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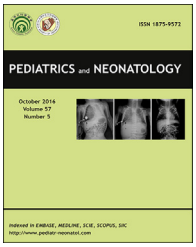

CASE REPORT

Fetal and Postnatal Magnetic Resonance Imaging of Unilateral Cystic Renal Dysplasia in a Neonate with Tuberous Sclerosis

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Tuberous sclerosis (TS) is an autosomal dominant condition associated with mutations in the TSC1 and/or TSC2 genes. Clinical manifestations are multisystemic, and they often include lesions in the brain, skin, heart, kidneys, and bones. TSC2 gene mutations can be seen concomitantly with autosomal dominant polycystic kidney disease gene mutations. We present a case of a fetus with prenatal diagnosis of TS that had unique asymmetrical distribution of renal cystic disease. We describe the extensive work up with both fetal and neonatal magnetic resonance imaging with correlating images of the unilateral polycystic renal disease in addition to typical TS brain findings.

1. Introduction

Tuberous sclerosis (TS) is a multisystemic disease that manifests with the growth of benign hamartomas in various organ systems, including the central nervous system, kidneys, and skin. TS has an incidence rate of roughly 1 in 6000 newborns and affects over 1.5 million people globally. TS is an autosomal dominant disorder caused by the TSC1 and TSC2 genes, which are located on chromosomes 9 and 16, respectively. TS development generally requires a combination of events, the first of which is a germline mutation that results in a loss of heterozygosity for an allele of either gene. The subsequent events necessary for TS manifestation are somatic mutations that cause the loss of the other TS allele. Patients with TS often manifest brain lesions

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(cortical/subcortical tubers, subependymal nodules, and subependymal giant cell tumors), angiomyolipomas, renal cysts, and skeletal lesions.[1]

The diagnosis of TS requires a combination of either two major criteria, or one major and two minor criteria. TS may also be diagnosed based on the presence of TS-associated lesions in two different organs, or two differing types of lesions within the same organ. Probable TS is diagnosed by one major and one minor feature, and TS may be suspected in the presence of either one major or two minor features. The most common major features are cortical tubers, facial angiofibromas, nontraumatic ungual or periungual fibromas, hypomelanotic macules (>3), shagreen patches, subependymal nodules, subependymal giant cell tumors, cardiac rhadomyoma (≥1), lymphangioleiomyomatosis, and renal angiomyolipomas. The minor features include pits in dental enamel, hamartomatous renal polyps, skeletal cysts, white matter migration tracts, gingival fibromas, nonrenal hamartoma, renal achromic patches, skin lesions, multiple renal cysts, and infantile spasms.[2]

2. Case report

A 28-year-old pregnant woman at 39 weeks of gestation was referred for fetal magnetic resonance imaging (MRI) to evaluate intracranial abnormalities that might support the prenatal diagnosis of TS. The fetus had just completed routine 3rd trimester sonographic evaluation where several fetal intracardiac masses with the sonographic appearance of rhabdomyomas were detected incidentally. Focused imaging of the fetal brain demonstrated subependymal nodules and cortical/subcortical signal abnormalities consistent with tubers (Figure 1). These findings confirmed the diagnosis of TS. On scout images for the fetal MRI, an abnormal T2 hyperintensity was seen within the fetal abdomen. After dedicated imaging of the fetal brain, focused fetal body MRI images were obtained. It was noted that the right kidney was abnormally enlarged and had a lobulated mass-like appearance (Figure 2) with moderate T2/Half Fourier-Acquired Single Shot Turbo Spin Echo (HASTE) hyperintensity. No T1 hyperintensity was seen within the right kidney. The left kidney was normal in appearance. Given the unilaterality and the moderate T2 isointensity, a differential diagnosis for the appearance of the right kidney was given. Both solid and cystic masses such as mesoblastic nephroma and lipid poor angiomyolipoma were included. The couple denied any family history consistent with TS and the patient was counseled by both maternal fetal medicine and genetics specialists regarding these findings.

