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THE CASE OF HNF-1β MUTATION WITH MEDULLARY CYSTS

A. Bensouda Mourri[1], M. Cassart[1], M. Hall[2], F.E. Avni[3]

We describe one case of long term post-natal follow-up of hyperechoic fetal kidneys related to HNF-1β mutation with cystic changes over a 9-year period in a female patient. This diagnosis was suspected on the basis of the renal US findings and was confirmed by complementary genetic examination. After birth, cortical cysts were detected and at the age of 4, medullary cysts were found, that disappeared with time. Currently our patient displays hyperechoic kidneys with only cortical cysts. This case report highlights the variability of US appearances in relation with HNF-1β genetic mutation.

Key-words: Kidneys, cysts – Kidney, US.

The hepatocyte nuclear factor (HNF-1β), encoded by the transcription factor 2 gene (TCF2) which maps to the short arm of human chromosome 17, plays a role in the specific regulation of gene expression in various tissues such as the liver, kidney, intestine, genital organs and pancreatic islets and is involved in the embryonic development of these organs. The heterozygous mutations of TCF2 are known to be responsible for Maturity-Onset Diabetes of the Young type 5 (MODY 5) (1). MODY is a monogenic form of diabetes mellitus that is inherited as an autosomal dominant trait. The diabetes typically presents before the age of 25 and is not associated with ketosis or obesity. The diagnosis of TCF2 mutations is based essentially on molecular genetic testing and radiological findings. The prevalent genetic anomaly is the complete heterozygous deletion of the TCF2 (83%) (2). A family screening revealed de novo TCF2 anomalies in more than half of the patients. The kidney is the organ most affected by the TCF2 mutation. In analyzing the renal sonographic signs (with TCF2 mutations), it was noted a bilateral hyperechoic kidneys in 80% and cortical microcysts in 84% of patients with HNF-1β mutation (2). The aim of the present case report is to provide the evolution of US patterns observed in one patient over a 9 year-period.

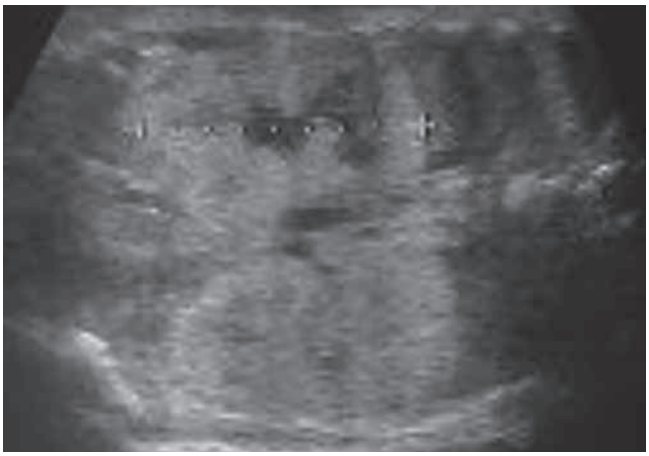

Fig. 1. — 32 weeks gestation. Coronal ultrasound scan of both kidneys shows hyperchogenicity of cortex and enlarged kidney. Renal length is 50 mm (+2 SD).

Case report

AB was a healthy 29 year-old woman in her second pregnancy. Her first child did not have any health problem. AB had no significant past medical history, was not taking any medication and there was no history of consanguinity. Regarding her family history, her cousin has a urinary reflux and her uncle has an undetermined moderate renal failure. Her husband was healthy with no significant past medical or family history. There is neither diabetes nor hypertension in the family.

She was referred to our center from her local hospital for a detailed obstetrical US scan held at 23 weeks because an obstetrical ultrasonographic examination had shown some anomalies.

