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BRIEF COMMUNICATION

Echogenic Kidneys as an Antenatal Clue to the Metabolic Etiology: A Case Report

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Abstract Antenatally diagnosed echogenic kidneys have several underlying etiologies such as aneuploidies, monogenic isolated or syndromic polycystic kidney disease, infections and rarely with inborn error of metabolism. Even a careful evaluation for additional abnormalities may not be able to provide a specific diagnosis. However with next generation sequencing, the diagnostic odyssey can be ended successfully. We report one such case of carnitine palmitoyltransferase II deficiency (CPT2) deficiency that manifested as isolated echogenic kidneys with early neonatal demise where successful early prenatal diagnosis was possible in the subsequent pregnancy.

Keywords Echogenic kidneys · Carnitine palmitoyltransferase II deficiency · Next generation sequencing

Introduction

Urogenital anomalies are commonly detected on the routine ultrasound and constitute 15–20% of all congenital anomalies [1]. Apart from the location and number, renal echogenicity and corticomedullary differentiation plays a major role in exact characterization of kidney involvement. When renal echogenicity is higher as compared to liver or spleen, it is defined as renal hyper echogenicity [2]. The presence of echogenic kidneys poses a diagnostic challenge both in terms of diagnosis and prognostication. After ruling out common causes of echogenic kidneys like aneuploidies, CMV infections, polycystic kidney disease, possibility of rare syndromes and metabolic abnormalities must be looked in, depending on presence of other associated malformations and history of recurrences [3]. Here, we report a family with two early neonatal deaths with antenatal history of bilateral echogenic kidneys diagnosed with carnitine palmitoyltransferase II deficiency (CPTII).

Case Report

A non-consanguineous couple visited for preconception counseling in view of previous two early neonatal deaths. In the first spontaneously conceived pregnancy, detailed anatomy scan at 20 weeks revealed echogenic kidneys and normal amniotic fluid. She delivered a male baby at 38 weeks that cried immediately after birth. Baby (Fig. 1II-1) was started on breast feeds but succumbed on day 2 and the cause could not be ascertained. During second pregnancy, a detailed ultrasound at 19 weeks gestation showed presence of bilateral hyperechoic enlarged kidneys with decreased corticomedullary differentiation. No other gross congenital anomaly was detected. As fetal karyotype was normal couple opted for continuation of pregnancy. Follow up scan at 32 weeks showed persistent echogenic kidneys with normal amniotic fluid. A full term male baby (Fig. 1II-2) was delivered at 39 weeks without any perinatal asphyxia. Postnatal routine ultrasound revealed simple cysts in both the kidneys. Child suddenly deteriorated at 30 h of life and had cyanosis, bradycardia followed by intubation. Investigations revealed persistent hyperkalemia, metabolic acidosis (arterial blood gas analysis- pH-7.20, sodium—138 meq/l, potassium—7.0 meq/l, bicarbonate—14.0) and hypoglycemia (random blood