Following uncomplicated spontaneous vaginal delivery, postnatal MRI of the brain confirmed the prenatal findings of subependymal nodules and cortical/subcortical tubers (Figure 1). Postnatal sonography of the kidneys demonstrated an enlarged right kidney with a polycystic appearance and a left kidney that appeared to be normal (Figure 2). The neonate was discharged home in good medical condition and follow-up was scheduled in a specialized TS clinic.

A follow-up ultrasound was performed at age 2 months, and there was an overall decrease in the size of the multiple cysts; however, there was a persistent unilateral polycystic appearance (Figure 3). MRI of the kidneys demonstrated a unilateral segmentally distributed polycystic appearance to the right kidney interspersed with more normally appearing renal parenchyma with a preserved corticomedullary appearance in focal areas. The right

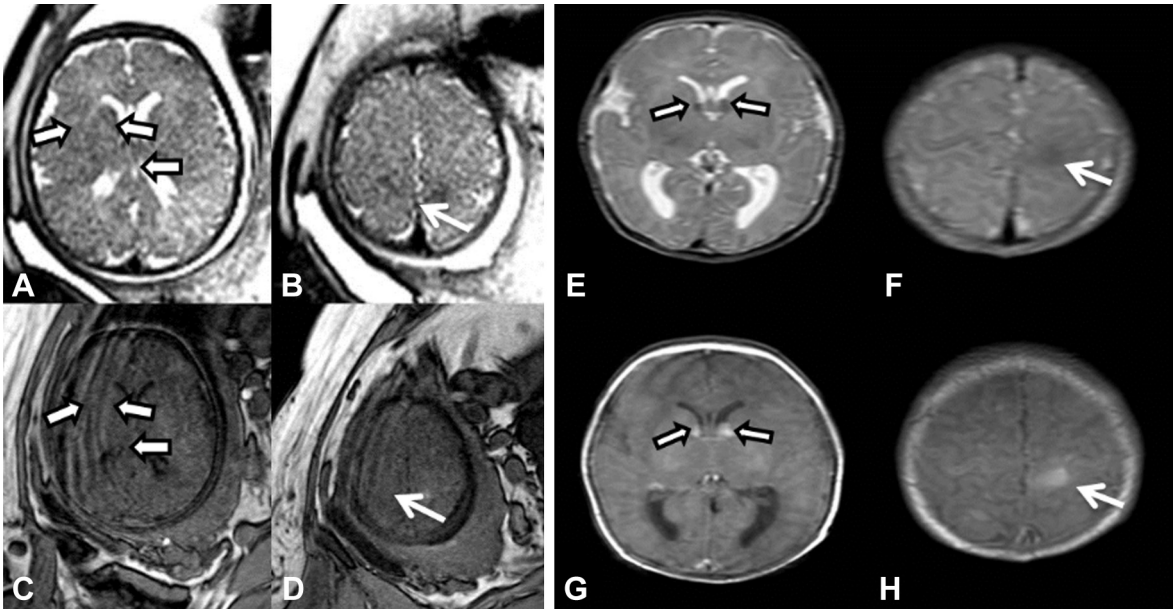

Figure 1 (A,B) Axial Half Fourier-Acquired Single Shot Turbo Spin Echo (HASTE) and (C,D) Axial T1 images from a fetal magnetic resonance scan demonstrating T2 hypointense and T1 hyperintense subependymal nodules (white arrow with black outline) and cortical/subcortical tubers (white arrows). (E,F) Axial T2 and (G,H) Axial T1 images from the postnatal magnetic resonance imaging demonstrating T2 hypointense and T1 hyperintense subependymal nodules (white arrow with black outline) and cortical/subcortical tubers (white arrows).

