or collecting ducts [1].

Simple renal cysts are commonly found in patients with advanced chronic kidney disease (CKD), whereas their association with early forms of kidney disease is uncertain and the available data are controversial [2–4]. Parapelvic cysts arise within the renal parenchyma adjacent to the renal sinus [5]. These lesions are rarely identified in children and they account for 2.8–6% of all renal cysts in adults; in 21% of cases, they are bilateral and their presence does not correlate with renal function or kidney injury [6–8]. According to Rule et al., the incidence of parapelvic cysts directly correlates with age and male sex in a general population of potential kidney donors; on the contrary, in Fabry disease we recently found a lack of statistical association between parapelvic cysts and patients' age and sex [9, 10].

On the basis of the most recent data concerning the role of parapelvic cysts as imaging markers of renal disease and the latest therapeutic advances in urological management, we reviewed the literature to provide a comprehensive overview of this rare condition, usually misdiagnosed and underestimated [11–13].

Bosniak Classification

In 1986, Bosniak proposed the first computed tomography (CT)-based classification of renal cysts, in order to assess the risk of malignancy and determine the management of cystic renal masses; it is characterized by four categories (I, II, III, and IV) according to the morphology and the enhancement features of renal cysts, after excluding infectious, inflammatory, and vascular aetiologies. Cysts included in the first two categories were considered benign whereas the last two categories represented potentially malignant lesions requiring surgical treatment. Due to the benign characteristics of many Bosniak III cysts detected by histological analysis, the category IIF (F for follow-up) was added in 2012 to indicate "probably benign" masses needing close follow-up, whereas Bosniak III cysts were defined as "indeterminate" with an approximate risk of malignancy of 50% and treated as Bosniak IV lesions (Table 1) [14–17]. The Bosniak classification has some limitations: it is based on the imaging characteristics alone and does not consider the other factors that might affect management, like the patients' age, comorbidities, cyst location, cyst pathology, or clinical history [18]; it is operator-dependent [19]; only 50% of type III are malignant, thus leading to the surgical removal of many benign lesions. For this reason, an updated Bosniak Classification (version 2019) was proposed to formally introduce magnetic resonance imaging (MRI) to better and more objectively define the characteristics of renal lesions, to incorporate a larger proportion of renal masses commonly encountered in clinical practice, and place a larger proportion of cysts in the lower classes in order to avoid unnecessary surgery [5].

Parapelvic or Peripelvic Cysts?

The term sinus cysts includes two different patterns of cyst presentation: peripelvic cysts and parapelvic cysts. Even if these two terms are generally used as synonyms, peripelvic and parapelvic cysts are completely different not only with regard to localization, but also to number, size, and origin [20, 21]. The former are small, multiple, confluent, and present an irregular shape; they are likely to represent a congenital embryologic remnant or the *sequelae* of acquired lymphatic obstruction. On the other hand, parapelvic cysts are single and larger, localized in the sinus and most likely originating from adjacent parenchyma; their aetiology is still controversial and divergent theories regarding their pathogenesis have been proposed. Moreover, although parapelvic cysts may not be completely surrounded by renal parenchyma like simple cortical cysts, their aetiology is probably similar. Ultrasound examination is able to differentiate parapelvic cysts from peripelvic cysts, which are characterized by the presence of multiple and thin linear *septa* that extend radially from the renal hilum; furthermore, peripelvic cysts rarely cause symptoms that require treatment [20] (Figs. 1, 2).

Diagnosis and Differential Diagnosis

Parapelvic cysts are an accidental finding during nephro-urological ultrasound examination and, although they are commonly asymptomatic, in a small, but non-negligible percentage of patients, they could result in lumbar discomfort, urinary tract infection, haematuria, renin-mediated arterial hypertension, obstruction with secondary hydronephrosis, urinary calculi (facilitated by obstruction and infection), pyelonephritis, spontaneous haemorrhage, renal function decline, and may even hide malignant lesions [22, 23]. At ultrasound evaluation, parapelvic cysts appear as hypoechoic lesions of spherical shape located in the renal pelvis, in close proximity to the collecting system, though without any communication; they appear as hypodense and non-enhancing lesions on CT scan whereas at MRI they are hypointense on T1-weighted images, and hyperintense on T2-weighted images without abnormal contrast enhancement.

Table 1 Bosniak classification of cystic renal masses

CLASS	Bosniak classification
I	Hairline-thin wall; water attenuation; no septa, calcifications, or solid components; non-enhancing
II	1. Few thin septa with or without perceived (not measurable) enhancement; fine calcification or a short segment of slightly thickened calcification in the wall or septa 2. Homogeneously high-attenuating masses ≤ 3 cm that are sharply marginated and do not enhance
IIF	1. Minimally thickened or more than a few thin septa with or without perceived (not measurable) enhancement that may have thick or nodular calcification 2. Intrarenal non-enhancing hyperattenuating renal masses > 3 cm
III	Thickened or irregular walls or septa with measurable enhancement
IV	Soft-tissue components (i.e., nodules) with measurable enhancement

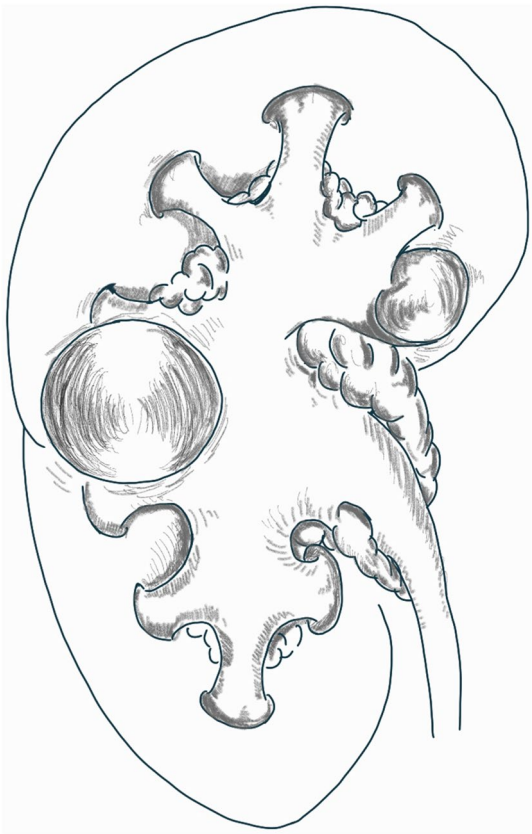


Fig. 1 Parapelvic cyst. Single and large cyst, presenting in the sinus and most likely originating from adjacent parenchyma