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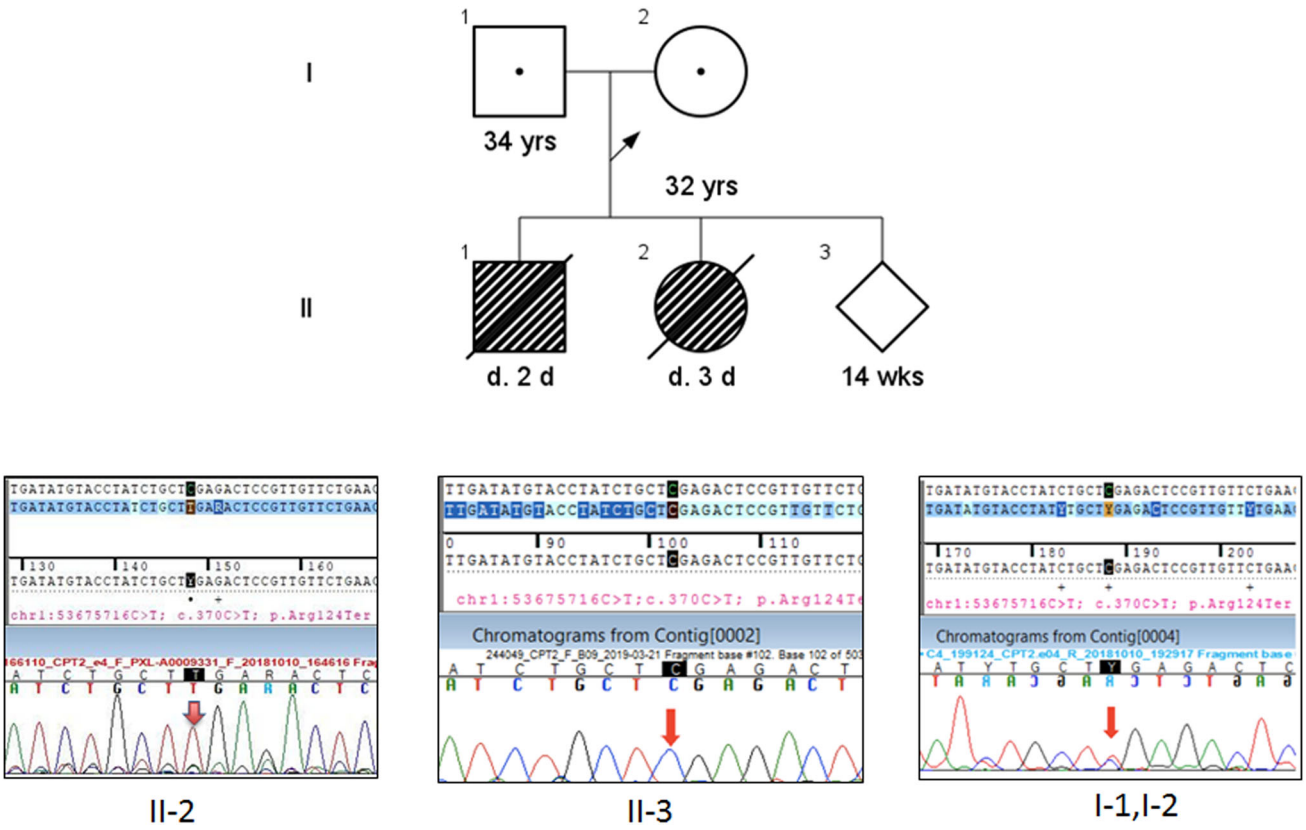

Fig. 1 Pedigree shows a homozygous pathogenc variant c.370C > T (p.Arg124Ter) in *CPT2* in II-2, homozygous wild type variant c.370C (p.Arg124) in II-3 at 12 weeks gestation and asymptomatic heterozygous variation c.370C > T (p.Arg124Ter) in parents (I-1, I-2) (The variant is indicated by red arrow)

sugar—30 mg/dl) for which corrective measures were started. Baby had acute renal failure (blood urea—111 mg/dl, serum creatinine—7.0 mg/dl) in the course of time and peritoneal dialysis was performed. Baby also developed cardiogenic shock and had poor myocardial contractibility on echocardiography that signified presence of cardiomyopathy. Inspite of maximum ventilator support and inotropes, the baby had sudden cardiac arrest at 60 h of life and could not be revived. Autopsy revealed multiple nodules in both kidneys with two simple cysts in right kidney and loss of cortex and medulla differentiation. Blood tandem mass spectrometry (TMS) and urine gas chromatography and mass spectrometry (GCMS) was performed on day 2. TMS showed slightly high levels of carnitines including C16 -12.70 μ/mol (range—0.80–6.00), C16:1–1.997μ/mol (< 0.18), ratio (C16 + C18:1)/C2-1.97 (< 0.5) and free carnitine levels of 13.50μ/mol. GCMS did not reveal any abnormality. Targeted exome sequencing was performed that involves massive parallel sequencing of exons of approximately 6000 genes.

