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ORIGINAL ARTICLE

The "salt and pepper" pattern on renal ultrasound in a group of children with molecular-proven diagnosis of ciliopathy-related renal diseases

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Abstract

Background While typical ultrasound patterns of ciliopathy-related cystic kidney diseases have been described in children, ultrasound findings can overlap between different diseases and atypical patterns exist. In this study, we assessed the presence of the "salt and pepper" pattern in different renal ciliopathies and looked for additional ultrasound features.

Methods This single-center, retrospective study included all patients with a molecular-proven diagnosis of renal ciliopathy, referred to our center between 2007 and 2017. Images from the first and follow-up ultrasound exams were reviewed. Basic ultrasound features were grouped into patterns and compared to genetic diagnoses. The "salt and pepper" aspect was described as enlarged kidneys with heterogeneous, increased parenchymal echogenicity.

Results A total of 41 children with 5 different renal ciliopathies were included (61% male; median age, 6 years [range, 3 days to 17 years]). The "salt and pepper" pattern was present in 14/15 patients with an autosomal recessive polycystic kidney disease (ARPKD). A similar pattern was found in 1/4 patients with an autosomal dominant polycystic kidney disease and in 1/11 patients with *HNF1B* mutation. Additional signs found were areas of cortical sparing, comet-tail artifacts, and color comet-tail artifacts.

Conclusion Although the "salt and pepper" ultrasound pattern is predominantly found in ARPKD, it may be detected in other ciliopathies. The color comet-tail artifact is an interesting sign when suspecting a renal ciliopathy in case of enlarged hyperechoic kidneys with no detectable microcysts on B-mode grayscale ultrasound.

Keywords Renal Ciliopathies · Cystic disease · Molecular genetics · Ultrasound

Introduction

Renal cystic diseases encompass a broad group of disorders with variable expressions [1], classified according to their genetic or nongenetic origin [2, 3]. Ciliopathies are a heterogeneous group of genetic pathologies which can involve all major organs, and the kidneys are the most commonly affected organ [4]. Cilia are present on the apical surface of almost

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every cell type in various tissues and organs [1, 5, 6]. In kidneys, they are localized on the tubular epithelial cells [7]. Normal cilium structure and function are essential for renal development and maintenance [7]. When affecting the kidneys, ciliopathies are responsible for renal cystic diseases, which can be isolated or syndromic [1, 4, 6, 8–10]. Autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), nephronophthisis (infantile and juvenile), glomerulocystic disease associated with *HNF1B* mutation, and Bardet-Biedl syndrome (BBS) are the most frequent and best described ciliopathy-related cystic kidney diseases [1–18].

Renal ultrasound is a major tool for the detection, characterization, and follow-up of renal cystic diseases in infants and children [1, 3, 5]. While typical patterns of these genetic cystic renal diseases have been described, ultrasound findings can overlap between different diseases and atypical patterns exist [1]. The "salt and pepper" pattern, characterized by a heterogeneous, increased parenchymal echogenicity, is due to multiple interfaces of innumerable millimetric tiny cysts, smaller than or just approaching the size necessary for detection, which disrupts the echo pattern without being clearly distinguishable [1, 12, 19]. It was first described in 1985 in patients with ARPKD [20], when medical ultrasound imaging was in its infancy and molecular genetic analyses were not available. Nowadays, ultrasound findings of enlarged kidneys with a "salt and pepper" pattern detected in the perinatal period still lead to a presumptive diagnosis of ARPKD [1, 12].

In this study, we reviewed the renal ultrasound images of children with a molecular diagnosis of ciliopathy, with the aim to assess the prevalence of the "salt and pepper" pattern in different renal ciliopathies and look for additional ultrasound features besides this pattern. We compared ultrasound features with genetic molecular diagnoses. Our secondary objective was to provide a pictorial review of ultrasound patterns in ciliopathy-related cystic kidney diseases.

Methods and patients

For the purpose of the study, we used a search engine from our clinical database, Dr. Warehouse [21]. This data warehouse integrates more than 600,000 patient records and all associated clinical data from our reference center, with a free text search. The queries used in the data warehouse aimed to select all patients aged 0–18 years, with a suspicion of ciliopathy, including ARPKD, ADPKD, nephronophthisis, glomerulocystic disease related to *HNF1B* mutation, and BBS, followed at our center between April 2007 and September 2017.