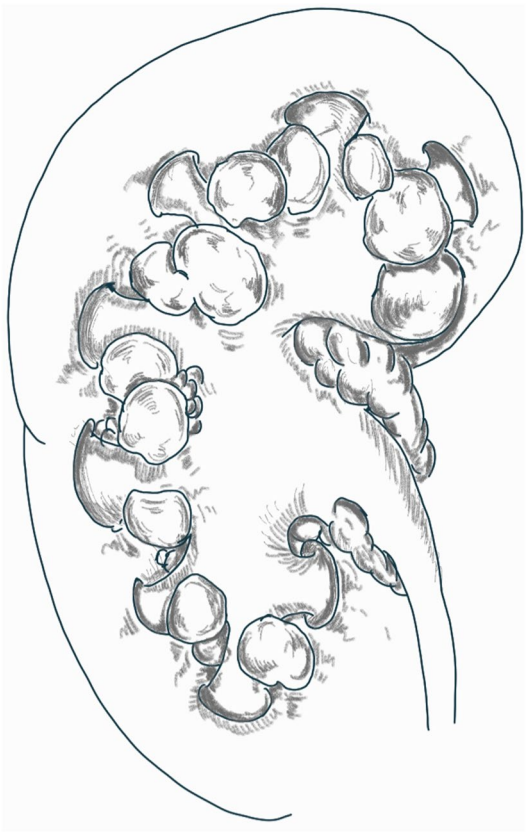


Fig. 2 Peripelvic cyst. Small, multiple, confluent and irregularly shaped cysts, raised in the renal sinus itself

Parapelvic cysts are more likely to be symptomatic compared to other types of simple renal cysts because of their close localization to vessels and urinary system [24, 25]. A careful history and physical examination, as well as other clinical findings such as hypertension, liver cysts or renal failure, facilitate the differential diagnosis. The mechanism of cyst-associated hypertension seems to be related to renal hypoperfusion and ischaemia, caused by cyst expansion and parenchymal compression which activates the renin–angiotensin–aldosterone system (the 'Page kidney' phenomenon) [26, 27]. In atypical clinical presentations, the differential diagnosis is fundamental because of the availability of specific treatments for some of the underlying conditions (Table 2) [28], such as TSC, PLD and ADPKD. TSC is a rare disease, predominantly affecting the brain, kidneys, heart, skin, and lungs, caused by the mutations of the TSC1 and TSC2 genes, encoding for hamartin and tuberin. These proteins form a complex which inhibits the mammalian target of rapamycin (mTOR) pathway and their mutation leads to the loss of cell division control resulting in renal angiomyolipoma and cysts [29]. Early diagnosis can dramatically impact the progression of the disease as specific treatments with mTOR inhibitors recently showed the ability to effectively slow the growth of cysts, reduce the need for surgery, and delay the beginning of renal replacement therapy [30–32]. PLD is another treatable rare disease, which can occur in two genetically distinct forms with similar clinical course: as a common extrarenal manifestation in ADPKD, caused by the mutation of the PKD1 and PKD2 genes, and more rarely by GANAB and DNAJB11, or as an isolated entity with limited or absent renal cysts (ADPLD), caused by the mutations in the PRKCSH and SEC63 genes that encode for sec-63 and hepatocystin proteins, which are expressed on hepatocytes and cholangiocytes, and are responsible for fluid transportation and epithelial cell growth. The use of somatostatin analogues recently showed the ability to decrease fluid production and cholangiocyte proliferation, thus reducing liver volume and improving patient symptoms [33]. ADPKD is another rare treatable condition characterized by the presence of multiple renal cysts; tolvaptan, a selective vasopressin V2 receptor antagonist, has recently been approved for the treatment of the disease as it showed that it was able to effectively slow down both kidney growth and the decline of renal function [34].

It is therefore crucial to make a differential diagnosis with hydronephrosis, which presents, instead, as interconnected

Table 2 Differential diagnosis of all kinds of renal cysts

Disease	Mutation	Genetic Transmission	Prevalence [28]	Clinical SIGNS	Treatment
Simple renal cyst	–	Acquired	Common, increases with age	Normal kidney function; normal-sized kidneys	–
Bilateral parapelvic cysts				Simple cysts that arise within the renal parenchyma adjacent to the renal sinus. They can cause obstruction of the ureter or renal pelvis	–
Acquired renal cystic disease	–	Acquired	Common	Cysts in a normal or small kidney with signs of CKD	–
Medullary cystic kidney disease	Uromodulin (encoding Tamm-Horsfall protein) on chromosome 16	Autosomal dominant	Unknown	Tubular interstitial fibrosis with normal to small-sized kidneys usually accompanied by early hyperuricemia and gout	–
Autosomal dominant polycystic kidney disease	PKD1 PKD2 GANAB DNAJB11	Autosomal dominant	39.6/100000	Multiple renal cysts that lead to renal function loss; liver, pancreas and seminal vesicles cysts, intracranial aneurisms, cardiac and vascular anomalies	[a]Tolvaptan (approved in Japan, Canada, FDA, EMA, AIFA) [b]Somatostatin analogues (approved by AIFA)
Polycystic liver disease	PRKCSH SEC63	Autosomal dominant	1/100000	Absence of cystic kidney disease, predominant polycystic liver disease and no ESRD	[b]Somatostatin analogues
Autosomal recessive polycystic kidney disease	PKD1 gene on chromosome 6	Autosomal Recessive	1: 20,000 births	Bilateral large echogenic kidneys with poor differentiation, few macrocysts, congenital hepatic fibrosis and/or Caroli's disease, no liver cystic disease	–
Fabry disease	α galactosidase A	X linked	0.22/100000	Angiokeratoma, pain, proteinuria, chronic kidney failure, cardiomyopathy, arrhythmia, cochleo-vestibular manifestations, transient ischemic attacks, strokes	[c]Enzyme replacement therapy, migalastat (FDA, EMA, AIFA)
Tuberous Sclerosis complex	TSC1 TSC2	autosomal dominant	1:5000 to 10,000	Angiomyolipomas of the kidneys, facial angiofibromas, retinal hamartomas, cerebral pathology benign neurocutaneous tumours	[d]mTOR inhibitors (approved by FDA, EMA, AIFA)
Von Hippel-Lindau syndrome	VHL	Autosomal dominant	1:50,000	Hemangioblastomas (retina and cerebellum), renal cell cancers, pancreatic tumours and pheochromocytoma. In the early stage, precancerous renal cysts	–

Table 2 (continued)

