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Diagnostic Imaging of Autosomal Dominant Polycystic Kidney Disease

Monika Gradzik¹✉, Mariusz Niemczyk²✉, Marek Gołębiowski¹✉, Leszek Pączek²✉

¹ Department of Clinical Radiology, Medical University of Warsaw, Warsaw, Poland

² Department of Immunology, Transplant Medicine and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

Author's address: Monika Gradzik, Department of Clinical Radiology, Medical University of Warsaw, Warsaw, Poland,
e-mail: mpolej@o2.pl

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Summary

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorders caused by a single gene mutation.

The disease usually manifests itself at the age of 30–40 years and is characterized by formation of renal cysts along with the enlargement of kidneys and deterioration of their function, eventually leading to renal insufficiency.

Imaging studies (sonography, computed tomography, magnetic resonance imaging) play an important role in the diagnostics of the disease, the monitoring of its progression, and the detection of complications. Imaging is also helpful in detecting extrarenal manifestations of ADPKD, most significant of which include intracranial aneurysms and cystic liver diseases.

Background

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorders caused by single gene mutations and occurs in 1 in every 1000 individuals in the overall population, based on the number of clinical diagnoses. Including the cases diagnosed during autopsies, the mean estimated incidence is about 1 in 400 individuals. ADPKD is considered to be one of the main causes of renal insufficiency [1].

The disorder is passed down in autosomal dominant pattern with varied expression, albeit nearly always with 100% penetrance of mutated genes PKD1 or PKD2. PKD1 gene was localized on the long arm of chromosome 16 (16p13.3-p13.12) as a gene encoding for polycystin-1 protein. PKD2 gene is located on the long arm of chromosome 4 (4q21-q23) and encodes for polycystin-2 protein. Both these transmembrane proteins are present within the primary cilia of renal tubular epithelial cells. Polycystin-1 is a ciliary mechanoreceptor while polycystin-2 is its coupled calcium channel. Abnormal structure and function of

the cilia leads to disturbed function of the calcium channels, increased intracellular calcium, disturbed homeostasis, deregulated proliferation of tubular cells, dilation of tubules and development of renal cysts. Renal cysts in the course of ADPKD originate from about 1–2% of nephrons and may develop in any of the kidney segments [1]. As the disease progresses and cysts are enlarged, the remaining part of the kidney deteriorates gradually.

Mutation of PKD1 gene occurs in 85% of patients while mutation of PKD2 gene occurs in 15% of patients. In Polish population, mutation of PKD1 was observed in 95% of patients. Usually passed down in a dominant pattern, the disease occurs spontaneously without any family history in 5–10% of cases [2]. The risk of the disease being passed down to the offspring is 50%.

Clinical manifestations of the disease caused by the mutation of either of the genes is similar. However, PKD1 mutation is responsible for an earlier onset and more severe course of the disease. On average, end-stage renal disease developing from type 1 ADPKD develops 10 years earlier

than in the case of type 2 ADPKD. Among the PKD1 mutation variants, individuals with mutation within the 5L' region are affected in a more severe manner than patients with mutation within the 3L' (18.9% vs. 39.7% of individuals with normal renal function at the age of 60). Intracranial aneurysms are also more common in the former group [3–5].

The disease is manifested at the age of about 30–40, and therefore is referred to in Polish as polycystic renal degeneration in adults (previously adult-type cystic kidney disease). It is associated with the development of numerous cysts progressing in an exponential manner [6,7]. Already in the initial period, renal blood flow becomes disturbed [8]. One of the first symptoms consists in poor urinary concentration; renal insufficiency develops at a later period [9].

Not only the kidneys are affected in the pathological course of ADPKD. Extrarenal manifestations include formation of cysts within other organs, most commonly liver, pancreas, and spleen. Seminal vesicle cysts and arachnoid cysts are also more common than in the general population.

Usually, ADPKD patients suffer from acute or chronic pains (mostly caused by infection or intracystic bleeding), hematuria, urinary tract infections, nephrolithiasis and arterial hypertension (occurring in all patients at later disease stages).

In some cases, the large, growing cysts are the direct cause of the pain.

Also observed are mitral valve prolapse, intracranial artery aneurysms or dolichoectasias, aortic aneurysms, abdominal (particularly inguinal) hernias, and diverticulitis. Due to the population of the study groups being too low and the disease being relatively rare, incidental concomitance of ADPKD with some of these pathologies (e.g. diverticulitis) is unlikely [10].

The clinical course and prognosis in ADPKD are affected not only by early detection, but also by the assessment of the kidney cyst enlargement process. The latter parameter determines the occurrence of arterial hypertension and decrease in glomerular filtration leading to secondary renal failure. Most important among the extrarenal disorders that accompany ADPKD are hepatic cysts and intracranial aneurysms. Other pathologies usually have no impact on the natural history of ADPKD.

Diagnosis

In ADPKD, the most sensitive diagnostic method consists in genetic testing. Currently, genetic testing is used only in research studies and in special clinical situations (e.g. as part of final diagnosis in a potential living kidney donor) [11–13]. This is due to the high cost and labor consumption of genetic tests compared with the relative ease of clinical diagnosis as well as to suboptimal sensitivity caused by a high number or possible mutation variants.

Therefore, basic components of diagnosis include the family history and diagnostic imaging. Diagnostic imaging

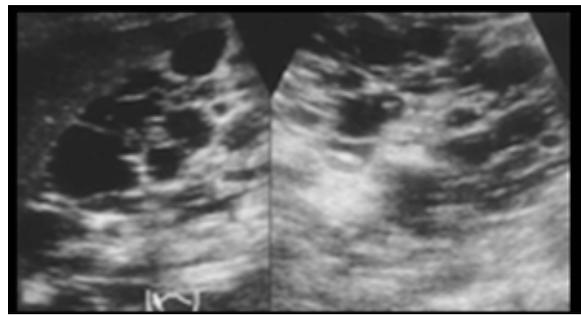


Figure 1. Renal US scan. Multiple cysts.

Table 1. Ultrasound-based Ravine's criteria for type 1 ADPKD diagnosis.

Age (years)	Number of cysts	
	Positive family history	Negative family history
<30	At least 2 in one or both kidneys	At least 5
30–59	At least 2 in each kidney	At least 5
>60	At least 3 in each kidney	At least 8

examinations should be the standard of care in individuals at 50% risk of the disease, i.e. in the offspring and the siblings of affected individuals. The diagnosis of ADPKD usually consists in visualization of multiple cysts in an abdominal ultrasound scan (Figure 1). The methodology of the US scan is not different from that in the standard abdominal ultrasound scan, with no necessity for the scan to be performed in fasting condition. USG is characterized by high (nearly 90%) sensitivity of renal cyst detection, low cost, wide availability, high repeatability and lack of adverse biological consequences of the scan. All the above factors determine the widespread use of ultrasonography in the ADPKD diagnosis and progression monitoring.