The exclusion criteria were patients with no available or registered ultrasound exams; poor quality ultrasound exam (non-diagnostic study); ultrasound exam after 18 years of age; renal transplant ultrasound; no renal disease in case of BBS; no performed or available genetic analysis; and differential diagnosis retained.

All genetic analyses were reported. Renal function, assessed by the glomerular filtration rate (GFR) estimation from the updated Schwartz's formula, was reported if performed within 1 month of the ultrasound exam.

Ultrasound exams were performed with an Aplio 500 from Toshiba Medical Systems and a Logiq E9 from General Electric Healthcare, with convex and linear transducers (6C1 and 12 L5 for Toshiba Medical Systems and C1–5 and 9 L for GE Healthcare).

For all children with a proven molecular diagnosis of one of these ciliopathies, the first good quality ultrasound exam and, when available, the first follow-up ultrasound after a delay of at least 2 years or the last ultrasound exam before renal transplantation (if delay less than 2 years) were extracted from our picture archiving and communication system.

Renal ultrasound images were reviewed by two radiologists blinded to any clinical or genetic data, a senior pediatric radiologist (LB, 15 years' experience) and a resident (PI). The items reported on a standardized grid for each kidney were kidney size (long axis considered as normal, decreased or increased compared to normal limits [22]), cortical echogenicity compared to liver or spleen (isoechoic, hyperechoic, or hypoechoic), corticomedullary differentiation (CMD) (present, absent, or questionable), absence or presence of cysts, and, when present, number (< 10, > 10, countless), size (infracentimetric, centimetric, or supracentimetric), location (cortical, corticomedullary junction, medullary or random), and associated uro-nephrological anomalies (pelvicalyceal/ureteral dilation).

The "salt and pepper" pattern was defined as enlarged kidneys with heterogeneous increased parenchymal echogenicity. We also reported areas of cortical sparing in case of extensive disease, comet-tail artifact, and color comet-tail artifact when color Doppler ultrasound was performed. The two artifacts are both special subtypes of reverberation artifacts due to closely spaced, highly reflective interfaces [23, 24].

In case of images suggesting pelvicalyceal and/or ureteral dilation, clinical backgrounds were retrieved for urological diagnosis.

Results

From April 2007 to September 2017, our data warehouse reported 179 patients with a suspicion of ARPKD, ADPKD, nephronophthisis, glomerulocystic disease associated with *HNF1B* mutation, or BBS.

A total of 138 patients were excluded from the study because of the following: no available or registered ultrasound

imaging ($n = 36$), poor quality ultrasound exam ($n = 9$), ultrasound exam performed only after 18 years old ($n = 15$), renal transplant ultrasound in patients after renal transplantation ($n = 19$), no renal disease in case of BBS ($n = 6$), no genetic analysis performed or available ($n = 44$), differential diagnosis retained ($n = 6$), multicystic dysplastic kidney, congenital anomalies of the kidney and the urinary tract, and Beckwith-Wiedemann syndrome. Finally, three patients with a molecular diagnosis of a rare ciliopathy (Meckel-Gruber syndrome, Sensenbrenner syndrome, and Joubert syndrome) were excluded because only one patient was identified for each mutation.

A total of 41 patients were included (median age, 6 years [range, 3 days to 17 years]; 61% male). Demographics of the children (gender and median age) categorized by ciliopathy are shown in Table 1 (also refer to the Online Resource 1 for detailed genotypes and Online Resource 2 for the renal function).

A total of 81 kidneys were analyzed (one child had a single kidney secondary to an involution of multicystic dysplastic left kidney). Ultrasound features of kidneys and cysts categorized by ciliopathy are, respectively, shown in Bar graphs 1 and 2.

Overall analysis of the kidneys on the first ultrasound available

Seventy two percent of kidneys (58/81) had a hyperechoic cortex (27 symmetrical kidneys and 2 asymmetrical); 93% ($n = 75$) had an abnormal CMD (absent or questionable); 46% of kidneys ($n = 37$) were enlarged, 48% ($n = 39$) were normal-sized, 6% ($n = 5$) had small kidneys; 17% ($n = 14$) had no detectable cysts on ultrasound exam. One patient had a normal ultrasound exam of his two kidneys (6 years old with BBS). The "salt and pepper" pattern was present in 32 kidneys (39%).