Disease	Mutation	Genetic Transmission	Prevalence [28]	Clinical SIGNS	Treatment
Orofaciodigital syndrome I	OFD1 gene	X-linked	1.2/100000	Craniofacial and digital defects, polycystic kidney disease	–
Nephronophtisis	NPHP1 to NPHP6	Autosomal recessive	1:10.000	Cysts at the corticomedullary junction without enlargement of the kidneys, ESRD generally before the second decade of life. Retinitis Pigmentosa, cerebellar ataxia, oculomotor apraxia and hepatomegaly	–
Bardet-Biedl syndrome	BBS 1–12	Autosomal recessive	0.5/100000	Polycystic kidney disease, several extrarenal defects, such as vision loss due to retinal degeneration, childhood obesity, mental retardation, malformation of the urogenital tract and polydactyly	–
Medullary sponge kidney	Unknown	Unknown	1:5000	Malformation of the distal collecting tubules with nephrolithiasis, CKD, tubular acidosis and recurrent urinary tract infections, rare ESRD	–
Localized cystic disease	–	Unknown	Rare	Unilateral location, negative family history, no progression to CKD and no extrarenal involvement	–
Renal cysts and diabetes syndrome	Hepatocyte nuclear factor 1β (HNF-1β)	Autosomal dominant	Unknown	Renal cysts, diabetes mellitus, genital tract abnormalities, hyperuricemia, hypomagnesaemia and elevated liver enzymes	–

[a]https://www.otsuka.co.jp/en/company/newsreleases/2018/20180425_1.html. https://www.ema.europa.eu/en/medicines/human/EPAR/jinarc. https://www.otsuka.co.jp/en/company/newsreleases/2019/20190828_1.html

https://www.gazzettaufficiale.it/eli/id/2020/01/08/20A00078/sg

[b]FDA grants Orphan Drug designation in the US for CAM2029 for the treatment of polycystic liver disease. News release. Camurus. Accessed September 16, 2021. https://www.prnewswire.com/news-releases/fda-grants-orphan-drug-designation-in-the-us-for-cam2029-for-the-treatment-of-polycystic-liver-disease-301378447.html

[c]https://www.ema.europa.eu/en/medicines/human/EPAR/fabrazyme

Desnick RJ. Enzyme replacement therapy for Fabry disease: lessons from two alpha-galactosidase A orphan products and one FDA approval. Expert Opin Biol Ther. 2004 Jul;4(7):1167–76. https://doi.org/10.1517/14712598.4.7.1167. PMID:15,268,683

https://www.drugs.com/history/galafold.html. https://www.ema.europa.eu/en/medicines/human/EPAR/galafold. https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004224_044884_RCP.pdf&retry=0&sys=m0b1l3

[d]https://www.ema.europa.eu/en/documents/overview/votubia-epar-medicine-overview_it.pdf

areas of decreased echogenicity and has a cauliflower appearance [11]. In patients with hydronephrosis assessed at ultrasound, parapelvic cysts should be excluded, especially when renal function is normal and there are no underlying obstructive causes. The ultrasound "convexity sign" is very useful for the differential diagnosis: it consists in identifying wall convexity of the parapelvic cysts by ultrasonographic assessment, while hydronephrosis is characterized by dilated calyces with linear walls [35]. A CT examination after intravenous injection of contrast medium is necessary in order to distinguish a dilated renal pelvis from a parapelvic cyst; in fact, a mass within the renal sinus is considered a parapelvic cyst at CT scan if it is homogeneous, with an attenuation coefficient similar to water, no enhancement after intravenous infusion of contrast medium and no visible wall of the portion projecting outside the renal margin. Koratala et al. recently described the case of a parapelvic cyst mimicking hydronephrosis, casually identified in a potential kidney donor during ultrasound assessment; it was further investigated by contrast-enhanced CT, in which parapelvic cysts demonstrated to be distinct from the normal contrast-filled collecting system thus demonstrating the absence of hydronephrosis [13, 36]; this case clearly showed that, even if ultrasound suffices in most cases to identify parapelvic cysts, some lesions have to be investigated by CT to determine their nature. Moreover, excretory urogram could be used to identify the mass and exclude hydronephrosis when CT is not performed. Noteworthy, ultrasound is operator-dependent compared to CT and other techniques, which could be required to differentiate parapelvic cysts from other lesions such as renal sinus lipomatosis, easily diagnosed by CT due to the characteristic attenuation of fat. On the other hand, radiation and contrast medium used for CT urography, could outweigh the clinical benefits, especially in asymptomatic patients who do not require intervention (Figs. 3, 4 and 5). Interestingly, in a recent retrospective study, Dong et al. demonstrated that pre-contrast dual-energy spectral CT imaging, a new CT imaging mode that produces virtual monochromatic images, may be used to differentiate parapelvic cysts from hydronephrosis with no calculi in asymptomatic patients, thereby avoiding contrast-enhanced CT or CT urography examination [37].

In the near future, renal cysts will be analysed by an artificial intelligence algorithm leading to an automatic estimate of the risk of malignancy, and many studies have already been performed to investigate the application of machine-learning to the diagnosis of these lesions [38].

Parapelvic Cysts in Fabry Disease

Fabry disease is a rare X-linked genetic disorder of glycosphingolipid catabolism caused by mutations in the α-galactosidase A gene [39]. It is characterized by a heterogeneous presentation and paucity of specific early markers, often leading to a delayed or missed diagnosis [40, 41]. The recognition of Fabry disease is important because effective treatments are available, including enzyme replacement therapy (agalsidase alfa and agalsidase beta) and the chaperone migalastat. Several new compounds are being studied, including new forms of enzyme replacement therapy, substrate reduction therapy, mRNA, and gene therapies [42]. Noteworthy, in order to achieve a significant clinical benefit, it is fundamental to start the treatment in an early phase, before the development of organ damage. In this perspective, the identification of parapelvic cysts should warn both nephrologists and radiologists to consider the diagnosis of Fabry disease and many literature data strongly support a correlation between this type of renal lesions and Fabry disease [43, 44]. Recently, we conducted a multicentre retrospective study in a nationwide cohort of Fabry disease patients to evaluate the real prevalence of parapelvic cysts which have already been associated with Fabry disease: parapelvic cysts were detected in 28.9% of patients with Fabry disease vs 1.1% of control subjects by ultrasonography. Therefore, a more accurate ultrasound evaluation led to a 43.3% higher detection rate of parapelvic cysts in the same subjects. These data confirmed the previous results which reported a prevalence of 50% of parapelvic cysts in Fabry disease patients detected by CT or MRI [45]. More recently, Neves et al. also highlighted the more frequent occurrence of parapelvic cysts in Fabry disease patients compared to different glomerulopathies, regardless of the age, gender, and stage of CKD [46]. It is not clear if the parapelvic cysts in Fabry disease could be related to the defect of glycosphingolipid metabolism; we may hypothesize that cyst genesis is multifactorial and is the result of a variety of gene mutations, suggesting that different positions of cysts correspond to different molecular pathways underlying their development [47–51]. Finally, it would be useful to investigate the relationship between different genotypes of Fabry disease and the phenotype of parapelvic cysts, and to determine whether these characteristic lesions could be a risk factor for a more rapid worsening of renal function.