Ultrasound-based diagnosis of type 1 ADPKD is based on Ravine's criteria (Table 1). Their sensitivity approaches 100% both in patients above the age of 30 as well as in younger patients. The applicability of Ravine's criteria in patients with PKD2 mutation is lower, particularly in the group below the age of 30 (in this case, the diagnostic sensitivity is about 67%) [14]. This is also true in patients with no family history of the disease, and therefore, the more accurate criteria developed by Demetriou et al. (Table 2) are recommended in suspected cases of type 2 ADPKD [15].

Pei et al. proposed a collective classification for ultrasonographic identification of both types of the disease to achieve the diagnostic sensitivity of as much as 93% in patients with positive family history of the disease (Table 3) [16]. According to these authors, detection of 2 or fewer cysts in individuals above 40 rules out the ADPKD. In addition, hepatic cysts were detected in 85% of ADPKD patients above the age of 30, possibly providing an important clue for the diagnosis of ADPKD in patients with negative family

Table 2. Ultrasound-based Demetriou criteria for type 2 ADPKD diagnosis in patients with a positive family history.

Age (years)	Number of cysts
15-19	One in each kidney or 2 unilaterally
20-29	>3 in total, at least 1 in each kidney
30-59	At least 2 in each kidney
>60	At least 4 in each kidney

history of the disease. Currently, Pei's criteria of 2009 are used in patients with positive family history.

Ultrasonographic detection or exclusion of the disease in patients below the age of 14 is unreliable. In children below the age of 5, as much as 38% of ADPKD diagnoses were false negative while as much as 25% were false positive [17]; therefore, individuals with positive family history of ADPKD are recommended to undergo ultrasound scans only after reaching 20–30 years of age, when the relatively reliable diagnosis allows for appropriate prevention or effective treatment of potential complications.

In addition, precise determination of renal morphology and size is required along with the ultrasound detection and evaluation of cysts.

In ultrasonographic scans, renal cysts have characteristic features including circular or oval shape, smooth and thin walls, lack of calcifications, compartments, or thickenings, echo-free internal structure (no reflections of ultrasound waves) and posterior acoustic enhancement proportional to the size of the cyst. These features facilitate diagnosis of simple cysts [18].

The applicability of contrast-enhanced ultrasonography (CEUS) in ADPKD is not significant. Despite the fact that CEUS is better than conventional US and SC in visualization of cystic walls and compartments as well as of the presence of solid elements, diagnostic limitation in ADPKD patients consists in the kidneys being enlarged as well as in the high number of lesions morphologically different from simple cysts. However, in certain clinical cases, CEUS may provide a valuable supplement to US-based diagnostics.

Besides ultrasound scans, diagnostic imaging techniques used in ADPKD patients include computed tomography (CT) and magnetic resonance imaging (MRI).

Renal CT scans are performed in supine position with hands raised above the body. Patients should be appropriately hydrated. The scans are acquired at inhale breath-hold and the scanning range is determined by the size of the kidneys; in end-stage disease, examination includes not only the upper part of the abdomen (down to the aortic bifurcation), but pelvis minor as well. Acquisition technique depends on the scanner type.

Scans dedicated to renal evaluation (particularly in ADPKD patients) should include in-phase images without contrast enhancement. These are acquired with the aim to detect

Table 3. Pei's criteria for ultrasonographic diagnosis of ADPKD in patients with positive family history.

Age (years)	Number of cysts
15–39	Total >3, uni- or bilateral
40–59	Total >4, at least 2 within each kidney
>60	Total >8, at least 4 within each kidney

small deposits and calcifications, bleedings, adipose tissue as well as to determine the baseline level for the contrast enhancement measurements. After intravenous administration of contrast agent, mono- or multiphase scans are acquired depending on the clinical problem. Scans should include the nephrographic phase, most useful in the assessment of focal lesions. In addition, corticomedullary phase (arterial phase for the assessment of bleeding and small, vascularized tumors) and excretory phase (for the assessment of pyelocalyceal systems) may be included. In patients with urinary stasis, significantly delayed phase scans may be required (>30 min after contrast administration).

Conventional renal MRI protocol includes T2-weighted images, chemical shift imaging (CSI, in-phase/anti-phase) sequences, and fat-saturated T1-weighted images before and after intravenous injection of paramagnetic contrast agent. Inclusion of dynamic contrast-enhanced MRI scans and DWI scans provides a multiparametric (MP) protocol of MRI examination that becomes the gold standard in renal MRI assessments. Inclusion of magnetic resonance urography (MRU) is also useful for the assessment of the pyelocalyceal systems [19]. MRU examination may be performed in dual manner: the first method consists in acquisition of hydrographic sequence visualizing static fluids based on heavily T2-weighted images. Several repetitions of this sequence (cine-MR urography) may be performed for better visualization of the pyelocalyceal systems and ureters. The other method consists in acquiring MRU scans after intravenous contrast administration; excretory function of kidneys must be conserved for this examination to be feasible. Administration of diuretics may be helpful, particularly in patients without pyelocalyceal system dilation [20]. Both urographic techniques are subject to significant limitations, particularly in patients with advanced-stage disease. In the hydrographic method, a large number of well-developed cysts obscures the contours of the pyelocalyceal system, whereas patients with advanced stage renal insufficiency have contraindications for parenteral administration of gadolinium contrast agents.

Blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI), employing deoxyhemoglobin as an endogenous marker of tissue oxygen saturation, is a novel technique used in the assessment of certain renal pathologies. Interpretation of the results is difficult as the acquired BOLD-MRI signals depend e.g. on patient hydration, circulating blood volume, age, sex, factors affecting the oxygen dissociation curve (body temperature, hematocrit, blood pH) [21]. Results of pilot studies that examined the BOLD effects in chronic nephropathies, diabetic

Table 4. Diagnostic criteria for ADPKD in MRI in patients with a positive family history.

Age in years	Number of cysts in both kidneys
<30	5 or more
30–44	6 or more
45–59 (women)	>6
45–59 (men)	>9

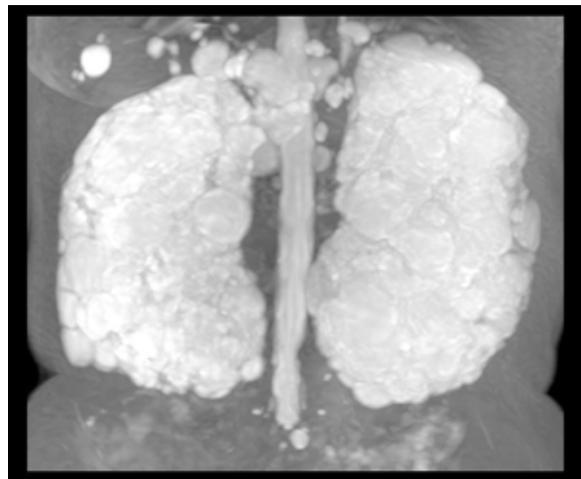
**Figure 2.** MRI scan, T2-weighted. ADPKD – enlarged kidneys with multiple cysts, no normal parenchyma present.

nephropathy, ischemic nephropathy, acute renal injury (acute ischemia, contrast-induced nephropathy) and congestive nephropathy.