Findings for the different ciliopathies

In patients with ARPKD, 14 out of 15 patients had enlarged kidneys with a "salt and pepper" pattern (Fig. 3a). Most of the detectable cysts were randomly distributed, millimetric, irregularly shaped (Fig. 3b).

The other child (3 years old) had enlarged kidneys with hyperechoic (left kidney) and isoechoic (right kidney) cortex, abnormal CMD, and a limited number of cysts in both kidneys.

Among children with the "salt and pepper" pattern (14/15), seven children presented some areas of cortical sparing, particularly well visible on images from high-frequency linear transducers (Fig. 4a), 11 children had some comet-tail artifacts (Figs. 3b and 4a), and 9 children (out of 11 for whom the color Doppler study was available) presented diffuse color comet-tail artifacts (Figs. 3c and 4b).

The number of patients with available Doppler color and the number of patients with a color comet-tail artifact according to each ciliopathy are specified in detail in the Online Resource 2, and all patients with comet-tail artifacts (B-mode) had a color comet-tail artifact.

In patients with ADPKD ($n = 4$), children could have enlarged or normal-sized kidneys, the cortex was mainly hyperechoic, and all demonstrated some cysts in both kidneys, infracentimetric in most cases (Online Resource 3). One patient (aged 10 days), who had a nonsense *PKD1* mutation, displayed the "salt and pepper" pattern with enlarged kidneys.

In patients with *HNF1B* mutation ($n = 11$), all patients had cysts of varying size and location.

Three children out of 11 had asymmetric kidneys due to congenital anomalies of the kidney and urinary tract (CAKUT): pelvi-ureteric junction obstruction, high-grade vesico-ureteral reflux, and multicystic dysplastic kidney.

Ten children (seven children with symmetric aspect of the kidneys and the three cases with unilateral CAKUT) had normal-sized kidneys with abnormal CMD and, in most cases,

Table 1 Demographics (gender and median age) of the children categorized by renal ciliopathy

	N (= 41)	Gender (male/female)	Age (years; median (min-max))
ARPKD	15	10/5	3 [0–17]
HNF1B	11	6/5	6 [0–13]
NPHP (infantile)	5	3/2	1[0–6]
NPHP (juvenile)	3	2/1	14 [13–15]
ADPKD	4	1/3	0 [0–4]
BBS	3	3/0	8 [6–15]

ARPKD autosomal recessive polycystic kidney disease; *HNF1B* glomerulocystic disease associated to HNF1B mutation; *NPHP* nephronophthisis (infantile and juvenile); *ADPKD* autosomal dominant polycystic kidney disease; *BBS* Bardet-Biedl syndrome

N number of patients

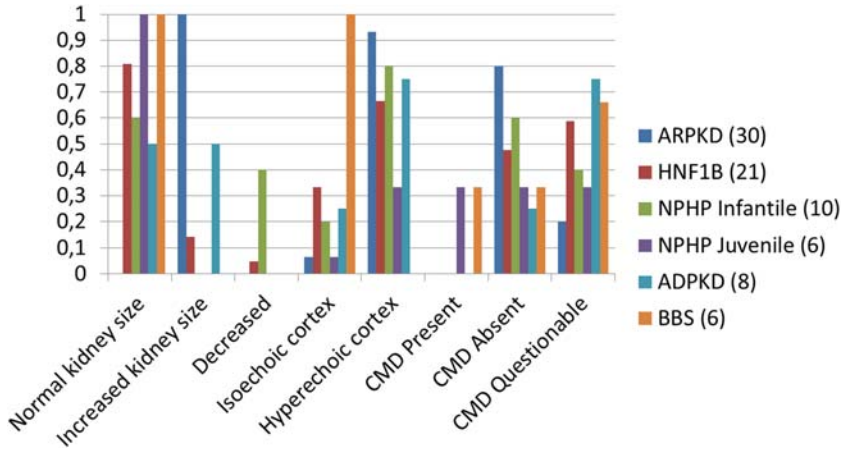

Fig. 1 Kidney's characteristics according to the ciliopathy disease. *CMD* CorticoMedullary Differentiation. *ARPKD* Autosomal Recessive Polycystic Kidney Disease; *HNF1B* Glomerulocystic Disease associated to *HNF1B* mutation; NPHP: Nephronophthisis (infantile and juvenile); *ADPKD* Autosomal Dominant Polycystic Kidney Disease; *BBS* Bardet Biedl Syndrome

a hyperechoic cortex (seven patients with a hyperechoic cortex, three with an isoechoic cortex), (Fig. 5 and Online Resource 4).