Treatment

Currently, there are no formal guidelines regarding the management and treatment of simple renal cysts. Moreover, parapelvic cysts represent a further concern due to their specific anatomical structure and deep location in the renal pelvis which could cause injury to renal blood vessels and collecting system [52, 53]. Renal cysts can be treated through minimally invasive procedures such as aspiration or sclerotherapy; both techniques are limited, respectively, by the high possibility of recurrence and the potential extravasation of

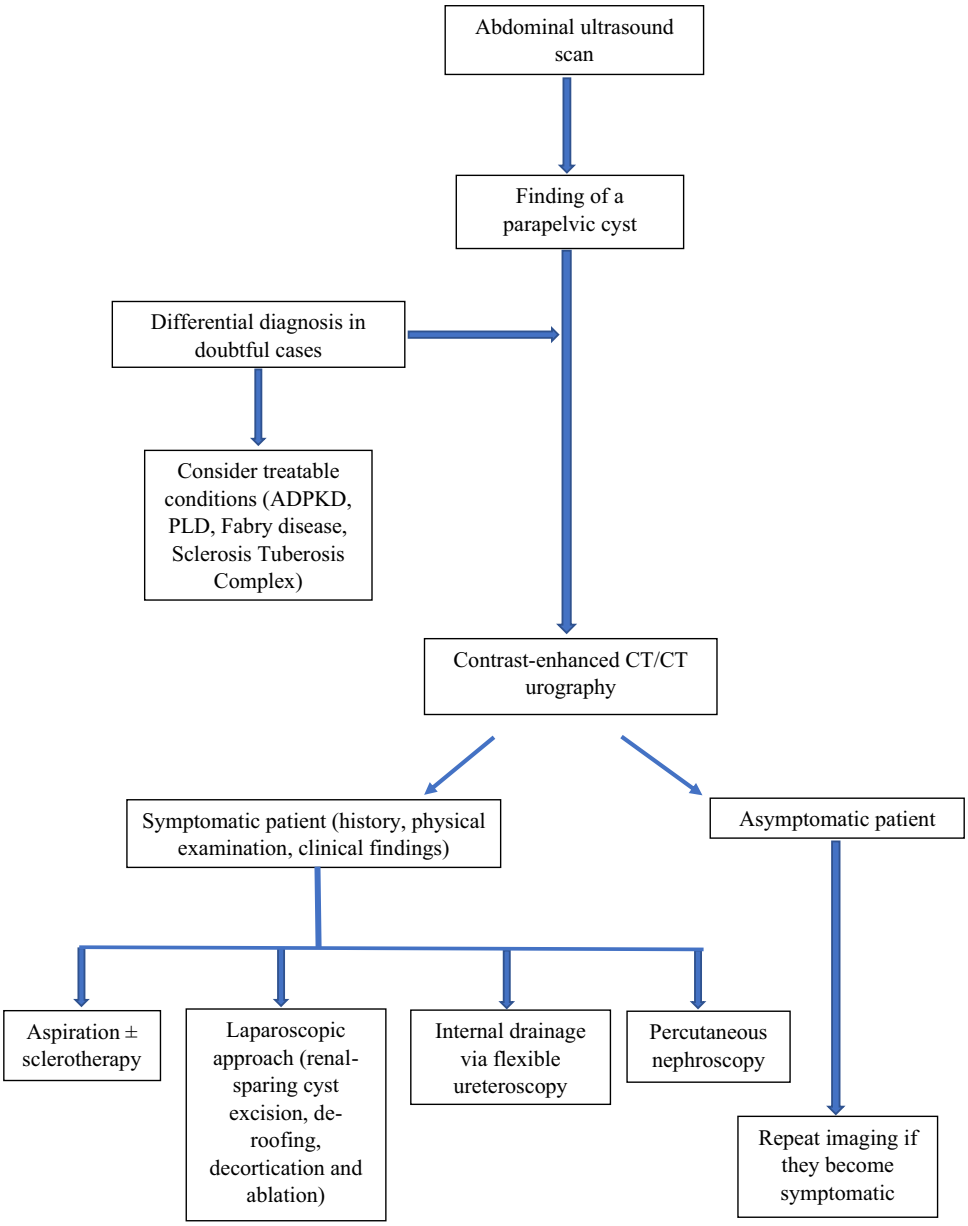


Fig. 3 Flow chart for diagnosis and treatment of parapelvic cysts

the sclerosing agents, which could lead to potentially serious complications such as retroperitoneal inflammation (further associated with ureteropelvic junction obstruction, fever, and pain) [54, 55]. Laparoscopic renal-sparing cyst excision, de-roofing, decortication, and ablation are currently considered the gold standard in the treatment of symptomatic cysts, with success rates reaching up to 96% and a limited rate of intra- and post-operative complications (1–1.4%) [56]. However, due to the peculiar anatomical characteristics of parapelvic cysts, specialized surgical skills are required to properly treat large parapelvic cysts [57]. More recently, due to the close anatomical proximity between parapelvic cysts and renal pelvis, internal drainage via flexible ureteroscopy has been reported as another feasible, effective, and safe alternative to the laparoscopic approach. In a comparative analysis between ureteroscopy and laparoscopic surgery, both techniques obtained a comparable rate of success, with fewer complications, shorter operative time, and reduced length of stay in hospital in the group undergoing ureteroscopic treatment [58]. The technique is indeed particularly advantageous: it consists in a limited cut (< 1 cm) performed with a Holmium laser under direct vision, and in the subsequent drainage obtained with a double J tube. In a case-series by Zhao et al., 27/28 patients were successfully treated and only 1 case recurred (median follow up 39 months) [22]. The use of the flexible ureteroscope has further extended the applicability of the retrograde approach, even in parapelvic cysts positioned in disadvantageous locations for the rigid