Both CT and MRI are characterized by high sensitivity of cyst detection, particularly with respect to cysts smaller than 1 cm in diameter. This is particularly true in case of detection of cyst-like lesions in T2-weighted MR images. At the same time, MRI is highly specific in diagnosing ADPKD (both the sensitivity and specificity of MRI scans in the diagnostics of ADPKD are 100%) [22]. Both methods are particularly useful in cases of negative family history when ADPKD should be diagnosed on identification of enlarged kidneys with multiple bilateral cysts, concurrent hepatic cysts and absence of symptoms of any other cystic kidney disease.

CT and MRI symptomatology of cystic lesions is quite typical.

In CT, cysts are thin-walled fluid-filled spaces with radiation attenuation coefficient typical to that of water (0–10 H.U.), not enhanced following intravenous contrast administration. The wall of a simple cyst should be free of thickenings (either diffuse or nodular), calcifications, internal compartments and solid elements enhanced following intravenous contrast administration.

**Figure 3.** MRI scan, MIP 3D reconstruction. ADPKD – enlarged polycystic disease of markedly enlarged kidneys.**Figure 4.** CT scan, contrast-enhanced. ADPKD.

In MRI scans, simple cysts generate signals that are typical for water T2-weighted images with low signal appearance in T1-weighted images; cysts are not enhanced after contrast administration (increased signal intensity in T1-weighted images may be observed in the delayed phase after one hour due to the diffusion of the contrast agent through the cystic wall rather than from typical contrast enhancement).

Due to the higher sensitivity of cyst detection, modified Ravine's criteria are used in diagnosing ADPKD (Table 4). Typical CT and MRI images of kidneys in ADPKD are presented in Figures 2–4.

In case of non-simple cysts, Bosniak's classification is used for determination of further diagnostic and therapeutic

Table 5. Differentiation between cognate cystic renal diseases and ADPKD.

	Symptomatology of renal lesions	Extrarenal symptoms
Medullary cystic kidney disease) [27–29], Figure 5	Numerous kidneys, usually not larger than 3 cm in diameter at the interface between renal medulla and cortex and within the renal medulla	
Von Hippel-Lindau syndrome [30,31]	Numerous cysts of varied size in slightly more than 50% of patients (59–63%), accompanied by solid lesions (often numerous): RCC	Hemangioblastoma of the central nervous system Pancreatic cysts Cystic adenomas Neuroendocrine tumors Pheochromocytoma
Tuberous sclerosis [32,33]	Numerous, bilateral renal cysts (in 14–32% of patients) with numerous accompanying angiomyolipoma-type lesions	Hamartoma-type lesions in various body regions Triad of classical clinical symptom: – Facial angiofibroma – Mental retardation – Epilepsy

Table 6. Differentiation between acquired cystic renal diseases and ADPKD.

	Symptomatology of renal lesions	Comments
Acquired cystic kidney disease [34]	Small kidneys in patients with end-stage renal disease originating from causes other than cystic kidney diseases numerous cysts (3 or more within each kidney)	Increased risk of bleeding and RCC development
Medullary sponge kidney (Lenarduzzi-Cacchi-Ricci disease) [35]	Medullary nephrocalcinosis, numerous tiny cysts within the renal medulla	Bilateral location of lesions
Multicystic dysplastic kidney [1] a few (i.e., cystic renal cell carcinoma, cystic nephroma, cystic partially differentiated nephroblastoma, mixed epithelial and stromal tumor	Non-functioning kidney numerous peripheral cysts with solid lesion in the center	Undeveloped or atrophic pyelocalyceal system and renal vessels
Localized renal cystic disease [36], Figure 6	A conglomerate of numerous simple cysts of various sizes, interspersed by normal or atrophic renal parenchyma	Unilateral lesions contralateral kidney unremarkable, cyst-free

management. [23]. Formulated on the basis of CT images, the classification may also be used in the case of MRI scans. Due to the higher selectivity of MRI scans in visualizing compartments and thickening, lesions classified as grade IIF using CT examinations may be classified as grade III following MRI examination [24].

The necessity for administration of a contrast agent for both CT and MRI scans is associated with risk of renal and nephrogenic complications, occurring particularly in case advanced renal insufficiency and including contrast-induced acute kidney injury (CI-AKI) for CT scans and nephrogenic systemic sclerosis (NSS) for MRI scans; hence the need to follow the recommendations of the Polish Medical Society of Radiology and the European Society of Radiology, provide specialist supervision, and perform laboratory analysis of renal function before scan acquisition [25]. In all patients, the contrast agent should be used in the lowest possible quantity. Despite the fact that patients should not be refused contrast-enhanced examinations in clinically justified situations, alternative and non-burdening imaging methods should be proposed in all cases. Decisions to administer contrast agents to patients

at increased risk of adverse effects should be made on a case-by-case basis, with clinical data and expected diagnosis being taken into account.

Differential Diagnosis

The main difficulty with diagnostic imaging of ADPKD consists in the fact that the disorder belongs to a wide spectrum of congenital, developmental or acquired cystic kidney diseases. Congenital pathologies include ARPDK, medullary cystic kidney disease, Von Hippel-Lindau syndrome and tuberous sclerosis. Diseases of non-genetic origin include acquired cystic kidney disease (in patients with end-stage renal disease), medullary sponge kidney, multicystic dysplastic kidney and localized renal cystic disease [26].

All these disorders should be taken into account in differential diagnostics of patients with suspected ADPKD. However, many of these disorders are very rare [10].

The main differentiating factors include cyst location and concomitance of focal lesions.

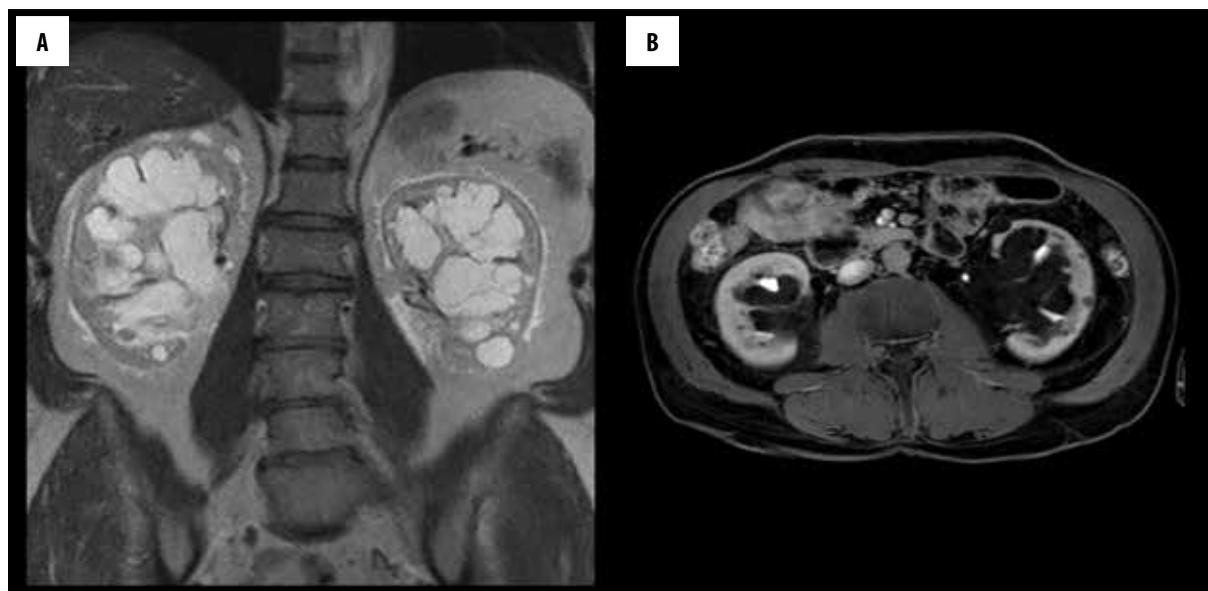


Figure 5. MRI scan: (A) T2-weighter image; (B) T1-weighted image, contrast-enhanced, excretory phase. Medullary kidney cystic disease.