When scanned in our center at a postmenstrual age of 32 weeks, the head and abdominal circumference and femur length measurements were appropriate for estimated gestational age. The kidneys are hyperechoic and enlarged (the left kidney measured 50 mm and the right one with 52 mm, +2 standard deviations) and associated with a large bladder (Fig. 1). The amniotic fluid volume was within normal limits. No other fetal abnormalities were detected. Following these results, an MRI imaging examination was performed at 33 weeks for depicting small cystic lesions. No cysts were visualized. No specific diagnosis was proposed at this stage.

Delivery occurred at term and the weight and size of the baby girl were normal. At birth, her Apgar score was 10/10/10, she had neither renal insufficiency nor hypertension.

A renal ultrasound scan performed on day 7 and confirmed the prenatal findings of bilaterally enlarged (the left kidney with 52 mm and the right one with 58 mm, +2 standard deviations) hyperechoic kidneys but with small cysts were detected in the peripheral cortex of both kidneys (Fig. 2).

A renal US scan at 2 months showed again enlarged kidneys measuring 56 mm for the left kidney and 58 for the right kidney in long

From: 1. Department of Radiology, Université Libre de Bruxelles (ULB), Brussels, Belgium, 2. Department of Nephrology, Université Libre de Bruxelles (ULB), Brussels, Belgium, 3. Department of Radiology, Centre Hospitalier Régional Universitaire de Lille (CHRU-Lille), Lille, France.
Address for correspondence: Dr A. Bensouda Mourri, M.D., Dept of Radiology, Institut Bordet (Université Libre de Bruxelles). Boulevard Waterloo 121, 1000 Brussels, Belgium. E-mail: abensoud@ulb.ac.be

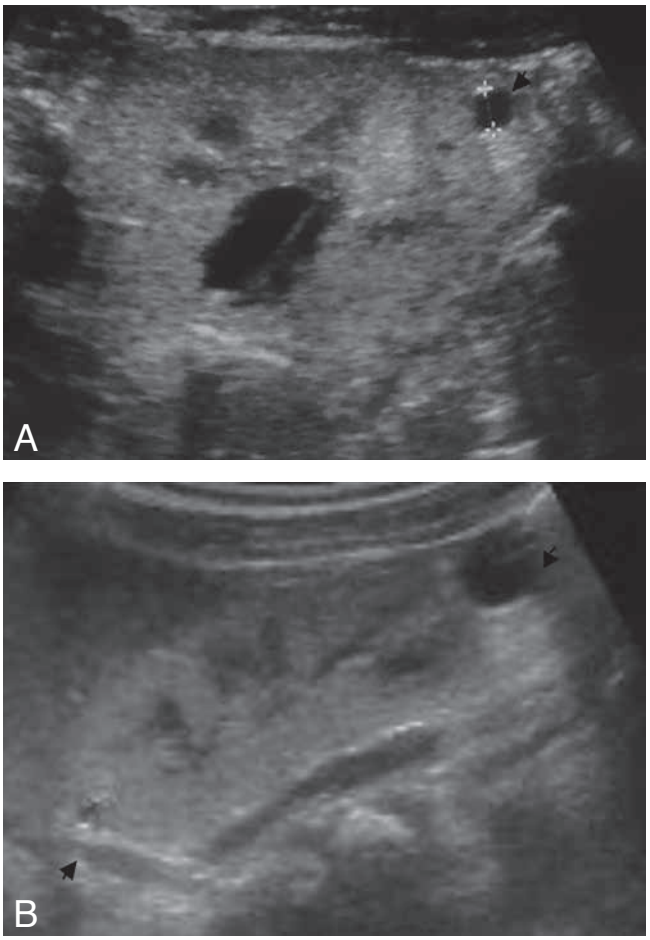

Fig. 2. — 7-day-old. Transverse (A) and coronal (B) ultrasound scan show right kidney with cysts (arrows) in the peripheral cortex.