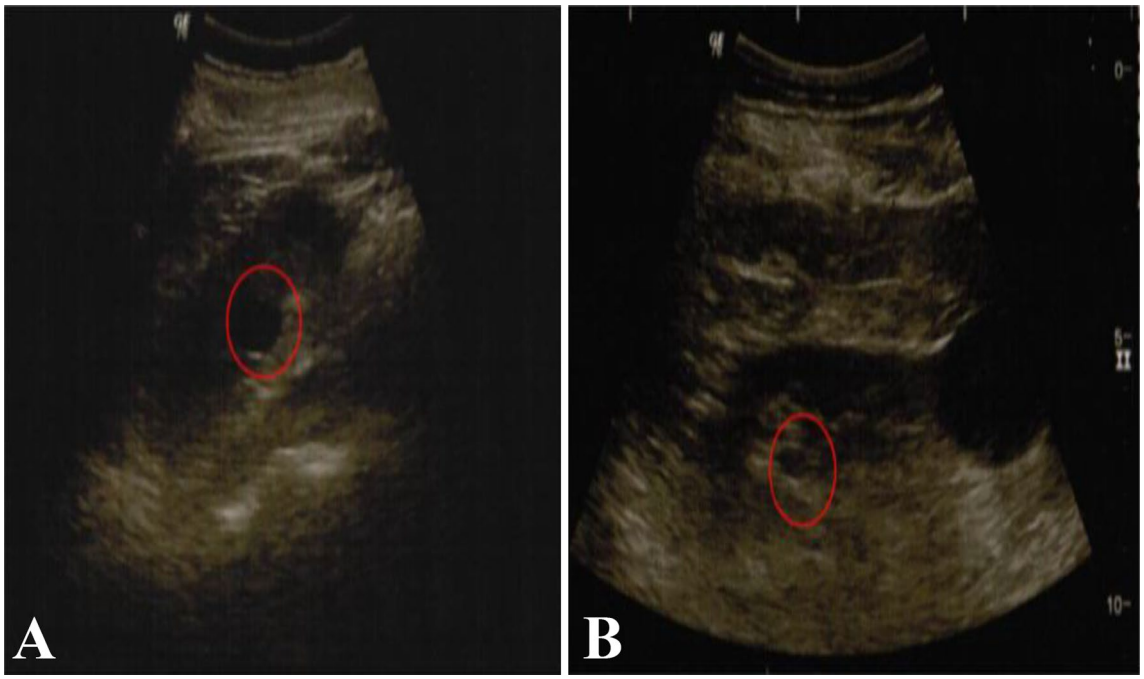


Fig. 4 Evaluation of parapelvic cysts with ultrasound imaging

ureteroscope (as the lower calices) [22, 54, 55]. The retrograde approach has, moreover, another significant advantage, i.e. the possibility to simultaneously treat parapelvic cysts and renal stones [56–59]. Interestingly, as an alternative to ureteroscopy, Yang et al. performed percutaneous nephroscopy in a single obese patient in order to treat parapelvic cysts and ipsilateral stones [60].

Lastly, the retrograde approach overcomes the relative and absolute limitations of the laparoscopic approach, which are, respectively, the treatment of obese patients and of patients who previously underwent abdominal or retroperitoneal surgery (Fig. 3) [61–64].

Limitations

Our work aims to provide an overview on a very rare condition and to update readers on this specific topic, playing a significant role in continuing education; this work has some important limitations that should be taken into account for the appropriate interpretation of this review. First, the selection of the literature underwent convenience sampling, this review was neither protocol-driven nor systematic. Therefore, bias cannot be ruled out. Second, we provide a qualitative synthesis with no statistical analysis, so our conclusions cannot be considered objective and comprehensive of all the available data; consequently, the synthesized evidence may be incomplete, selected in a biased way and difficult to interpret because of the lack of quality assessment. Nevertheless, this narrative review provides a deep, reflective, and thoughtful understanding of the clinical importance of the diagnosis of parapelvic cysts.

Conclusions

Parapelvic cysts are rare lesions accidentally found on imaging tests, more often symptomatic compared to other renal cysts. Although parapelvic cysts were considered clinically unimportant and not associated with the decline of kidney function, more recent data suggest that their incidence in some rare renal pathological conditions such as Fabry disease can be higher than in the general population, raising the awareness that parapelvic cysts could lead to the diagnosis of rare and otherwise likely undiagnosed treatable conditions. Parapelvic cysts have to be differentiated from renal cysts with different localizations, which can be found in other treatable conditions such as ADPKD, PLD, TSC. In this perspective, parapelvic cysts could represent an important imaging marker of some renal diseases even before their clinical manifestation thus allowing nephrologists to early and properly start specific treatments.