Figure 6. MRI scan, T2-weighted. Unilateral cystic disease of left kidney; right kidney free of focal lesions.

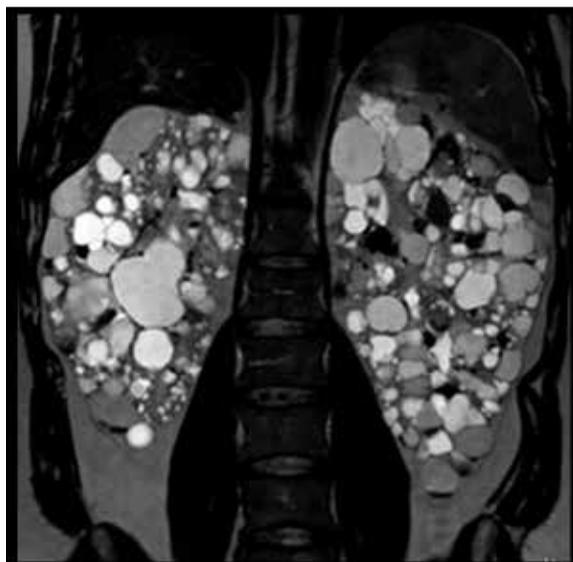


Figure 7. MRI scan, T2-weighted. ADPKD. Polymorphism of the cyst signal due to complications (high-protein content and bleeding), wall calcifications.

Radiological symptomatology of cystic kidney diseases is presented in tables (Tables 5, 6) as well as Figures 5, 6.

Complications

Image polymorphism is a characteristic feature of cystic kidneys (Figure 7). Cyst complications develop quickly, leading to their abnormal appearance in diagnostic imaging examinations (i.e. different from diagnostic criteria characteristic for simple cysts) (Table 7). Bleeding into the cyst lumen (explained by abnormal cystic wall structure) is relatively common. Cyst infection is the second most common cause of deaths in ADPKD patients. It may be difficult to differentiate between the infection and bleeding into the cyst lumen using ultrasonography, CT, or even, MRI. Symptomatology of non-simple cysts is presented in

Table 8 as well as Figures 7 and 8. Due to the need to initiate appropriate therapeutic management, diagnosis must be closely correlated with clinical presentation.

Characteristic features of infected cysts in diagnostic images include the presence of fluid/fluid interface, disturbed (restricted) diffusion (increased intensity of signals in DWI-MR images) and wall thickening. According to the new criteria for the diagnosis of infected cysts, at least two of the above conditions should be detected. Gas bubbles may not be visualized in all cases [37].

Differentiation of non-simple cysts from solid focal lesions is a significant diagnostic problem. In CT and MRI, the diagnosis of RCC and other solid lesions (other malignant tumors, metastases and benign solid lesions, such as

Table 7. Complications of renal cysts in imaging examinations.

	Usefulness of imaging examinations		
	US	CT	MRI
Wall thickening	+	+	+
Compartments/nodular solid elements	+	+	++
Calcifications in the wall	+	++	-
Thick (high-protein content)	+		+
Fluid/fluid level	+/-	+	++

Table 8. Increased cyst density (bleeding, infection) in diagnostic imaging examinations.

Methodology of examination	Symptoms
Ultrasonographic scan	Non-homogeneous content Echo reflection within the cyst lumen Echo enhancement beyond the posterior wall
CT	Hyperdensity (above 10 H.U.) Fluid/fluid level
MRI	Hypointense signals in T2-weighted and DWI (b=0) images Hyperintense signals in T1-weighted images Fluid/fluid level

oncocytoma, angiomyolipoma) in ADPKD patients is based on general criteria which usually require contrast administration (Figure 9). When assessing CT examinations, one should keep in mind the contrast-induced pseudo-enhancement of cysts, i.e. the cyst density being increased by 10–20 H.U. after contrast administration. The phenomenon was observed both in phantom studies as well as in vital stains and was found to be dependent on the size of the lesion, the methodology of examination (slice thickness, scanner type (number and size of detectors, reconstruction algorithm)), and the size of the region of interest (ROI). Contrast pseudo-enhancement is observed mainly in small cysts (below 20 mm in diameter) and usually does not exceed 20 H.U. Therefore, pathological attenuation coefficient of at least 20 H.U. should be considered as indicative of pathological contrast enhancement despite the fact that Sai et al. observed an enhancement of more than 20 H.U. in 30%

