A case of 17q12 deletion syndrome that presented antenatally with markedly enlarged kidneys and clinically mimicked autosomal recessive polycystic kidney disease

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Abstract

The gene encoding hepatocyte nuclear factor 1 β (HNF1B), a transcription factor involved in the development of the kidney and other organs, is located on chromosome 17q12. Heterozygous deletions of chromosome 17q12, which involve 15 genes including *HNF1B*, are known as 17q12 deletion syndrome and are a common cause of congenital anomalies of the kidneys and urinary tract (CAKUT) and may also present as a multisystem disorder. Autosomal recessive polycystic kidney disease (ARPKD), on the other hand, is a severe form of polycystic kidney disease caused by mutations in *PKHD1* (polycystic kidney and hepatic disease 1). It is important to differentiate between these two diseases because they differ significantly in inheritance patterns, renal prognosis, and extrarenal manifestations. Here we report a case of 17q12 deletion syndrome that clinically mimicked ARPKD in which genetic testing was essential for appropriate genetic counseling and monitoring of possible extrarenal manifestations. The patient presented antenatally with markedly enlarged kidneys and showed bilaterally hyperechoic kidneys with poor corticomedullary differentiation and multiple cysts on ultrasonography. There was no family history of renal disease. ARPKD was clinically suspected and genetic testing was performed to confirm diagnosis, resulting in an unexpected finding of 17q12 deletion including *HNF1B*. While some research has been done to identify patients that should be tested for *HNF1B* anomalies, this case illustrates the difficulty of recognizing *HNF1B*-related disease and the importance of genetic testing in appropriately managing CAKUT cases.

Keywords Hepatocyte nuclear factor 1 β (HNF1B) · 17q12 deletion syndrome · *HNF1B*-associated disease · Autosomal recessive polycystic kidney disease (ARPKD) · Congenital anomalies of the kidneys and urinary tract (CAKUT) · Genetic testing

Introduction

Hepatocyte nuclear factor 1 β (HNF1B) is a transcription factor involved in the development of the kidney, urogenital tract, pancreas, liver, and parathyroid gland [1]. Heterozygous mutations in *HNF1B* are the most common monogenic cause of developmental renal disease and may also present as a variable multisystem disorder. Heterozygous deletions of

17q12, which involve 15 genes including *HNF1B*, are known as 17q12 deletion syndrome and result in similar renal and extrarenal manifestations. Renal phenotypes of *HNF1B*-associated disease are highly heterogeneous with cystic disease, including cystic dysplasia, being predominant. Other renal phenotypes include congenital anomalies of the kidneys and urinary tract (CAKUT) such as renal hypoplasia, unilateral renal agenesis, horseshoe kidney, and collecting system abnormalities. Renal function can range from normal to end-stage renal disease (ESRD). Extrarenal phenotypes of *HNF1B*-associated disease include early-onset diabetes mellitus (known as maturity-onset diabetes of the young type 5), pancreatic hypoplasia, elevated liver enzymes, genital tract malformations, and in the case of 17q12 deletions, autism spectrum disorders and cognitive impairment [2].

Autosomal recessive polycystic kidney disease (ARPKD), on the other hand, is a severe form of polycystic

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kidney disease caused by mutations in *PKHD1* (polycystic kidney and hepatic disease 1). ARPKD usually presents antenatally or in early childhood with enlarged, hyperechoic kidneys and impaired renal function which in most cases progresses to ESRD. Developmental biliary defects are invariable features of ARPKD and can lead to portal hypertension with resulting esophageal varices, splenomegaly, and thrombocytopenia. Ascending cholangitis is also an important complication in ARPKD with high morbidity and mortality [3].

Here we report a case of 17q12 deletion syndrome that clinically mimicked ARPKD and presented antenatally with markedly enlarged kidneys. Genetic testing enabled to differentiate between the two diseases and was essential for accurate genetic counseling and appropriate monitoring for renal and extrarenal symptoms.

Case report

The mother, G3P2, was referred to our hospital at 26 weeks of gestation because of enlarged fetal kidneys. The parents were nonconsanguineous with no family history of renal disease. Fetal magnetic resonance imaging (MRI) at 30 weeks (Fig. 1a) showed bilaterally enlarged and polycystic kidneys. Amniotic fluid levels were normal throughout the pregnancy. Vaginal delivery occurred at 37 weeks 6 days. The male newborn weighed 3513 g and had Apgar scores of 8 and 8 at 1 and 5 min, respectively. He was admitted to the NICU because of respiratory distress and was diagnosed with transient tachypnea of the newborn.

Clinical course in the NICU was unremarkable except for a mildly elevated urinary output. His blood pressure was normal and stable. He was discharged on day 17 of life with good feeding and weight gain.