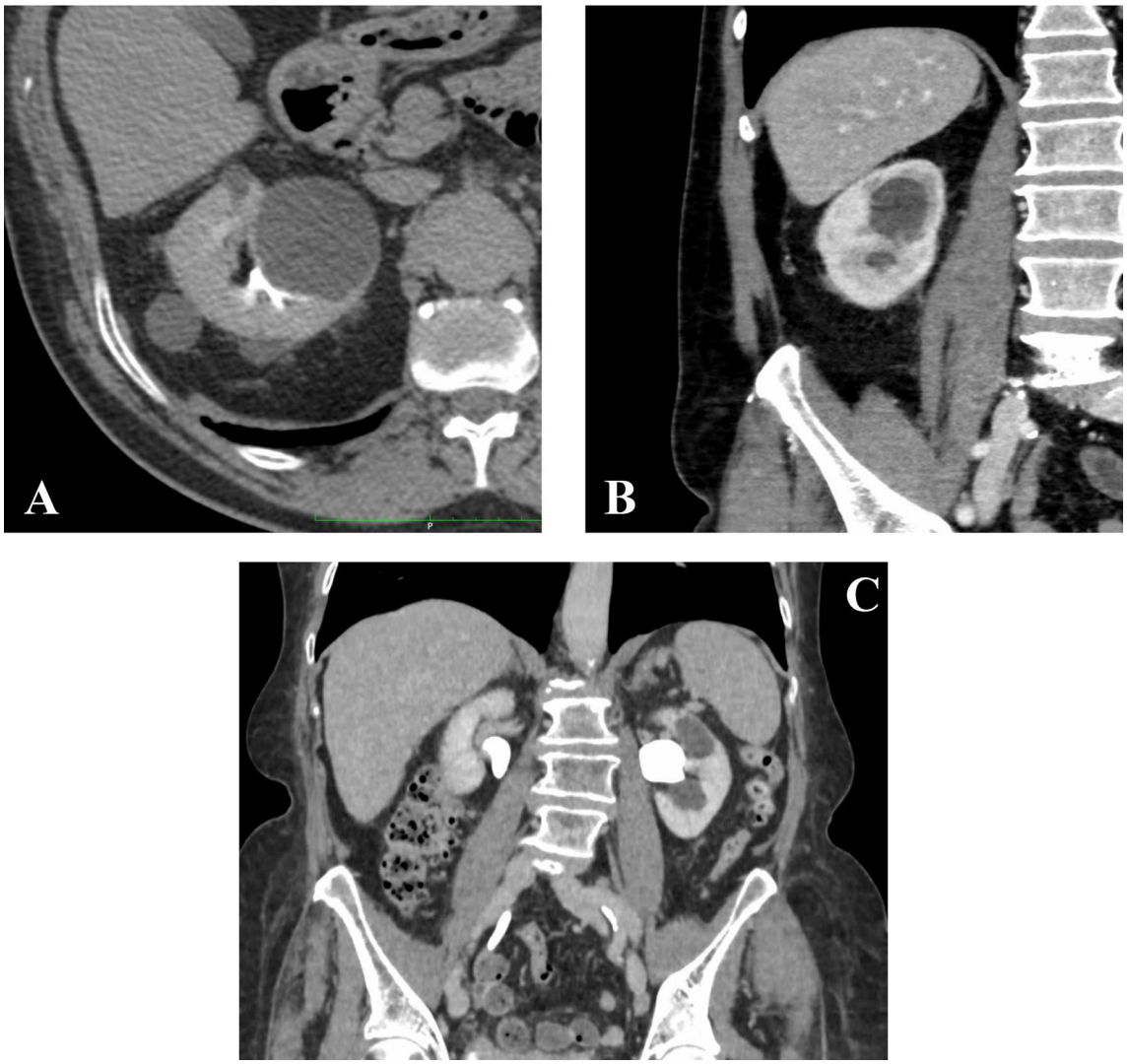


Fig. 5 Evaluation of parapelvic cysts with computed tomography imaging

Data availability statement The data underlying this article are available in the article.

Declarations

Conflict of interest statement None declared.

Ethical approval For this type of study (i.e. review article) ethical approval is not required.

References

1. Skolarikos A, Laguna MP, de la Rosette JJ (2012) Conservative and radiological management of simple renal cysts: a comprehensive review. BJU Int 110(2):170–178. https://doi.org/10.1111/j.1464-410X.2011.10847.x (**Epub 2012 Mar 13 PMID: 22414207**)
2. Levine E (1996) Acquired cystic kidney disease. Radiol Clin N Am 34(5):947–964 (**PMID: 8784391**)
3. Chin HJ, Ro H, Lee HJ, Na KY, Chae DW (2006) The clinical significances of simple renal cyst: is it related to hypertension or renal dysfunction? Kidney Int 70(8):1468–1473. https://doi.org/10.1038/sj.ki.5001784 (**Epub 2006 Aug 30 PMID: 16941027**)
4. Ozdemir AA, Kapucu K (2017) The relationship between simple renal cysts and glomerular filtration rate in the elderly. Int Urol Nephrol 49(2):313–317. https://doi.org/10.1007/s11255-016-1414-9 (**Epub 2016 Sep 9 PMID: 27613295**)
5. Silverman SG, Pedrosa I, Ellis JH et al (2019) Bosniak classification of cystic renal masses, version 2019: an update proposal and needs assessment. Radiology 292(2):475–488. https://doi.org/10.1148/radiol.2019182646 (**Epub 2019 Jun 18. PMID: 31210616; PMCID: PMC6677285**)
6. Henthorne JC (1938) Peripelvic lymphatic cysts of the kidney: a review of the literature on perinephric cysts. Am J Clin Pathol 8(1):28–38. https://doi.org/10.1093/ajcp/8.1.28
7. Jordan WP Jr (1962) Peripelvic cysts of the kidney. J Urol 87:97–101. https://doi.org/10.1016/s0022-5347(17)64914-0 (**PMID: 14452449**)