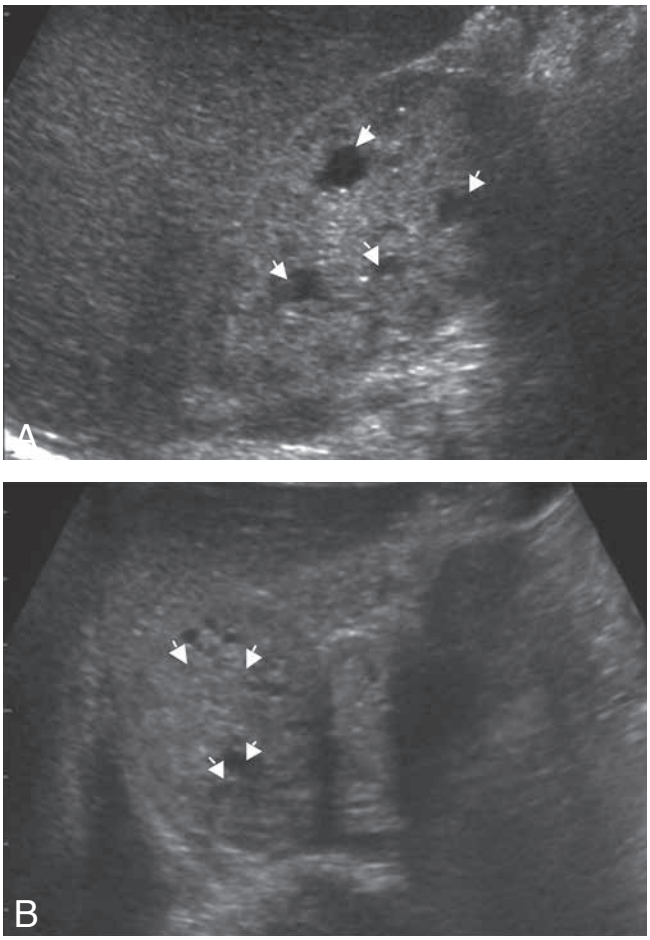

Fig. 3. — 4-year-old. Transverse ultrasound scans (A and B) show multiple cysts in the medullary areas (arrows).

axis with cortical hyperechogenicity and increasing cortico-medullary differentiation. It also showed 2-3 small peripheral cortical cysts of 3 to 4 mm of diameter in both kidneys. There was no dilatation of pelvicalyceal system.

Up to the age of 4 years, controls US were made during regular follow-up examinations. Ultrasound results were similar. The last US performed at age of 4 years revealed this time the cysts to be predominant by the medullary areas (Fig. 3). Throughout this period, she was healthy.

The patient was further examined at the age of 9 years. The Biology and urinalysis were normal. Renal sonography revealed echogenic parenchyma and renal cysts of maximum 3 mm diameter within the cortex, the medullary cysts disappeared (Fig. 4). The bipolar diameter of the kidneys was 70 mm (normal for age).

Genetic evaluation, performed at this time, showed the presence of a heterozygous deletion carrying the entire gene HNF-1β (exons 1-9). Further investigation is now being carried among the rest of the family.

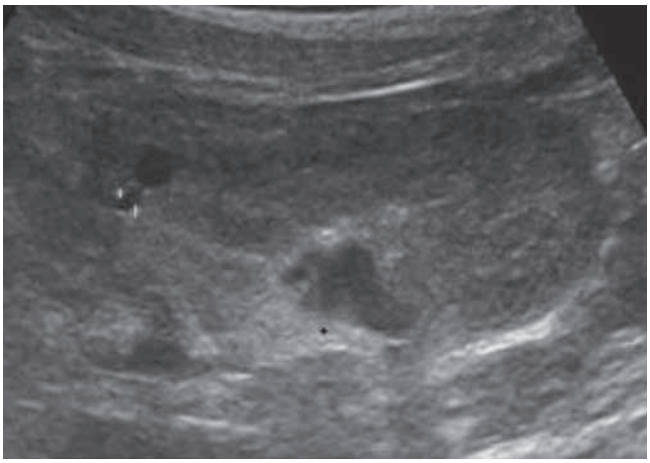

Fig. 4. — 9-year old. Ultrasound scan in partial sagittal view shows two small cysts (arrows) in the cortex. No medullary cysts are found.