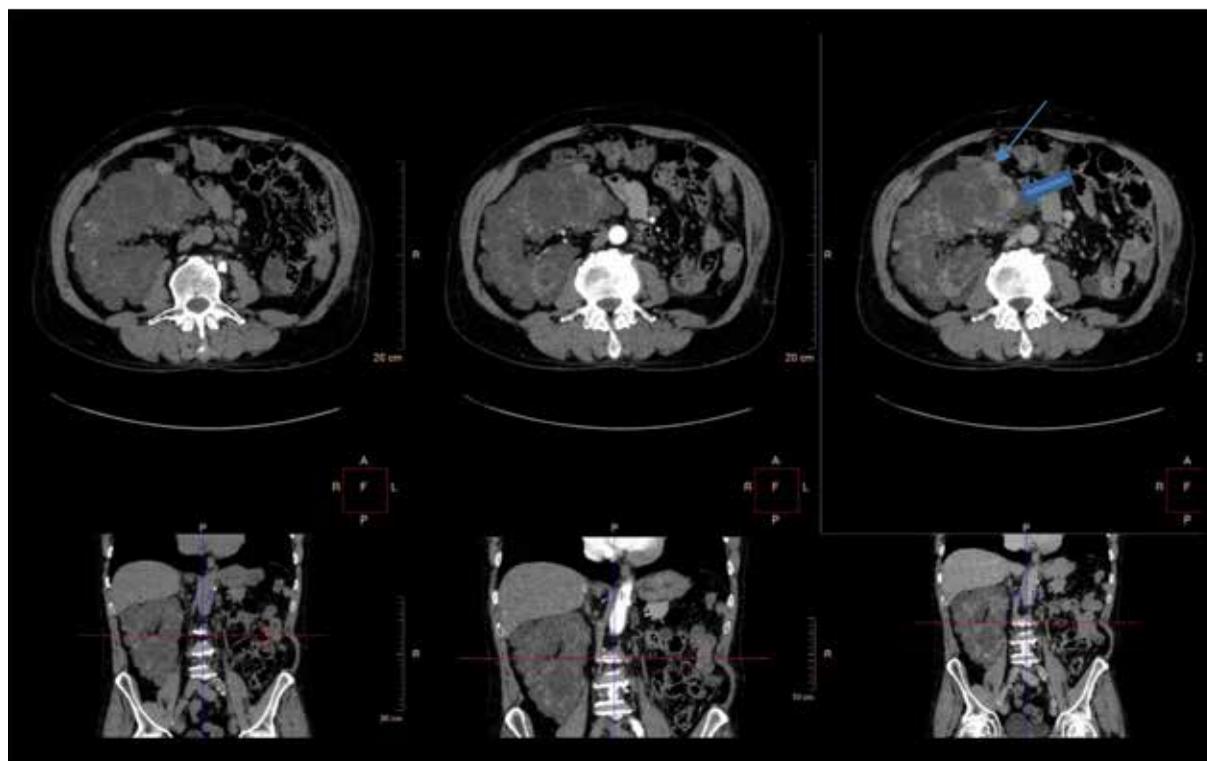


Figure 8. Multiphase CT scan. Cystic right kidney, status post-left-sided nephrectomy. High protein-content cyst (hyperdense in-phase image without contrast enhancement) – marked with the dark arrow. Normal enhancement of renal parenchyma – marked with the bold arrow.

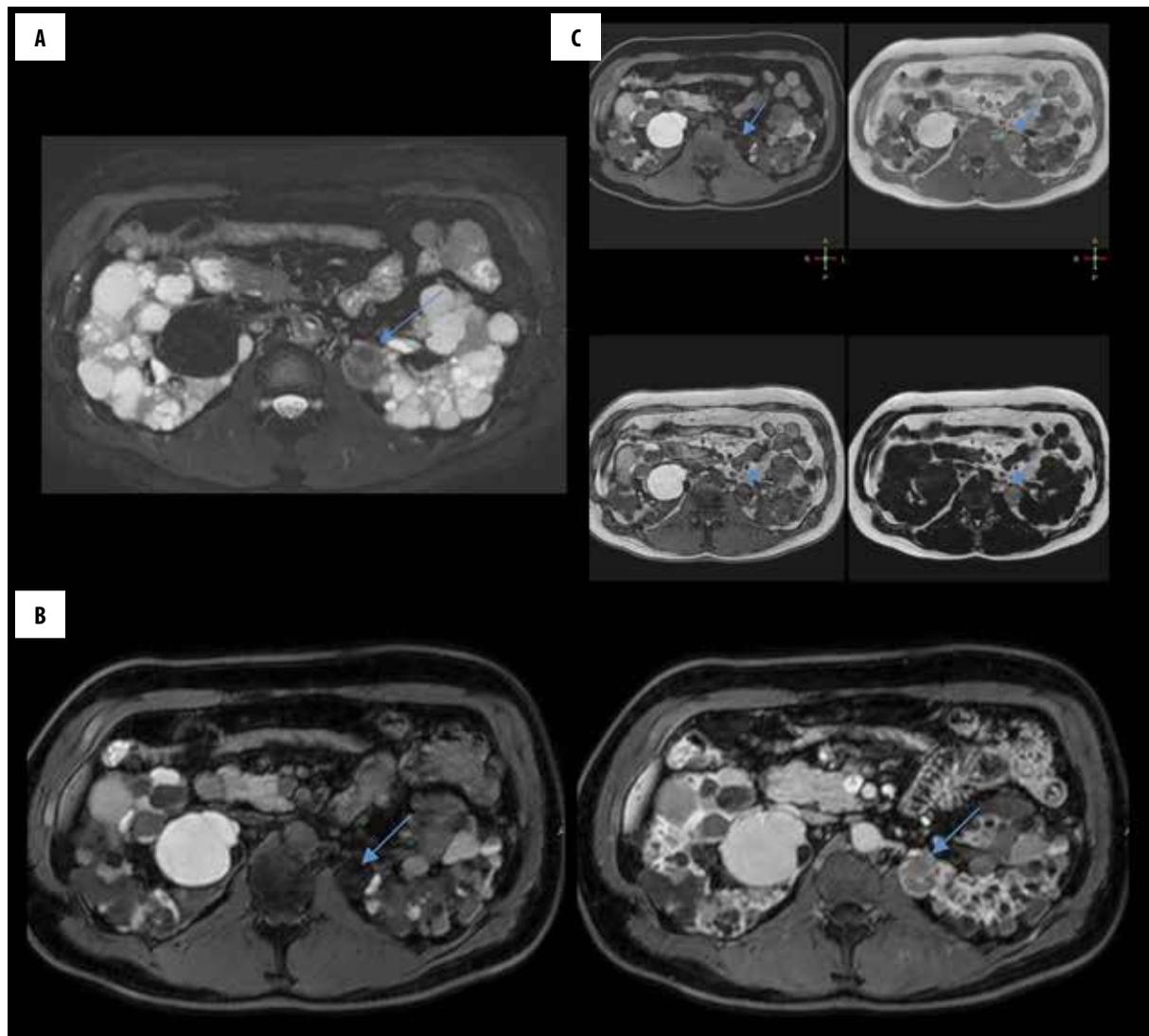


Figure 9. MRI scan. Angiomyolipoma (arrows) in an ADPKD patient (A – T2-weighted image with fat saturation; B – T1-weighted image with and without contrast enhancement, C – T1-weighted image with fat saturation, in-phase/antiphase, water saturation). Lesion difficult to differentiate from polymorphic lesion.

of simple cysts [38]. At the same time, significantly lower pseudo-enhancement of cysts sized 20–30 and absence of pseudo-enhancement of cysts with diameters larger than 30 mm is observed.

CT scans TK should include the native phase (i.e. before intravenous administration of contrast). In cases when non-enhanced phase is missing, it is advisable to assess the lesion's radiation attenuation coefficients in two phases following contrast administration (arterial phase and parenchymal phase). Solid kidney lesions (tumors) present with enhancement differences of more than 10 H.U. Hypodense lesions with differences lower than 10 H.U. are most likely thick-content cysts (although tumor can't be ruled out on the basis of this assessment) [39]. This is all the more complicated due to the different behavior of histopathological subtypes of renal cell carcinoma-RCC in CT studies. The clear-cell subtype (ccRCC) is usually hypervascular in the aortic phase with the contrast agent being washed out in the subsequent phases. The papillary

subtype (pRCC) is usually hypovascular and presents with constant or increasing enhancement [40]. Usually, pRCC enhancement is weaker than that of the renal cortex; the enhancement may be so weak that it may be misinterpreted as cyst pseudo-enhancement. In addition, some pRCCs may remain not enhanced and present with cyst-like components. Small regions of interest (ROI) located within the peripheries of the lesion may be helpful in CT differentiation [41].