Sequencing analysis revealed previously reported homozygous pathogenic stop gain variant (c.370C > T) (p.Arg124Ter) in carnitine palmitoyltransferase II (*CPT2*) gene. This sequence change creates a premature translational stop signal (p. Arg124*) in the *CPT2* which results in an absent or disrupted protein product and thus causing the severe phenotype. Segregation analysis confirmed both parents to be heterozygous for this variant (Fig. 1). The patient is currently 14 weeks pregnant and prenatal testing by chorionic villus sampling confirmed the fetus to be unaffected.

Discussion

Prenatal manifestations of Inborn error of metabolism (IEM) includes hydrops fetalis, structural brain anomalies such as gyration anomalies, polymicrogyria, cobblestone lissencephaly, hyperechoic kidneys, intrauterine growth retardation (IUGR), stippling and dysostosis [4]. Hyperechoic kidneys may represent a large group of disorders including autosomal recessive and dominant polycystic kidney disease (AR/ADPKD), aneuploidies, other rare syndromes like Beckwith syndrome, Joubert syndrome and several metabolic disorders including peroxismal disorders, carnitine palmitoyltransferase II deficiency (CPT2) and other disorders as listed in Table 1 [5]. The mechanism of enlarged echogenic kidneys in CPT2 deficiency has been

Table 1 Shows the various rare syndromes associated with hyperechoic kidney detected on antenatal ultrasound [8, 11]

Category	Disorders
Non metabolic	1. Beckwith Weidemann syndrome
	2. Meckel Gruber syndrome
	3. Short rib- polydactyly syndromes
	4. Bardet Biedl syndrome
	5. Cilliopathy
	6. Jeune asphyxiating thoracic dysplasia
Metabolic	1. Smith Lemli Opitz syndrome
	2. Peroxisomal disorders
	3. Carnitine palmitoyltransferase II deficiency
	4. Multiple acyl –CoA dehydrogenase deficiency
	5. Congenital disorder of glycosylation

postulated due to Warburg effect (aerobic glycolysis), which has been initially associated with tumorigenesis and recently with PCKD [6, 7]. In CPT2 deficiency, due to incomplete oxidation of fatty acids, there is less production of acetyl CoA, deviating the path to enhanced glycolysis and lactic acidosis. There is generation of multiple carbon molecules during this metabolic switch which stimulate protein and nucleic acid synthesis which indirectly enhance the cell proliferation [8]. In our patient, presence of hyper echoic kidneys in recurrent pregnancies with history of sudden neonatal deaths provided a clue to suspect a lethal neonatal form of IEM. In this case, clinical exome confirmed the diagnosis of lethal neonatal form of CPT2 deficiency. This presents as hypoglycemia, liver failure, respiratory insufficiency, cardiomyopathy, seizures and ultimately death [9]. Our cases had metabolic acidosis with renal failure, cardiomyopathy and respiratory failure and expired with in 72 h of life. CPT2 deficiency has been associated with multiple prenatal presentations including CNS malformations like hydrocephalous, dandy walker malformation, cerebral dysgenesis, corpus callosum agenesis, cardiomegaly, renal cystic dysplasias, which can be easily detected on ultrasound [10]. Our cases had only isolated echogenic kidneys without any CNS malformations on antenatal ultrasound.

This case illustrates that echogenic kidneys could be one of the antenatal clue towards metabolic etiology especially in the presence of consanguinity, a positive family history, and early neonatal deaths in the absence of any other associated congenital malformations on antenatal ultrasound. Molecular diagnosis remains the gold standard as acyl carnitine profile on amniotic fluid for diagnosis of CPT2 deficiency could be inconclusive [10].

Exome sequencing of the index case remains a most economical way of ending the diagnostic odyssey and assists in appropriate genetic counseling and early prenatal diagnosis in subsequent pregnancies.

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Compliance with Ethical Standards

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

Informed Consent Informed consent was obtained from all individual participants included in the study.

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