Fig. 1 Imaging findings of the patient's kidneys. **a** Fetal magnetic resonance imaging at 30 weeks gestation. The kidneys were bilaterally enlarged with lengths of 63 mm and 55 mm in the left and right kidney, respectively. Multiple small cysts were detected in both kidneys. No abnormalities were found in the lungs and the amniotic fluid

level was normal. **b** Renal ultrasonography on day 16 of life. The kidneys were enlarged and hyperechoic with poor corticomedullary differentiation. The left and right renal lengths were 72 mm and 66 mm, respectively. Bilateral multiple cysts of maximum 10 mm in diameter were found

Postnatal ultrasonography (Fig. 1b) revealed bilaterally hyperechoic and enlarged kidneys with poor corticomedullary differentiation and multiple cysts. No abnormal findings in the liver or biliary tract was found on ultrasonography. No abnormalities in brain structure were observed in cranial MRI. Serum creatinine levels were mildly elevated at 0.42 mg/dL at 1 month of age. No electrolyte imbalance, proteinuria or hematuria was observed.

The ultrasonography findings and the clinical course suggested ARPKD and genetic testing was performed with informed consent of the parents. The CAKUT gene panel analysis of the patient detected no known pathogenic variants in *PKHD1* or in any of the genes analyzed. Array comparative genomic hybridization identified a heterozygous 1.35-Mb deletion in the patient at 17q12 including *HNF1B* (Fig. 2). Multiplex ligation-dependent probe amplification analysis of the patient and his parents revealed that the deletion was de novo. The genetic analyses were approved by the Central Ethics Board of the University of Tokyo and Kobe University.

The patient has been followed up for 2 years and is showing normal growth and development. He has not developed diabetes or elevations in liver enzymes thus far. His serum creatinine levels remain at around 0.4 mg/dL and no further deterioration in kidney function has been observed.

Discussion

In our patient, hyperechoic and markedly enlarged kidneys presenting before birth clinically suggested ARPKD and genetic testing was performed to confirm diagnosis, resulting in an unexpected finding of 17q12 deletion including

HNF1B. Studies that performed genetic testing on patients clinically diagnosed with ARPKD have also detected deletions or mutations in *HNF1B*. Szabó T et al. analyzed 36 unrelated patients with the clinical diagnosis of ARPKD and identified three patients with de novo heterozygous *HNF1B* deletion [4]. Similarly, Krall et al. analyzed 59 patients diagnosed or suspected with ARPKD and found 2 cases with *HNF1B* mutation [5]. These findings suggest that in some cases, *HNF1B*-associated disease may clinically mimic ARPKD and be misdiagnosed as such. It is important to differentiate between these two diseases, however, because they differ significantly in inheritance patterns, renal prognosis, and extrarenal manifestations. The absence of arterial hypertension and electrolyte imbalance in our patient was not typical of ARPKD and may serve as a differential point against ARPKD in future cases.

Clinically, there are other genes whose mutations may cause ARPKD-like kidneys. Mutations in *DZIP1L*, which encodes a ciliary protein that localizes to centrioles and the ciliary basal bodies, has recently been reported to demonstrate an ARPKD-like phenotype with a moderate course [6]. Either dominant or recessive mutations in *PKD1* and *PKD2*, genes that generally cause autosomal dominant polycystic kidney disease, can mimic ARPKD in cases that manifest prenatally or during childhood. Nephronophthisis and other ciliopathies should also be considered as differential diagnoses for ARPKD [7]. Table 1 provides a summary of gene mutations that may clinically present as ARPKD-like kidneys.

Renal function in *HNF1B*-associated disease varies widely from normal renal function in adulthood to prenatal renal failure leading to oligohydramnios, pulmonary hypoplasia and prenatal death [10]. In our patient, his renal

Fig. 2 Array comparative genomic hybridization (CGH) of the patient. Array CGH showed a heterozygous deletion in the patient at 17q12 including *HNF1B*

Table 1 Summary of gene mutations that may clinically present as ARPKD-like kidneys

Gene(s)	Disease	Renal presentation	Extrarenal manifestations
<i>HNF1B</i>	<i>HNF1B</i> -associated disease	Highly variable, including cystic dysplasia, unilateral renal agenesis, renal hypoplasia, horseshoe kidney [2]	Early-onset diabetes mellitus, pancreatic hypoplasia, elevated liver enzymes, genital tract malformations
<i>DZIP1L</i>	ARPKD-like	Enlarged polycystic kidneys with poor cortico-medullary differentiation [6]	Hypertension from early childhood
<i>PKD1, PKD2</i>	ADPKD	Cysts of variable sizes along all regions of the nephron	Polycystic liver disease, intracranial aneurysms, hypertension
<i>NPHP1-NPHP20, NPHP1L, NPHP2L</i> [8]	Nephronophthisis	Hyperechoic kidneys with poor corticomedullary differentiation; multiple cysts at the corticomedullary junction and the medulla	Retinitis pigmentosa, skeletal defects, hepatic fibrosis, situs inversus
<i>INPP5E, TMEM216, AHI1, NPHP1, CEP290, TMEM67</i> and others [9]	Jubert Syndrome	Nephronophthisis or cystic dysplasia	Cerebellar vermis hypoplasia, hypotonia in infancy with later ataxia, intellectual disability, episode tachypnea and/or apnea, abnormal eye movements
<i>BBS1-BBS18</i> [9]	Bardet-Biedl Syndrome	Nephronophthisis or cystic dysplasia	Retinal dystrophy, obesity, postaxial polydactyly, intellectual disability, hypogonadism
<i>MKS1, TMEM216, TMEM67, CEP290, RFGRIPL, CC2D2A</i> and others [9]	Meckel-Gruber Syndrome	Nephronophthisis or cystic dysplasia	Occipital encephalocele, hepatic ductal plate malformation, perinatal death