8. Patel K, Caro PA, Chatten J (1988) Parapelvic renal cyst causing UPJ obstruction. Investigation by IVP, ultrasound and CT. Pediatr Radiol 19(1):2–5. https://doi.org/10.1007/BF02388397 (**PMID: 3065710**)
9. Rule AD, Sasiwimonphan K, Lieske JC, Keddis MT, Torres VE, Vrtiska TJ (2012) Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. Am J Kidney Dis 59(5):611–618. https://doi.org/10.1053/j.ajkd.2011.12.022 (**Epub 2012 Mar 6. PMID: 22398108; PMCID: PMC3328591**)
10. Pisani A, Petruzzelli Annicchiarico L, Pellegrino A et al (2018) Parapelvic cysts, a distinguishing feature of renal Fabry disease. Nephrol Dial Transplant 33(2):318–323. https://doi.org/10.1093/ndt/gfx009 (**PMID: 28371803**)
11. Tarzamni MK, Sobhani N, Nezami N, Ghiasi F (2008) Bilateral parapelvic cysts that mimic hydronephrosis in two imaging modalities: a case report. Cases J 1(1):161. https://doi.org/10.1186/1757-1626-1-161 (**PMID:18801196;PMCID:PMC2577646**)
12. Ma TL, Neild GH (2013) Parapelvic cyst misdiagnosed as hydronephrosis. Clin Kidney J 6(2):238–239. https://doi.org/10.1093/ckj/sfs189 (**Epub 2013 Feb 1. PMID: 26019858; PMCID: PMC4432443**)
13. Choi HS, Kim CS, Bae EH, Ma SK, Kim SW (2019) Bilateral parapelvic cyst misdiagnosed as hydronephrosis. Chonnam Med J 55(1):65. https://doi.org/10.4068/cmj.2019.55.1.65 (**Epub 2019 Jan 25. PMID: 30740344; PMCID: PMC6351317**)
14. Bosniak MA (2012) The Bosniak renal cyst classification: 25 years later. Radiology 262(3):781–785. https://doi.org/10.1148/radiol.11111595 (**PMID: 22357882**)
15. Silverman SG, Israel GM, Herts BR, Richie JP (2008) Management of the incidental renal mass. Radiology 249(1):16–31. https://doi.org/10.1148/radiol.2491070783 (**PMID: 18796665**)
16. Herts BR, Silverman SG, Hindman NM et al (2018) Management of the incidental renal mass on CT: a white paper of the ACR incidental findings committee. J Am Coll Radiol 15(2):264–273. https://doi.org/10.1016/j.jacr.2017.04.028 (**Epub 2017 Jun 23 PMID: 28651987**)
17. Schoots IG, Zaccai K, Hunink MG, Verhagen PCMS (2017) Bosniak classification for complex renal cysts reevaluated: a systematic review. J Urol 198(1):12–21. https://doi.org/10.1016/j.juro.2016.09.160 (**Epub 2017 Mar 9 PMID: 28286071**)
18. Israel GM, Bosniak MA (2005) An update of the Bosniak renal cyst classification system. Urology 66(3):484–488. https://doi.org/10.1016/j.urology.2005.04.003 (**PMID: 16140062**)
19. Siegel CL, McFarland EG, Brink JA, Fisher AJ, Humphrey P, Heiken JP (1997) CT of cystic renal masses: analysis of diagnostic performance and interobserver variation. AJR Am J Roentgenol 169(3):813–818. https://doi.org/10.2214/ajr.169.3.9275902 (**PMID: 9275902**)
20. Amis ES Jr, Cronan JJ (1988) The renal sinus: an imaging review and proposed nomenclature for sinus cysts. J Urol 139(6):1151–1159. https://doi.org/10.1016/s0022-5347(17)42845-x (**PMID: 3286890**)
21. Wilson SR, Withers C, Wilson S, Charboneau W (2005) The urinary tract. diagnostic. Ultrasound 1:373
22. Hinman F Jr (1978) Obstructive renal cysts. J Urol 119(5):681–683. https://doi.org/10.1016/s0022-5347(17)57588-6 (**PMID: 660744**)
23. Umemoto Y, Okamura T, Akita H, Yasui T, Kohri K (2009) Clinical evaluation of parapelvic renal cysts: do these represent latent urological malignant disease? Asian Pac J Cancer Prev 10(6):1119–1120 (**PMID: 20192595**)
24. Zhao Q, Huang S, Li Q et al (2015) Treatment of parapelvic cyst by internal drainage technology using ureteroscope and holmium laser. West Indian Med J 64(3):230–235. https://doi.org/10.7727/wimjopen.2014.220 (**Epub 2015 Sep 14. PMID: 26426175; PMCID: PMC4763897**)
25. Lee J, Darcy M (2011) Renal cysts and urinomas. Semin Intervent Radiol 28(4):380–391. https://doi.org/10.1055/s-0031-1296080 (**PMID:23204636;PMCID:PMC3312170**)
26. Lüscher TF, Wanner C, Siegenthaler W, Vetter W (1986) Simple renal cyst and hypertension: cause or coincidence? Clin Nephrol 26(2):91–95 (**PMID: 3530568**)
27. Johnson JD, Radwin HM (1976) High renin hypertension associated with renal cortical cyst. Urology 7(5):508–511. https://doi.org/10.1016/0090-4295(76)90192-8 (**PMID: 1274011**)
28. Rath A, Yamakazi M (2022) Prevalence of rare diseases: Bibliographic data », Orphanet Report Series, Rare Diseases collection, January 2022, Number 2: Diseases listed by decreasing prevalence, incidence or number of published cases. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf. Accessed 2 May 2022.
29. Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ, Cantley LC, Blenis J (2002) Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc Natl Acad Sci USA 99(21):13571–13576
30. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group (2013) Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol 49(4):243–254
31. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Belousova E, Frost MD et al (2017) Everolimus long-term use in patients with tuberous sclerosis complex: four-year update of the EXIST-2 study. PLoS ONE 12(8):e0180939
32. Vabret E, Couchoud C, Lassalle M, Vigneau C (2021) From tuberous sclerosis complex to end stage renal disease: who are these patients? J Nephrol 34(2):607–615. https://doi.org/10.1007/s40620-020-00714-3 (**Epub 2020 Mar 4 PMID: 32130718**)
33. Garofalo C, Capuano I, Pennino L, De Gregorio I, Riccio E, Provenzano M, Crocetto F, Buonanno P, Pandolfo SD, Andreucci M, Pisani A (2021) The effects of somatostatin analogues on liver volume and quality of life in polycystic liver disease: a meta-analysis of randomized controlled trials. Sci Rep 11(1):23500. https://doi.org/10.1038/s41598-021-02812-z (**PMID:34873228;PMCID:PMC8648823**)
34. Capuano I, Buonanno P, Riccio E, Rizzo M, Pisani A (2022) Tolvaptan vs. somatostatin in the treatment of ADPKD: a review of the literature. Clin Nephrol 97(3):131–140. https://doi.org/10.5414/CN110510 (**PMID: 34846296**)
35. Trapani AR, Tamburri L, Di Giandomenico V, De Pascale A, Bonomo L (1992) Idronefrosi e cisti peripieliche. Un nuovo segno ecografico per la diagnosi differenziale [Hydronephrosis and peripelvic cysts. A new echographic sign for the differential diagnosis]. Radiol Med 83(6):777–782 (**Italian. PMID: 1502358**)
36. Koratala A, Alquadan KF (2018) Parapelvic cysts mimicking hydronephrosis. Clin Case Rep 6(4):760–761. https://doi.org/10.1002/ccr3.1431 (**PMID:29636957;PMCID:PMC5889270**)
37. Han D, Ma G, Wei L et al (2017) Preliminary study on the differentiation between parapelvic cyst and hydronephrosis with non-calculous using only pre-contrast dual-energy spectral CT scans. Br J Radiol 90(1073):20160632. https://doi.org/10.1259/bjr.20160632 (**Epub 2017 Mar 10. PMID: 28281789; PMCID: PMC5605099**)
38. Miskin N, Qin L, Matalon SA et al (2021) Stratification of cystic renal masses into benign and potentially malignant: applying machine learning to the bosniak classification. Abdom Radiol (NY) 46(1):311–318. https://doi.org/10.1007/s00261-020-02629-w (**Epub 2020 Jul 1 PMID: 32613401**)