In MRI, contrast-enhanced T1-weighted sequences are universally considered the diagnostic standard in differentiation of solid lesion (Figure 10). Due to the concomitant renal insufficient, they are often contraindicated in ADPKD patients. Hence, diffusion-weighted imaging (DWI) was attempted (Figure 11). However, no uniform methodology was developed to date with regard to this examination while current recommendations remain ambiguous. Typically, at least two values of the b coefficient are selected: low, i.e. <200 [s/mm²] and high, i.e. >500 [s/mm²];

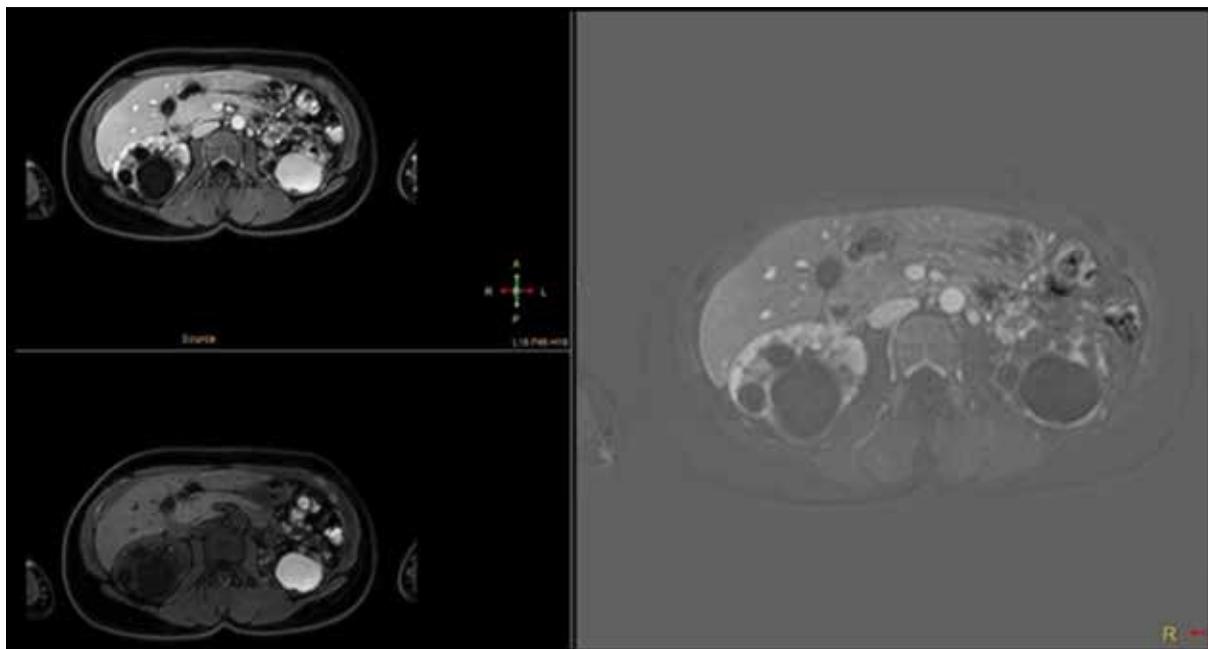


Figure 10. MRI subtraction. T1-weighted scans acquired without contrast enhancement are subtracted from contrast-enhanced T1-weighted scans to facilitate the assessment of the contrast enhancement of high signal intensity lesions. ADPKD.

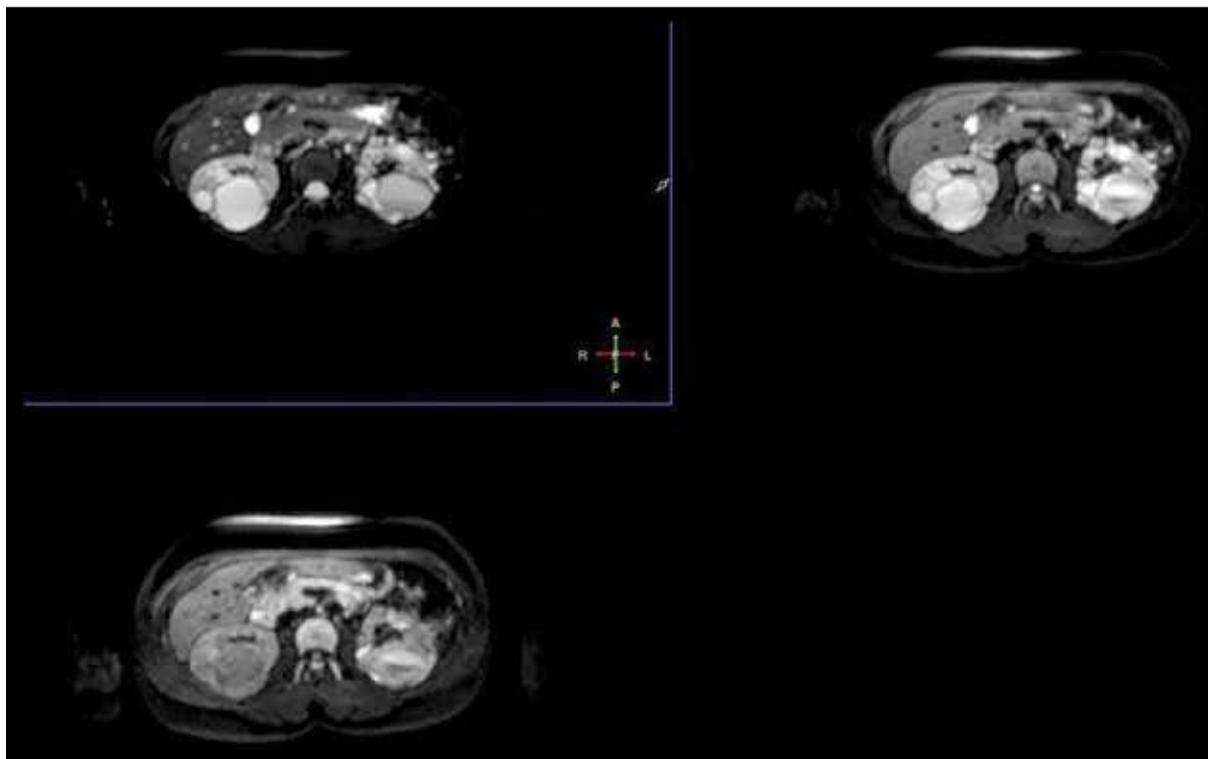


Figure 11. MRI scan, DWI (b=0, b=300, b=1000). ADPKD.

for the purposes of renal imaging, the preferred b value is about 1000 [s/mm²]). In 2014, there were published the results of a meta-analysis that assessed the applicability of DWI in differentiation of focal lesions in kidneys [42]. The authors compared the apparent diffusion coefficient (ADC) values for normal renal parenchyma, cysts, solid benign lesions (including oncocytoma and angiomyolipoma (AML)) to those for malignant lesions (RCC, urinary

tract epithelioma) to conclude that lower ADC values may be indicative of malignant lesions. After normal parenchyma and cysts were excluded, the differences obtained from the comparison of ADC values for oncocytoma and AML to those for malignant lesions (RCC) were statistically significant ($p < 0.0001$). In ADC imaging, simple renal cysts present with high signal intensities at low values of b; the intensity is reduced for $b > 500$ [s/mm²], and wanes