One 6-year-old child had a similar pattern to the "salt and pepper" pattern with abnormal CMD, countless cysts, enlarged kidneys, diffuse comet-tail, and color comet-tail artifacts and large areas of cortical sparing (resulting in a whole aspect of isoechoic cortex) (Fig. 6).

In patients with infantile nephronophthisis (5), three had normal-sized kidneys, and two had small kidneys. The CMD was abnormal, and in most cases, the cortex was hyperechoic (Online Resources 5 and 6). Three out of five children had no cysts detected (aged 6 days, 5 months, 2 years old). When present, the appearance of cysts was variable (Table 3). The child (aged 6 days) with a color Doppler analysis available did not present color comet-tail artifact.

The three children with juvenile nephronophthisis had normal-sized kidneys. One (13 years old) had a hyperechoic cortex with questionable CMD and one millimetric cortical cyst in the left kidney (Fig. 7). The next one (13 years old) had an isoechoic cortex with abnormal CMD and > 10 cysts in each kidney localized in the medulla. The last one (15 years old) had an isoechoic cortex with normal CMD and no cysts.

In the three children with BBS, all had normal-sized kidneys and an isoechoic cortex. One patient had normal kidneys on

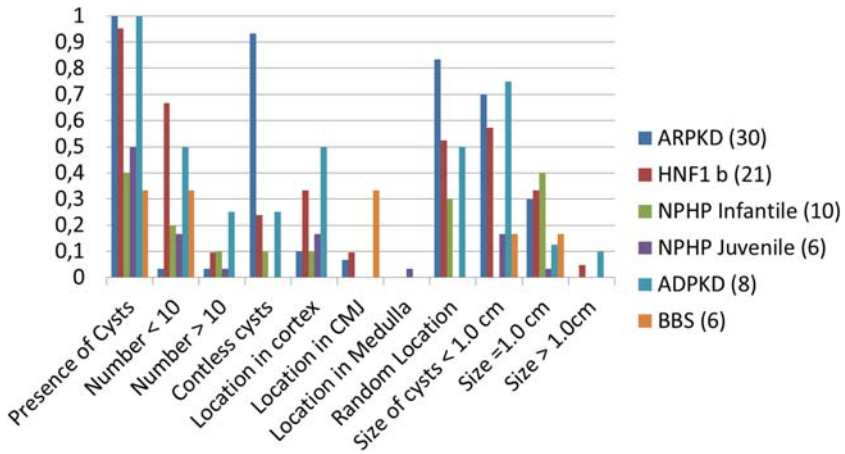

Fig. 2 Cyst's aspects by kidney according to the ciliopathy disease. *ARPKD* Autosomal Recessive Polycystic Kidney Disease; *HNF1B* Glomerulocystic Disease associated to HNF1B mutation; NPHP: Nephronophthisis (infantile and juvenile); *ADPKD* Autosomal Dominant Polycystic Kidney Disease; *BBS* Bardet Biedl Syndrome. *CMJ* corticomedullary junction