ARPKD autosomal recessive polycystic kidney disease, ADPKD autosomal dominant polycystic kidney disease

function was relatively preserved compared to those of early-onset ARPKD patients, but the histology behind his condition is unclear. Few renal biopsies have been performed in cases of *HNF1B*-associated disease. Clissold et al. reviewed histological data of 19 patients with *HNF1B*-associated renal disease and reported considerable variation in the histopathological findings, including hypoplastic glomerulocystic kidney disease in 6 patients, oligomeganephronia in 3 patients, and cystic renal dysplasia in 2 patients [2]. While these findings suggest abnormal nephron development in the patients, there is not sufficient evidence to rule out the involvement of ARPKD-like collecting duct dilatations in other cases of *HNF1B*-associated renal disease.

Research in mouse models indicates an association between *Hnf1b* and *Pkhd1* in kidney development. Renal-specific inactivation of *Hnf1b* in mice results in polycystic kidneys. *Pkhd1*, along with cystic disease genes *Umod* and *Pkd2*, contains *Hnf1b* binding sites and is drastically downregulated in *Hnf1b*-inactivated cystic cells [11]. *Hnf1b* directly activates the *Pkhd1* promoter in mice and renal-specific expression of a dominant-negative mutant *Hnf1b* develops renal cysts and reduces *Pkhd1* mRNA in cystic collecting ducts but not in the surrounding noncystic tubules [12, 13].

Although these transcriptional networks may explain the mechanism of ARPKD-like cyst formation in some cases, little is known about the reasons for the high heterogeneity of phenotypes in *HNF1B*-associated disease. No clear genotype–phenotype correlation has been established and phenotypes may vary even within family members that have the same mutation [14]. The heterogeneity of phenotypes, incomplete penetrance, and the high frequency (50–60%) of de novo mutations make it difficult to clinically diagnose *HNF1B*-associated disease [15–17]. Faguer et al. described a scoring system as a screening tool to determine which patients should be genetically tested for *HNF1B* anomalies [18]. The *HNF1B* score was developed based on a weighted combination of the most typical findings according to the frequency or specificity reported in the literature. Characteristics that were considered most distinctive and thus attributed the highest score were hyperechoic kidneys, renal cysts, maturity-onset diabetes of the young, pancreatic hypoplasia or pancreatic exocrine insufficiency, and genital tract abnormalities. In the case of our patient, his *HNF1B* score adds up to 18 with bilateral hyperechoic kidneys, renal cysts and antenatal renal abnormalities, which is above the threshold of 8 for *HNF1B* gene testing proposed in the study (sensitivity 98.2%, specificity 41.1%, positive predictive value 19.6%, and negative predictive value > 99%). However, the authors also state that other recognized causes of renal cysts such as ARPKD should be excluded before evaluating the *HNF1B* score, and therefore cases mimicking other diseases may still be overlooked [18].

Virtually all patients with a whole-gene deletion of *HNF1B* is found to have a 1.4-Mb 17q12 deletion involving 15 genes [19]. This region of chromosome 17 is susceptible to genomic rearrangement mediated by non-allelic homologous recombination between segmental duplications [20]. Verbitsky et al. performed a genome-wide analysis of copy number variants in 2824 CAKUT cases and found that out of 112 patients carrying a known genomic disorder, 23 (20.5%) had a 17q12 deletion [21]. In addition to the various renal and extrarenal manifestations of *HNF1B*-associated disease, 17q12 deletion syndrome is associated with an increased risk of neurodevelopmental disorders such as autism spectrum disorders and cognitive impairment [2]. Although whether *HNF1B* is responsible for these neurological features remain unclear, patients with *HNF1B* deletions should be monitored for neurodevelopmental problems. These findings also highlight the need for both sequence and dosage analyses for genetic testing in CAKUT.

In summary, we have reported a case of 17q12 deletion including *HNF1B* that clinically mimicked ARPKD and illuminated the importance of genetic testing in appropriately managing CAKUT cases. Further research is required to improve the recognition of *HNF1B*-related disease and to refine the identification of patients that should be tested for *HNF1B* anomalies.

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Declarations

Conflict of interest The authors declared that they have no conflict of interests.

Human and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient's parents.

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