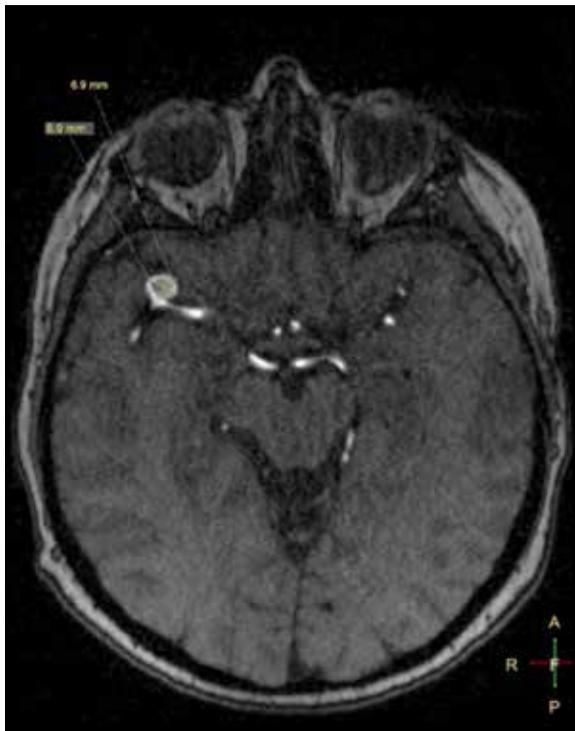


Figure 12. Angio-MRI, TOF. Aneurysm at the bifurcation of the right middle cerebral artery in an ADPKD patient.

completely at b of about $1000 \text{ [s/mm}^2\text{]}$. Also attempted were DWI assessments of different histological subtypes of RCC [43–47].

In addition, the assessment of tissue diffusion in line with the contrast-enhanced phase of MRI scans is very helpful in the diagnostics of inflammatory abscesses as well as in differentiation of these abscesses from cyst-like tumor lesions.

It is a matter of dispute whether ADPKD should be considered a risk factor of RCC. Despite the fact that RCC

was observed in 5% [48] to 12% [5] of patients, the role of ADPKD as a risk factor of RCC is still unclear. Due to the absence of epidemiological, clinical, or molecular biology studies that would elucidate the increased incidence of RCC in ADPKD patients, the concomitance of both disorders is considered to be incidental. On the other hand, however, the nature of the disease consists in enlargement and deteriorated function of kidneys leading to end-stage kidney disease and, as a consequence, to long-term dialysis treatment which is an undeniable RCC risk factor [48]. Hence the particular importance of unambiguous differentiation of non-simple cyst from solid tumor lesion, particularly when sparing surgical treatment is possible.

Diagnostic Imaging of Concomitant Pathologies

Most important extrarenal symptoms of ADPKD include cystic liver disease and increased incidence of intracranial aneurysms as compared to the overall population (Figure 12). Other symptoms usually have no impact on the course of the disease.

Despite the widely known fact of the incidence of intracranial aneurysms leading to subarachnoid hemorrhages being higher in ADPKD patients (4% to 22.5%), no general guidelines have been established to date with regard to the diagnostics of these patients [49]. Postulates to introduce screening examinations are becoming common, particularly in relation to their importance before the end-stage renal disease as aneurysmal ruptures are common before dialysis treatment is initiated [50,51]. This pertains in particular to patients after the age of 45 with high fluctuations of arterial blood pressure [49]. Intracranial aneurysms in ADPKD patients are detected mainly by angio-MR imaging with time-of-flight (TOF) detection. The method is absolutely safe for patients with renal insufficiency; however, it is characterized by limited sensitivity, particularly with regard to detection of small aneurysms. In addition, false positive results may be obtained. When assessing angiographic examinations, one should be particularly accurate in differentiation between potential fusiform aneurysms

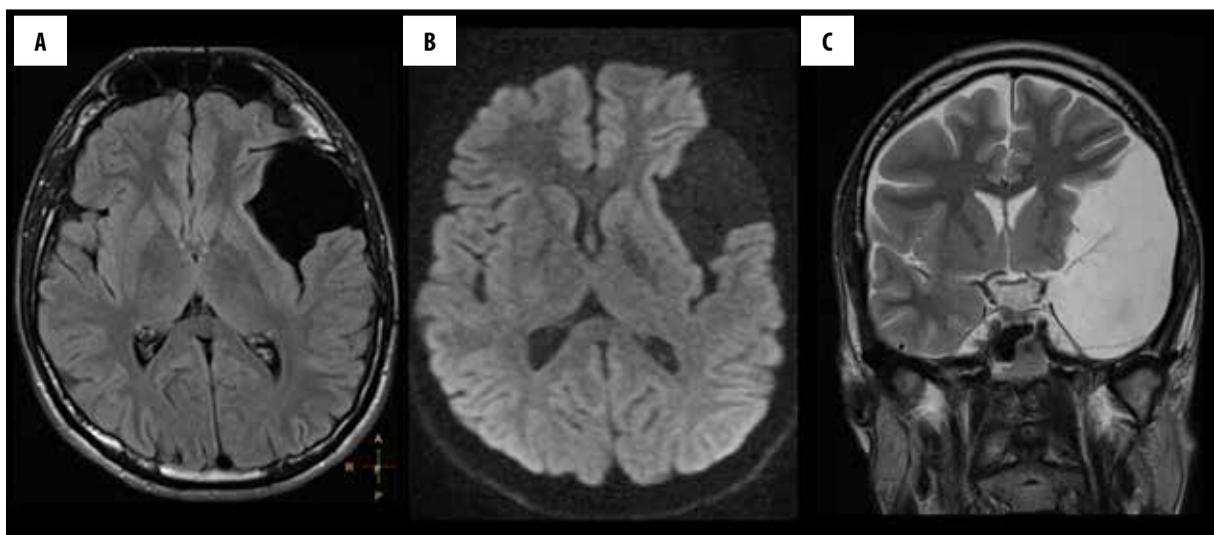


Figure 13. MRI scan: (A) FLAIR image; (B) DWI, image; (C) T2-weighted image. Middle cranial fossa arachnoid cyst on the left.

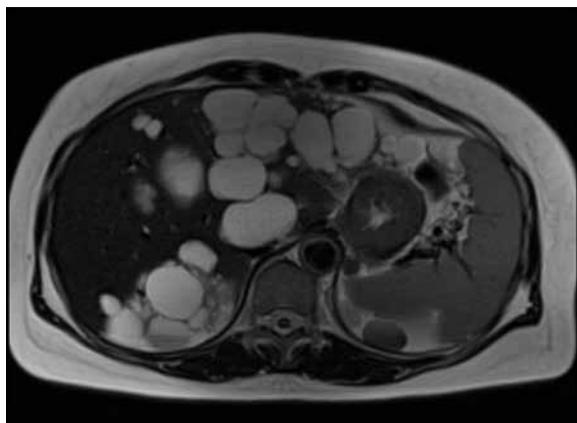


Figure 14. MRI scan, T2-weighted. Hepatic cysts in an ADPKD patient. Also visible are cysts within the upper parts of both kidneys.

and dolichoectasies, more common in this group of patients. In case of ambiguous images, MRI is recommended as second choice, with angio-CT being reserved only for patients whose aneurysms are growing in size [50].