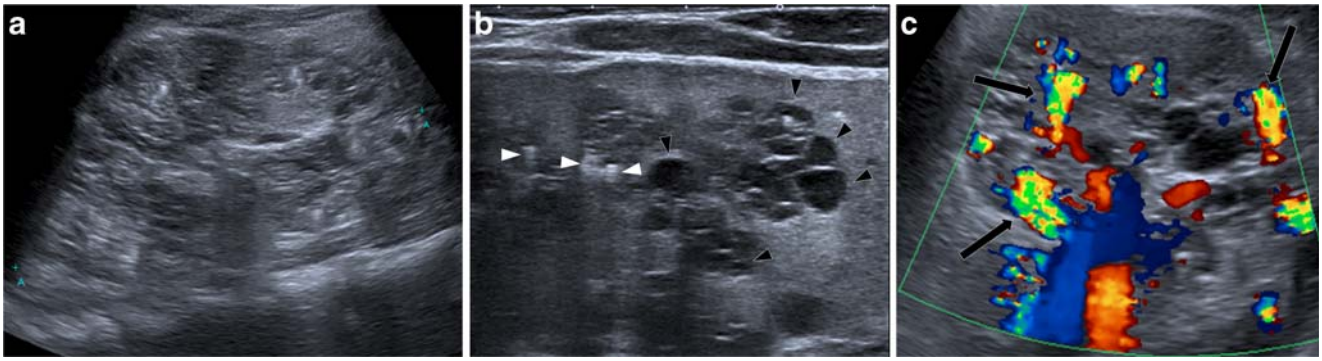

Fig. 3 Girl of 6 years old with *HNF1B* mutation B-mode linear probe Normal-sized kidney, hyperechoic cortex, and abnormal corticomedullary differentiation. Few millimetric confluent cysts, located in the corticomedullary junction and the medulla (arrowheads)

ultrasound (6 years old). One patient had only an abnormal CMD. One child of 15 years old had < 10 cysts/kidney localized at the corticomedullary junction and abnormal CMD.

Follow-up data

Ultrasound exams, performed at least 2 years after the first exam, were available for 19 children, ultrasound features were stable for 12 children, some macrocysts appeared in 2 patients with ARPKD, the renal size asymmetry increased for two children with *HNF1B* mutation, and the size and number of macrocysts increased in 2 patients with ADPKD (refer to Online Resource 2 for more details).

Discussion

In our group of 41 patients with a molecular proven diagnosis of ciliopathy-related renal disease, we were able to identify the "salt and pepper" pattern characterized by enlarged kidneys, heterogeneous increased parenchymal echogenicity, and countless infracentimetric cysts. We also noticed additional interesting features, such as areas of cortical sparing, comet-tail, and color comet-tail artifacts.

The "salt and pepper" pattern was present in 14 out of 15 children affected by ARPKD, at any age. We could also confirm an overlap of ultrasound findings between ciliopathies. Indeed, a similar pattern was occasionally found in children with ADPKD and glomerulocystic disease related to *HNF1B* mutation.

Another ultrasound pattern could be seen in most children with nephronophthisis and glomerulocystic disease related to *HNF1B* mutation: normal- or small-sized kidney, abnormal CMD, and hyperechoic cortex with cysts varying in aspect, size, number, and location.

To our knowledge, this is the first systematic ultrasound analysis of a group of children with a proven molecular diagnosis of ciliopathy-related renal disease.

ARPKD was the most frequent ciliopathy (37%) in our group of patients, in accordance with the literature [1–4, 7, 9, 11, 12].

Previous descriptions of the typical ultrasound aspect of ARPKD include enlarged kidneys, hyperechoic cortex, abnormal CMD, and many tiny microcysts [1, 2] due to fusiform tubular dilatation [1, 4, 7, 11], which is concordant with our results.

In our population, some children demonstrated areas of cortical sparing, particularly well seen with high-frequency probes. The comet-tail artifact was also present in some of these children, probably due to the increased acoustic

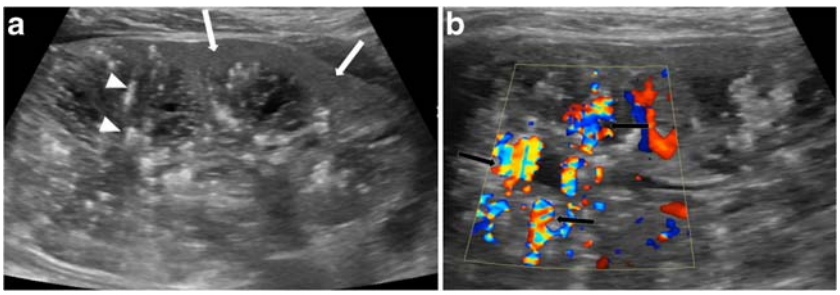

Fig. 4 Boy of 6 years old with *HNF1B* mutation B-mode convex (**a**) and linear (**b** and **c**) probes; color Doppler (**b**) Enlarged kidney, abnormal corticomedullary differentiation with areas of cortical sparing (white arrows) Countless cysts randomly distributed, infracentimetric, irregularly shaped and confluent (black arrowheads); comet-tail artifacts (white arrowheads); color comet-tail artifacts (black arrows)