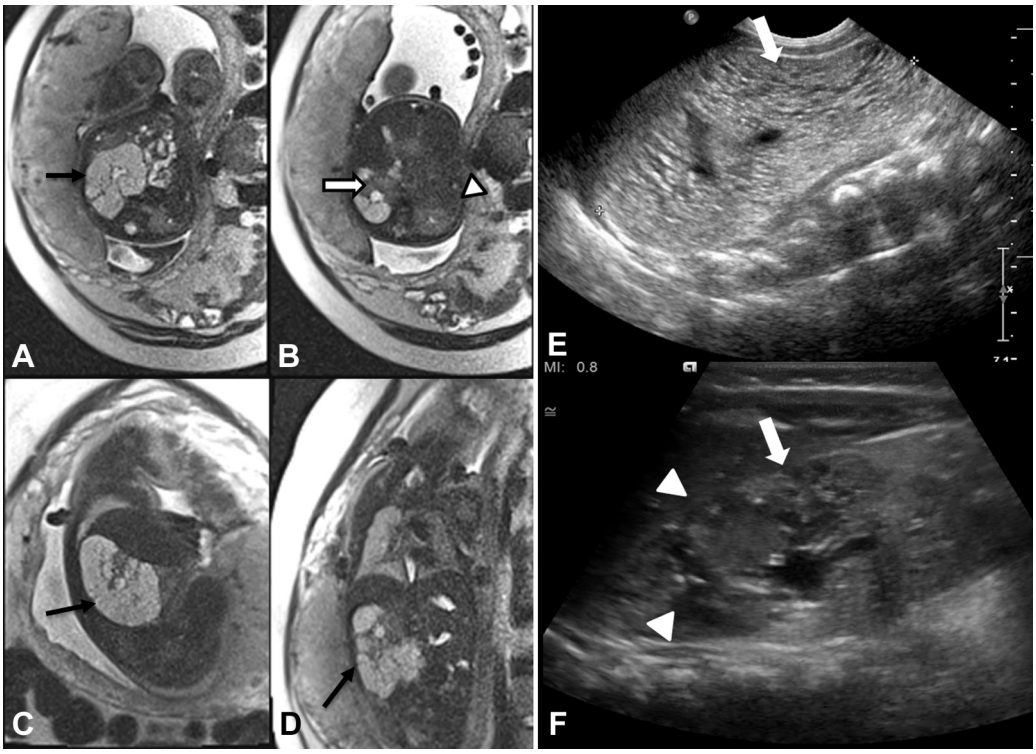

Figure 2 (A,B) Axial, (C) sagittal, and (D) coronal Half Fourier-Acquired Single Shot Turbo Spin Echo (HASTE) images through the fetal body demonstrating a large hyperintense lobulated appearance of the fight kidney (black arrows) with areas of normal-appearing renal parenchyma (white arrow with black outline). The left kidney has a normal appearance. Postnatal sonography of the right kidney (E) as a newborn and (F) at age 2 months. The kidney is enlarged and echogenic with focal areas of small cyst formation (arrows) and areas of relative sparing (white arrowhead) seen.

kidney demonstrated normal enhancement and excretion of intravenous contrast. The left kidney appeared normal with a single tiny cyst being noted (Figure 3).

The clinical course of the neonate has been uncomplicated, with no evidence of seizure activity, electroencephalogram abnormality, or laboratory evidence of renal dysfunction up to this point. The renal function of this child is normal as evidenced by blood urea nitrogen and creatinine of 8 mg/dL and 0.2 mg/dL, respectively, at age 14 months, and 12 mg/dL and 0.3 mg/dL, respectively, at age 30 months. Her electrolytes are normal. There has been no indication for additional imaging or renal function tests. To date, the parents have not undergone genetic testing for themselves or for their child.

3. Discussion

This is a unique case of TS with unilateral renal polycystic disease presenting *in utero*. The presence of renal cysts in TS may be due to the proximity of the autosomal dominant polycystic kidney disease (ADPKD) gene, PKD1, to the TSC gene located on chromosome 16. Because these genes are adjacent, a mutation in the TSC gene may also have effects on the ADPKD gene. ADPKD typically presents as bilateral development of cysts in the kidneys. It ultimately leads to end-stage renal failure in the majority of patients. Cyst development is not limited exclusively to the kidneys; it may also be seen in other organs such as the liver, pancreas, and spleen.[3]