39. Riccio E, Capuano I, Visciano B, Marchetiello C, Petrillo F, Pisani A (2013) Terapia enzimatica sostitutiva in pazienti con malattia di Fabry [Enzyme replacement therapy in patients with Fabry disease: state of the art and review of the literature]. G Ital Nefrol 30(5):gin/30.5.5 (**Italian. PMID: 24402625**)
40. Capuano I, Garofalo C, Buonanno P et al (2020) Identifying Fabry patients in dialysis population: prevalence of GLA mutations by renal clinic screening, 1995–2019. J Nephrol 33(3):569–581. https://doi.org/10.1007/s40620-019-00663-6 (**Epub 2019 Oct 24 PMID: 31650418**)
41. Riccio E, Sabbatini M, Capuano I, Pisani A (2019) Early biomarkers of fabry nephropathy: a review of the literature. Nephron 143(4):274–281. https://doi.org/10.1159/000502907 (**Epub 2019 Oct 15 PMID: 31614349**)
42. Garbade SF, Zielonka M, Mechler K et al (2020) FDA orphan drug designations for lysosomal storage disorders—a cross-sectional analysis. PLoS ONE 15(4):e0230898. https://doi.org/10.1371/journal.pone.0230898 (**PMID:32267884;PMCID: PMC7141691**)
43. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Sousa N, Cunha D (2020) Fabry disease therapy: state-of-the-art and current challenges. Int J Mol Sci 22(1):206. https://doi.org/10.3390/ijms22010206.PMID:33379210;PMCID:PMC7794923
44. Sayer JA, Haslam P, Brennan P (2008) Parapelvic cysts leading to a diagnosis of Fabry disease. Kidney Int 74(10):1366. https://doi.org/10.1038/ki.2008.141 (**PMID: 18974770**)
45. Ries M, Bettis KE, Choyke P et al (2004) Parapelvic kidney cysts: a distinguishing feature with high prevalence in Fabry disease. Kidney Int 66(3):978–982. https://doi.org/10.1111/j.1523-1755.2004.00846.x (**PMID: 15327390**)
46. Azambuja Neves RFC, Varela P, Fernandes DE et al (2020) Renal ultrasound contributes to Fabry disease diagnosis. J Rare Dis Res Treat 5(2):19–23. https://doi.org/10.29245/2572-9411/2020/2.1195
47. Deshmukh GD, Radin NS, Gattone VH II et al (1994) Abnormalities of glycosphingolipid, 7 sulfatide and ceramide in the polycystic (cpk/cpk) mouse. J Lipid Res 35:1611–1618
48. Chatterjee S, Shi WY, Wilson P et al (1996) Role of lactosylceramide and MAP kinase in the proliferation of proximal tubular cells in human polycystic kidney disease. J Lipid Res 37:1334–1344
49. Janich P, Corbeil D (2007) GM1 and GM3 gangliosides highlight distinct lipid microdomains within the apical domain of epithelial cells. FEBS Lett 581:1783–1787
50. Natoli TA, Smith LA, Rogers KA et al (2010) Inhibition of glucosylceramide accumulation results in effective blockade of polycystic kidney disease in mouse models. Nat Med 16(7):788–792. https://doi.org/10.1038/nm.2171 (**Epub 2010 Jun 20. PMID: 20562878; PMCID: PMC3660226**)
51. Capuano I, Buonanno P, Riccio E, Amicone M, Pisani A (2021) Therapeutic advances in ADPKD: the future awaits. J Nephrol. https://doi.org/10.1007/s40620-021-01062-6 (**Epub ahead of print. PMID: 34009558**)
52. Yoder BM, Wolf JS Jr (2004) Long-term outcome of laparoscopic decortication of peripheral and peripelvic renal and adrenal cysts. J Urol 171(2 Pt 1):583–587. https://doi.org/10.1097/01.ju.0000103642.29044.71 (**PMID: 14713764**)
53. Mao X, Xu G, Wu H, Xiao J (2015) Ureteroscopic management of asymptomatic and symptomatic simple parapelvic renal cysts. BMC Urol 6(15):48. https://doi.org/10.1186/s12894-015-0042-5 (**PMID:26048408;PMCID:PMC4456808**)
54. Rossi SH, Koo B, Riddick A, Shah N, Stewart GD (2018) Different successful management strategies for obstructing renal parapelvic cysts. Urol Int 101(3):366–368. https://doi.org/10.1159/000475886 (**Epub 2017 May 12 PMID: 28494441**)
55. Agarwal M, Agrawal MS, Mittal R, Sachan V (2012) A randomized study of aspiration and sclerotherapy versus laparoscopic deroofing in management of symptomatic simple renal cysts. J Endourol 26(5):561–565. https://doi.org/10.1089/end.2011.0559 (**Epub 2012 Jan 25 PMID: 22091534**)
56. Nalagatla S, Manson R, McLennan R, Somani B, Aboumarzouk OM (2019) Laparoscopic decortication of simple renal cysts: a systematic review and meta-analysis to determine efficacy and safety of this procedure. Urol Int 103(2):235–241. https://doi.org/10.1159/000497313 (**Epub 2019 Mar 19 PMID: 30889610**)
57. Ma Z, Li S, Chen FM et al (2020) The preliminary experience of methylene blue assisted laparoscopy in the treatment of renal parapelvic cysts. Sci Rep 10(1):18757. https://doi.org/10.1038/s41598-020-76006-4 (**PMID:33128007;PMCID:PMC7599209**)
58. Chen H, Chen G, Pan Y, Jin X (2021) Minimally invasive surgeries in the management of renal parapelvic cysts: a retrospective comparative study. Urol J 18(4):389–394. https://doi.org/10.22037/uj.v16i7.6466 (**PMID: 33495985**)
59. Basiri A, Hosseini SR, Tousi VN, Sichani MM (2010) Ureteroscopic management of symptomatic, simple parapelvic renal cyst. J Endourol 24(4):537–540. https://doi.org/10.1089/end.2009.0326 (**PMID: 20092413**)
60. Yang B, Li J, Liu J, Bao Y, Mishra P, Guo H, Li P, Jiang Y (2018) Safe surgical treatment of peripelvic renal cyst combined with renal calculi by percutaneous nephroscopy. Clin Case Rep 6(2):370–375. https://doi.org/10.1002/ccr3.1302 (**PMID: 29445479; PMCID: PMC5799636**)
61. Zewu Z, Hequn C, Yu C et al (2019) Long-term outcome after flexible ureteroscopy with holmium laser for simultaneous treatment of a single renal cyst and ipsilateral renal stones. J Int Med Res 47(8):3601–3612. https://doi.org/10.1177/0300060519855573 (**Epub 2019 Jun 20. PMID: 31218939; PMCID: PMC6726797**)
62. Mancini V, Cormio L, d'Altilia N et al (2018) Retrograde intrarenal surgery for symptomatic renal sinus cysts: long-term results and literature review. Urol Int 101(2):150–155. https://doi.org/10.1159/000488685 (**Epub 2018 May 2 PMID: 29719301**)
63. Shen J, Chen Y, Wang R (2019) Efficacy and complication of flexible ureteroscopic holmium laser incision for simple renal cysts: a retrospective study. J Endourol 33(11):881–886. https://doi.org/10.1089/end.2019.0515 (**PMID: 31710258**)
64. Kang N, Guan X, Song L, Zhang X, Zhang J (2018) Simultaneous treatment of parapelvic renal cysts and stones by flexible ureterorenoscopy with a novel four-step cyst localization strategy. Int Braz J Urol 44(5):958–964. https://doi.org/10.1590/S1677-5538.IBJU.2018.0074.PMID:30088721;PMCID:PMC6237515