Can prenatal renal pelvicalyceal echogenic foci support the diagnosis of cystinuria?

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Abstract

Cystinuria is an inherited disease caused by a defect in renal and intestinal tubular transport affecting cystine and dibasic amino acids (lysine, ornithine and arginine). It is transmitted as an autosomal recessive disease. On fetal ultrasound, the colon is usually seen as hypoechoic or isoechoic. Antenatal hyperechoic appearance of the fetal colon was previously considered as a normal variant. However, recent studies have shown that hyperechoic colon is associated with cystinuria. We present a case of cystinuria, who was referred to us due to fetal hyperechogenic colon at 32 weeks of gestation. Additional fetal pericalyceal echogenic focal structures were observed on ultrasonography. The diagnosis of cystinuria was confirmed in the postnatal period. (J Turk Ger Gynecol Assoc 2022; 23: 327-9)

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Introduction

Cystinuria is an autosomal recessive disease characterized by renal tubular reabsorption defect of cystine, which is a dibasic amino acid, and cystine is the only dibasic amino acid that is insoluble at normal urine pH (1). Cystine stones make up 6-8% of childhood urinary tract stones (2).

During the prenatal period, the fetal colon usually appears as either hypoechoic or isoechoic. When the fetal colon has a hyperechoic appearance, this was previously considered to be a normal variant (3). However, in subsequent studies, this finding was discovered to be associated with cystinuria (4,5). Cystinuria is a urinary tract, lithogenic, congenital disease characterized by a cystine resorption dysfunction due to a defect in the rBAT/b0, + AT amino acid transporter which is expressed in the apical border of the proximal renal tubule and epithelial cells of the digestive tract. In fetal life, tubular maturation begins after the 14th week of pregnancy, and after 20 weeks the kidney is responsible for more than 90% of the amniotic fluid volume. Kidney-defective cystine transport results in increased urinary excretion of this amino acid, and the digestive defect reduces digestive absorption, both of which result in cystine accumulation in the amniotic fluid. Swallowing of amniotic fluid begins at week 12 and leads to ingestion of large volumes of cystine. Since the anal sphincter is not physiologically functional at this time, colonic cystine does not accumulate until the 22nd gestational week. However, from 22 weeks on, the closure of the anal sphincter due to the maturation of the three anal sphincter muscles leads to a progressive accumulation of cystine in the colon. At high concentration, cystine precipitates to form radio-opaque stones, which on ultrasound show as hyperechogenicity of the colon. In a series of 16 patients, Amat et al. (5) showed that this finding was associated with cystinuria in 50% of the cases. These authors reported that if a hyperechogenic colonic appearance is observed before the 36th gestational week, the diagnosis may be cystinuria with a probability of 88.9%. Written informed consent was obtained for publication of this report.

Case Report

A 27-year-old mother presented during her first pregnancy. The parents had no history of any disease or kidney stones. In the family history the mother's grandmother had a history

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of hypertension and sabulous urolithiasis. There was rhesus incompatibility between her and her husband. Consanguinity was not present between his parents and family history was negative for any renal diseases. During the pregnancy, the patient was diagnosed with gestational diabetes mellitus, which was adequately controlled by diet. No fetal anomaly was detected until the 32nd week of the pregnancy. However, at the 32nd gestational week, she was referred to us because the fetal colon was found to have a hyperechoic appearance. This finding was confirmed by ultrasonography (USG) performed at our center where the hyperechogenic appearance extended throughout the entire colon to the sigmoid level. During the ongoing examination, the same hyperechogenic appearance was found in the pelvicalyceal and peripyramidal regions of the lower regions of both kidneys (Figure 1, Video 1). The entire colonic segment had a hyperechogenic appearance and there was no dilatation. The anal sphincter had a normal appearance. Existing findings were thought to be related to cystinuria. No invasive procedure was performed on the patient. The family was also informed about the prognosis of the disease.