Discussion

Our case represents an example of hyperechoic fetal kidneys related to HNF-1β mutation and the evolution of the US patterns over a 9 year period.

Various types of renal cystic diseases are encountered in case of HNF-1β mutation; they include bilateral renal cysts, mainly detected after birth (which was the case of our

patient), multicystic dysplastic kidney (MCDK), and glomerulocystic kidney disease under its hypoplastic form. In addition to the formation of cysts, other congenital renal anomalies have been described in association with HNF-1β mutation including oligomeganephronia, solitary kidney, renal hypoplasia/dysplasia, and horseshoe kidney (3). At histology the predominant cystic lesions are glomerular cysts, more rarely oligomeganephronia, associated with interstitial fibrosis.

Recently, mutations of HNF-1β have been reported as the most frequent genetic abnormality detected in fetuses with bilateral hyperechoic kidneys (2). The mechanism by which HNF-1β might be involved in the development of hyperechoic kidneys is most probably related to the type of cysts associated with the mutation. Gresh et al. have shown in animal studies that HNF-1β controlled the expression of 3 genes expressed in tubular epithelial cells whose mutations resulted in cystic renal diseases: UMOD (leading to medullary cystic kidney diseases (MCKD)), PKHD-1 (autosomal recessive polycystic kidney diseases (ARPKD)), PKD-2 (autosomal dominant polycystic kidney diseases (ADPKD)) (4, 5). These genes all play a crucial role in cilium formation. Inactivation of HNF-1β leads to a decreased expression of these genes, thus reducing the number of proteins encoded, which normally inhibits growth through a calcium-dependent mechanism (6, 7), and thus leads to a malfunction of the primary ciliary structure leading to the formation of cysts. The multiplicity of cysts creates numerous interfaces leading to hyperechoic kidney. These results obtained on animal models suggest that HNF-1β might be a major actor in kystogenesis.

The present case gave us the opportunity to follow a HNF-1β case with cystic changes over a 9 year period. The US evolution of our case displays some typical as well as atypical features of HNF-1β mutation related cystic kidneys changes. The first stage in utero was the classical hyperechoic fetal kidney with normal cortico-medullary differentiation. The second stage after birth was the detection of cortical cysts. The third stage was the unusual detection of medullary cysts at age 4 that disappeared with time.

These different patterns must be related to the anomalies induced by the mutation. In our clinical case, inactivation of HNF-1β could be responsible for a decrease in the expression of the gene UMOD and/or PKD-2 and/or PKHD-1 which would then explain the presence of medullary cysts in addition to cortical cysts that were found in 84% of patients with HNF-1β mutation (2, 4, 5).

Noteworthy, at each stage, there is a differential diagnosis. The most common differential diagnosis that might be suggested for the first stage is: autosomal recessive polycystic kidney diseases (ARPKD), autosomal dominant polycystic kidney diseases (ADPKD) and cystic dysplasia. With the emergence of cortical cysts, HNF-1β mutation case must be included in the differential diagnosis of renal cysts in children as causes for glomerulocystic kidney disease (GCKD), autosomal dominant polycystic kidney diseases (ARPKD) and polymalformative syndrome (Zellweger syndrome). The unusual development of medullary cysts could raise the diagnosis ARPKD, nephronophtisis and medullary cystic dysplasia (8).

In conclusion, one US follow up highlights that different US patterns including medullary cysts can be present in a patient with a HNF-1β mutation. Therefore, it is very important to make a follow up to see the evolution of lesions and it is important to note that the presence of medullary cysts may occur at any time and should not exclude the diagnosis of HNF-1β mutation.

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