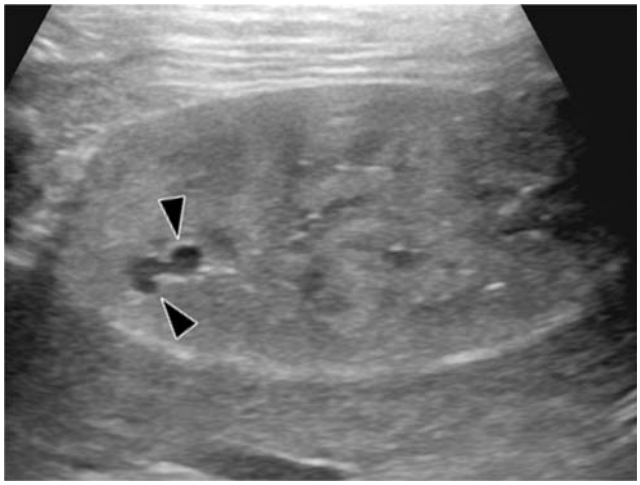

Fig. 5 Boy of 13 years old with juvenile nephronophthisis B-mode convex (**a**) and linear (**b**) probes Normal-sized kidney, hyperechoic cortex (black star) compared to the liver (white star), and abnormal corticomedullary differentiation. One cyst (6 mm), located in the cortex (arrowhead)

interfaces of innumerable millimetric cystic collecting ducts [3]. We also found an interesting additional sign: the color comet-tail artifact, which was seen in eight out of ten children in which color Doppler was performed. This artifact, which could also be explained by the increased acoustic interfaces [23, 24], could be a sensitive test in case of enlarged hyperechoic kidneys with no detectable microcysts on gray-scale imaging.

Although ADPKD is the most common inherited cystic kidney disease (approximatively 1/1000 people worldwide) [3, 4, 12–15], it was less represented in our group (10%). This represents a selection bias in our group due to its retrospective design and former practices. Indeed, over the inclusion period, genetic testing was rarely performed in children when familial history and ultrasound features were typical because ADPKD was rarely thought to be responsible for clinical symptoms in children [12, 25], and neither treatment nor recommendations for nephroprotection were available until recently [26].

In addition, routine genetic testing is currently not recommended outside specific situations, such as atypical and sporadic cases.

ADPKD is usually responsible for progressive renal cyst formation and leads to enlarged kidneys with numerous diffuse macrocysts [3, 8], but in early disease, it can be impossible to distinguish it from ARPKD with ultrasound [7, 10, 15, 25]. Similarly, in our group, one child with ADPKD demonstrated a similar pattern to patients with ARPKD: enlarged kidneys, "salt and pepper" pattern, and eventually color comet-tail artifacts. This patient had a nonsense *PKD1* mutation. However, the analysis of a larger number of ADPKD patients would be necessary in order to search for correlation between ultrasound pattern and genotype.

In our group, it was impossible to distinguish patients with nephronophthisis and glomerulocystic disease related to *HNF1B* mutation by ultrasound. We found a similar pattern in both these diseases: kidneys were normal or small in size with abnormal CMD and hyperechoic cortex, in accordance with the literature [1, 2, 4, 9, 17].

As previously described in patients carrying an *HNF1B* mutation, three children from our group had asymmetric kidneys due to associated CAKUT, which are known to be quite frequent in these patients [6, 17]. Moreover, it should be noted that, in the child with a single kidney, there was no compensatory hypertrophy and the kidney was thus small for age. One 6-year-old child carrying an *HNF1B* mutation had an ultrasound pattern similar to patients with ARPKD: enlarged kidneys, a similar "salt and pepper" pattern with isoechoic cortex that could be explained by areas of cortical sparing and diffuse color comet-tail artifacts. In fetuses and neonates, *HNF1B* nephropathy can result in ultrasound features similar to those of ARPKD [2]; however, to our knowledge, this has never been described in older children.

BBS is known as a differential diagnosis for ARPKD on prenatal ultrasound, with enlarged hyperechoic kidneys, loss of