There were no additional problems during follow-ups and spontaneous labor started at 39 gestational weeks. She was later taken to cesarean section (C/S) with the indication of arrested labor. A baby boy with a birth weight of 3940 grams was delivered via C/S with APGAR scores 7 and 9 at the 5th and 10th minutes, respectively. Newborn assessment revealed nothing abnormal. Spontaneous stool and urine output were detected. On the abdominal USG examination, crystalloid structures were observed in both kidneys. Cystine level in 24-hour urine and urinary cystine/creatinine ratio were requested. This showed a cystine output of 60.96 mg/day (normal range: 0-13 mg/day) and a urinary concentration of 1180.30 mg/g creatinine (normal range: 50-163 mg/g creatinine). Amoxicillin suspension (Largopen, Bilim, Turkey) was started. At the time of writing the baby is six months old and has only had one urinary tract infection. Due to persistent pericalyceal echogenic foci, prophylactic treatment continues.

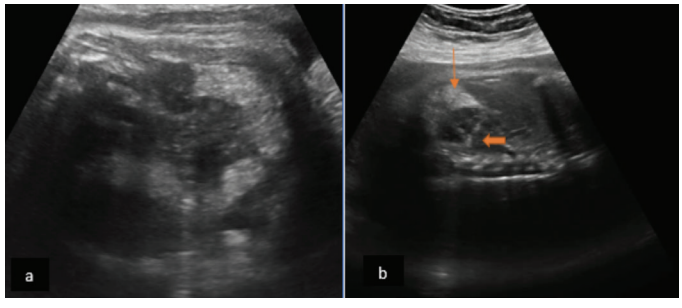

Figure 1. a) Fetal hyperechogenic colon. b) Fetal pericalyceal hyperechogenicity (thin arrow: colon, thick arrow: renal pelvis

In the postnatal period, a heterozygous mutation in the *SLC7A9* gene was detected in the genetic analysis of our patient.

Written informed consent was obtained from the patient.

Discussion

The prevalence of cystinuria in the European population is around 1 in 7000 (6). Cystine stones account for about 1% to 2% of all kidney stones but represent variably 6% to 8% of all pediatric calculi. Eighty percent of cystinuria patients will have their first stone during their first two decades of life. Compared to calcium stone formers, cystine nephrolithiasis patients will be likely to make larger stones, need more urological procedures, make stones more often, and start at an earlier age. They also face a greater risk of subsequent kidney damage and chronic renal failure compared to calcium nephrolithiasis patients. Cystinuria patients also report relatively poor health-related quality of life scores as a result of multiple recurrent stone episodes and related surgical procedures.

The clinical spectrum of the disease depends on the type of mutation and is very variable. It causes infections and stones in the kidneys and impairs kidney function. In patients with cystinuria, renal function is monitored regularly and the urine should be alkalized to prevent the progression of the disease. The aim of follow-up and treatment is to prevent renal failure due to disease progression (7).

It was previously reported that fetal hyperechogenic colon should raise suspicion of cystinuria. However, as far as we know, there is no published evidence that the stones seen in people with cystinuria can also form antenatally and that these structures can also be seen as hyperechogenic pelvicalyceal anomalies in the kidneys of affected fetuses. We suggest that a high degree of cystinuria, when the excess cystine is not absorbed and the level of which increases in the renal pelvis, will lead to a hyperechogenic appearance of the fetal renal pelvis that can be detected by USG in the prenatal period. The present case became symptomatic within the first week after birth, and renal hyperechogenic structures were detected on USG examination. We propose that monitoring renal hyperechogenic pelvicalyceal structures together with fetal hyperechogenic colon will increase the accuracy of cystinuria diagnosis in the prenatal period.

Video 1.

https://www.doi.org/10.4274/jtgga.galenos.2022.2021-11-5.video1

Informed Consent: *Written informed consent was obtained for publication of this report.*

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