Besides dolichoectasies, cerebral MRI scans in ADPKD patients reveal more common incidence of arachnoid cysts (Figure 13) [51].

Single cysts and polycystic liver disease (PLD) are one of the most common extrarenal manifestations of the disease. PLD is diagnosed when the number of hepatic cysts exceeds 20, both in patients with PKD1 or PKD2 gene mutations as in patients without any defects within these genes [53]. The disease may also be observed without concomitant renal cysts (isolated polycystic liver disease, PCLD). Similar to ADPKD, PCLD is a genetically heterogeneous group of disorders. Two genes of isolated polycystic liver disease, not associated with ADPKD, were identified (PRKCSH and SEC63) [52–54].

Symptomatology of hepatic cysts (Figure 14) in imaging examinations is the same as in the case of renal cysts. Complications of cysts are observed most commonly in patients undergoing dialytic treatment or patients after renal transplants. Most commonly, these include infection, bleeding, or rupture.

In addition, common biliary duct (CBD) should be assessed in detail in hepatic US, CT, or MRI examinations. Asymptomatic dilation of CBD (Figure 15) is observed only in about 40% of ADPKD cases [55].

Symptomatology of other lesions that may accompany ADPKD (e.g. splenic or pancreatic cysts) is typical and affords no special diagnostic difficulties.

Follow-Up Examinations

Imaging techniques are used not only for diagnosing the disease and its complications, but also for assessing the disease progression. The assessment of disease progression requires determination of the number and size of cysts as well as the size of kidneys. Although ultrasonography

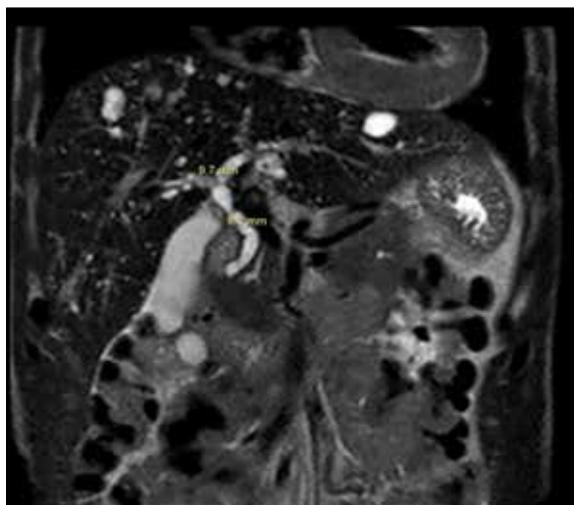


Figure 15. MRI scan, T2-weighted. Common bile duct dilation in an ADPKD patient.

is the method of choice in ADPKD diagnosis, CT and MRI scans are more useful in assessing the disease progression. Limitations of ultrasonography are associated, among other factors, with its dependence on methodology and operator reliability. In addition, ultrasound scanning is ineffective in the assessment of small cysts, smaller than 1 cm in size.

One of the parameters assessed by the imaging examinations when evaluating disease progression is the size of the kidneys expressed by renal volume. In US scans, one may attempt the assessment of kidney size by using the three dimensions (maximum length, width, and posteroanterior dimension) and subsequent calculation of volume using the formula for calculating the volume of rotational ellipsoid. This method underestimates the size of the kidneys (by ca. 25%) as compared to the MRI-based volume assessment [56]. Differences were also observed between the assessment of renal volume in stereological MRI scans and measurements including the three largest dimensions (using the formula for calculating the volume of rotational ellipsoid). The second method also underestimates the renal volume due to various factors including the irregular shape of cystic kidneys, often much different from that of rotational ellipsoid.

Initially, computed tomography was used to estimate the size (volume) of kidneys in ADPKD patients; this was all the more justified, that the accuracy of volumetric measurements is similar for CT and MRI. However, due to the use of ionizing radiation and the use of nephrotoxic contrast agents, the method is markedly worse in long-term follow-up of ADPKD patients. Currently, MRI is considered to be the gold standard in the assessment of renal volume.

As demonstrated by the Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), the size of kidneys is correlated with their efficiency as measured by eGFR [7]. In the study, the total volume of kidneys increased by 5.3% over one year of follow-up. The measurements were used by contrast-enhanced stereological T1-weighted MR images acquired in frontal plane. Due to the risk associated with potential development of nephrogenic systemic fibrosis (NSF), the study protocol was modified so as to

abandon the contrast-enhancement phase. The increase in renal volume was faster in patients with faster deterioration of renal function. It was also observed that in patients with total kidney volume (TKV) of above 1500 cm³, eGFR was reduced at the rate of 4.3 ml/min/year [7]. Besides the renal volume measurements, cyst volume measurements were also performed (using T2-weighted images) with the observed increase rate of 12% during a year.

Currently, the assessment of renal volume is made independent of patient's dimensions (height) by using the ratio of TK to the weight in meters (height-adjusted TKV, htTKV). High risk of disease progression and renal insufficiency was observed in a 8-year follow-up of patients with htTKV ≥600 cm³/m, indicating that htTKV is an important prognostic biomarker [57].

Radiological examinations are useful not only in diagnosing and monitoring the disease progression, but also as a supportive tool in the treatment.

Both hepatic and liver cysts may cause complaints due to their large size and compression of neighboring organs, particularly abdominal or back pain. In persistent complaints, the treatment method of choice includes sclerotization with alcohol, performed under ultrasonographic control. A large group of symptoms is caused by bleeding into the cyst or by cyst infection. Symptomatic cysts, particularly infected cysts, are treated by transcutaneous puncture and aspiration of cyst content under ultrasonographic

control. Multiple cysts of liver and kidneys that require treatment are subjected to multi-stage therapy eliminating the need for surgical intervention [58].

Currently, the management of ADPKD patients consists in the treatment of complications within the urinary system (pain, infections), arterial hypertension and renal replacement therapy in the end-stage chronic renal disease. Elucidation of genetic principles and pathomechanisms responsible for the development of cysts contributed to the studies on novel directions in ADPKD treatment aimed at the reduction in the number and size of the cysts and thus at reduction of the total kidney volume. In such cases, MRI provides the best tool for the monitoring of treatment efficacy.

Conclusions

To sum up, the key role of diagnostic imaging methods (ultrasound, CT, and MRI) in the diagnosis and monitoring the progression of ADPKD must be highlighted.

MRI scans are gaining in importance, particularly when used as part of advanced technique protocols. Due to the lack of negative biological consequences, MRI scans may be repeated multiple times which is particularly important in patients at higher risk of RCC or patients after kidney transplants. Volumetric MRI techniques are useful in the assessment of disease progression and the monitoring of treatment efficacy.

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