There are two key genes that are postulated to be involved in ADPKD. The PKD1 gene encodes for polycystin-1, which is an integral membrane protein; *in vitro* studies have shown that this glycoprotein localizes to lateral cell junctions and is responsible for mediation of intercellular adhesion. The PKD2 gene, which is located on chromosome 4, encodes polycystin-2. It has also been shown that alterations in TSC2 can cause the loss of function of polycystin-1. The presence of extensive cystic disease suggests that the patient also has polycystic kidney disease in addition to tuberous sclerosis. These findings indicate that she probably has the dual manifestation known as TSC2 and PKD1 contiguous gene syndrome.[4] Renal cystic disease associated with TS typically is present bilaterally, and unilateral manifestations are rare.[5,6] In the few cases that are described in the literature, pathology specimens have demonstrated glomerulocystic kidney disease and the most recent case suggested mammalian target of rapamycin-positive epithelial cells within these cysts. Interestingly, mammalian target of rapamycin inhibitors have been used both in the treatment of subependymal giant cell astrocytomas associated with TS as well as in clinical trials for ADPKD.[7,8]

In our case, fetal MRI initially demonstrated typical brain findings of TS and the enlarged and cystic appearance of the right kidney. Postnatal ultrasound and MRI confirmed brain abnormalities and demonstrated the unilateral renal polycystic appearance with areas of interspersed normally appearing renal parenchyma. Normal enhancement and excretion suggest significant function of the affected

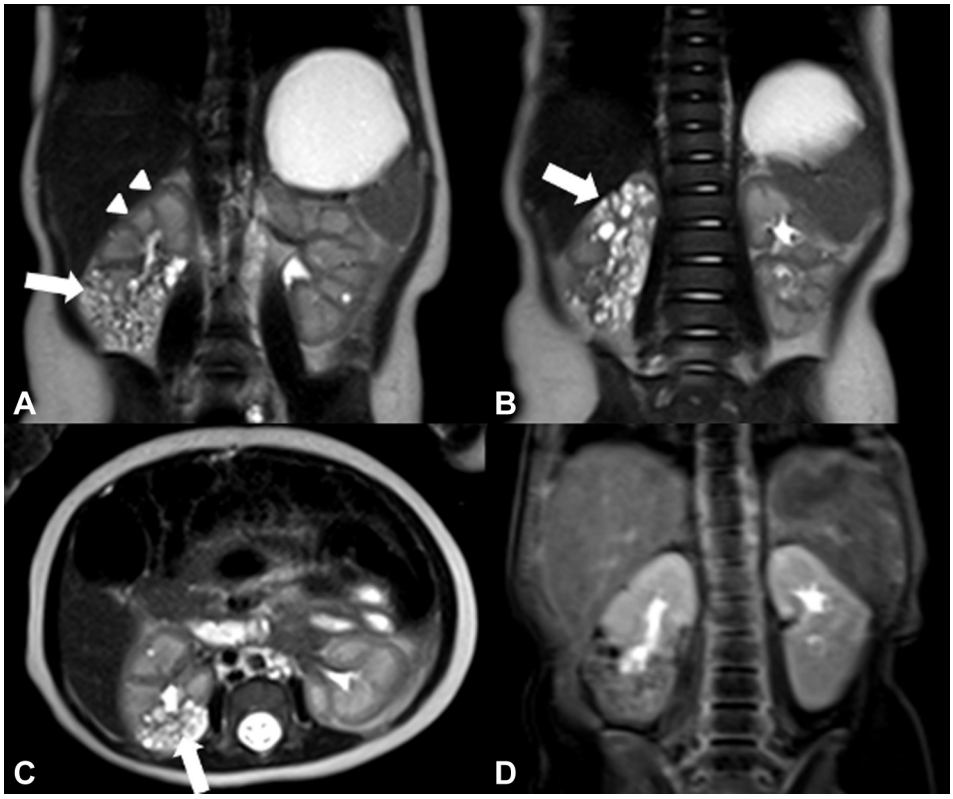

Figure 3 (A,B) Coronal T2 and (C) Axial T2 images through the kidneys demonstrate small cysts replacing right renal parenchyma (arrows), with focal areas of sparing (arrowhead). (D) Coronal T1 postcontrast image demonstrating parenchymal renal enhancement without a solid right renal mass.

kidney. Although the only other report of unilateral renal cystic disease in an infant was a pathology description status post nephrectomy,[5] it was determined that given the significant function of this kidney, a nephrectomy was unnecessary at this time. The patient will be closely followed for renal and neurologic function. As the patient is currently asymptomatic, she is not receiving any current medication.

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