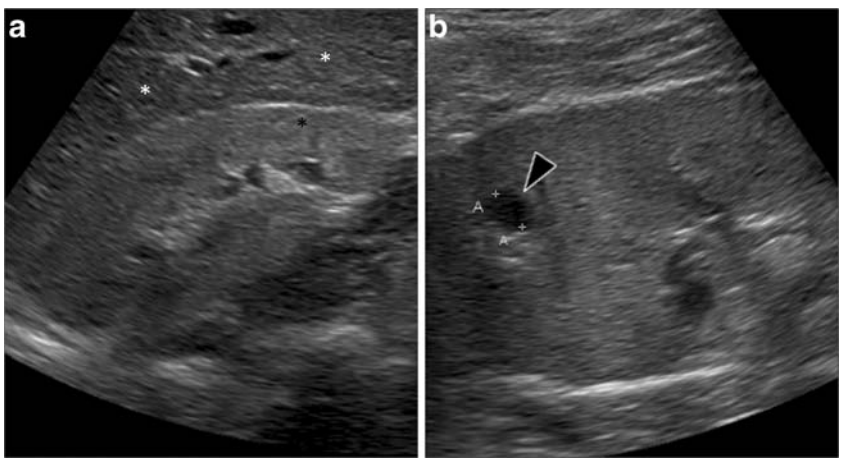

Fig. 6 Boy of 6 years old with *HNF1B* mutation B-mode convex (**a**) and linear (**b** and **c**) probes; color Doppler (**b**) Enlarged kidney, abnormal corticomedullary differentiation with areas of cortical sparing (white arrows) Countless cysts randomly distributed, infracentimetric, irregularly shaped and confluent (black arrowheads); comet-tail artifacts (white arrowheads); color comet-tail artifacts (black arrows)

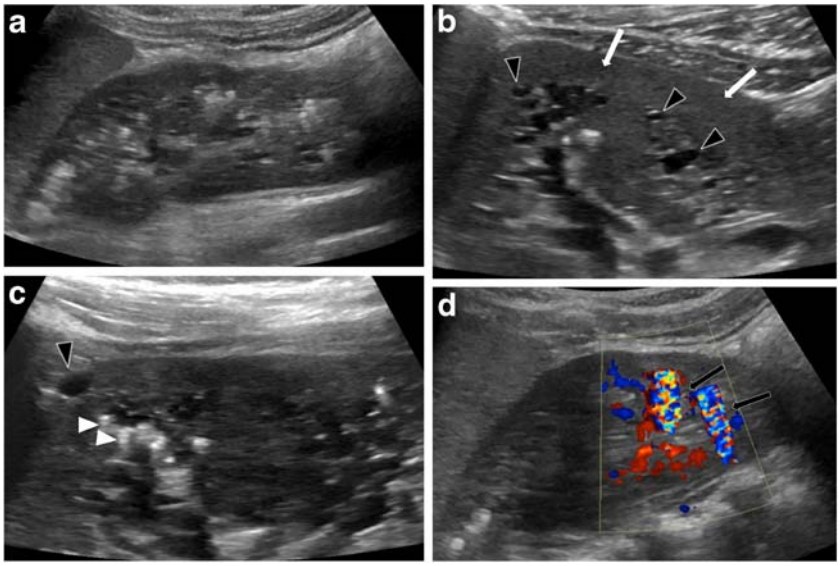

Fig. 7 Boy of 13 years old with juvenile nephronophthisis B-mode convex (**a**) and linear (**b**) probes Normal-sized kidney, hyperechoic cortex (black star) compared to the liver (white star), and abnormal corticomedullary differentiation. One cyst (6 mm), located in the cortex (arrowhead)

CMD, with or without macrocysts [1, 11]. In our small sample, the three children had normal-sized kidneys with an isoechoic cortex (one with normal CMD, two with abnormal CMD). Only one child aged 15 demonstrated some cysts on ultrasound.

There are some limitations to our study including its retrospective design and the small sample of patients for each genetic disease, with variable time points of ultrasound examinations and disease progressions. However, our local data warehouse enabled us to retrieve all patients referred to our pediatric center for suspicion of renal ciliopathy over a 10-year period and to study all patients with an identified mutation. Thus, we could analyze the ultrasound features of a group of 41 children with a molecular diagnosis of renal ciliopathy, despite the low prevalence of ciliopathies in the general population. Moreover, a follow-up was available for 19 children, showing a global stability of ultrasound features in most of them.

In conclusion, in a group of 41 children with a molecular diagnosis of ciliopathy involving kidneys, we found that the "salt and pepper" pattern was almost always seen in ARPKD but may also be seen in other ciliopathies, probably more frequently than usually thought. Furthermore, the color comet-tail artifact may be useful when suspecting a renal ciliopathy in case of enlarged hyperechoic kidneys with no detectable microcysts on B-mode grayscale ultrasound.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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