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Dilemma of Fetal Autosomal Dominant Polycystic Kidney Disease, a Disease Rare to Present in Fetal Life!

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Authors' contributions

This work was carried out in collaboration between all authors. Author Namrata wrote the draft of the manuscript along with the literature search. Author MP provided the case and figures and supervised the work. Authors NS and SY contributed to the correction of the draft and further editing. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Prenatal presentation of fetal ADPKD is rare, however the disease is seen to present in fetal life also. We realize that ADPKD has varied presentations. It can present as isolated enlarged echogenic kidneys with or without any cystic change in fetal life or any decline in renal function. Their presence in fetal life makes a difficult situation to explain the parents the uncertain risk of progression in utero, immediate postnatal or in later years of life. We report two cases each with different presentation and different outcome of similar disease in fetus. It is yet important to diagnose maternal ADPKD in females presenting with early onset hypertension so as to reach at an early diagnosis of fetal ADPKD and similarly screen the parents if the disease presents for the first time in fetus.

Keywords: Fetal; Autosomal dominant polycystic kidney disease; prenatal.

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1. INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease is the most common hereditary renal cystic disease. Apart from kidney, cysts can also be seen in pancreas, spleen and brain. Kidneys are enlarged, echogenic and replaced by cysts. Importantly, renal enlargement can occur significantly before the renal functions began to decline.

Ultrasonography shows symmetrically enlarged echogenic kidneys, bladder is usually seen and liquor volume may not be reduced. Corticomedullary junction (CMD) may appear attenuated or indistinct. Cyst may or may not be seen within enlarged kidneys. Rarely the condition could be unilateral. ADPKD in initial stages might masquerade as normal appearing kidneys and a second trimester anomaly scan might look normal. It is only the high index of suspicion with which the condition is diagnosed in follow up scans. As a golden rule, it is a must to scan the parents for presence of renal cysts. Diagnosis in parents is usually made if renal sonography of either parent shows at least two renal cysts (unilateral or bilateral) if age less than 30 yrs and two cysts in each kidney if parental age is more than 30 years. Associated anomalies include mitral valve prolapsed, skeletal abnormalities, pyloric stenosis and intracranial aneurysm. All these might be beneficial to screen once diagnosis of ADPKD is ascertained.

Once ADPKD becomes the provisional diagnosis the exact prognosis is not very clear. If there is strong family history and a previously affected child, the best indicator of outcome is fetched from previously affected siblings. The situation requires a thorough counselling because it is upon the parents to make a decision to continue pregnancy after being told all the possible outcomes. Since the condition is Autosomal dominant, the recurrence risk is 50%. Ninety percent cases are linked to PKD1 gene on short arm of chromosome 16 while 5% are linked to PKD2 gene on chromosome 4. Prenatal diagnosis can be further confirmed through chorionic villous sampling or amniocentesis.

Long back in 1986, ST Reeders et al. [1], used a highly polymorphic DNA probe genetically linked to the locus of Autosomal dominant polycystic kidney disease in linkage studies for prenatal diagnosis in a 9 week fetus at risk for the disease. The fetus was judged to have inherited the polycystic kidney disease mutation, and this was confirmed by microscopic examination of the fetal kidneys at necropsy.

Karyotype of fetus is indicated only when the diagnosis of ADPKD is dubious in presence of other associated anomalies. Most important differential becomes Autosomal Recessive Polycystic Kidney Disease. However there is indeed a clear point of difference in that there is a unique history of Autosomal recessive inheritance pattern and more importantly essentially reduced liquor volume. Other differentials could be Finnish type nephritic syndrome, Beckwith Weidemann syndrome, Perlman syndrome, Meckel gruber syndrome, Patau's syndrome, congenital CMV affection and renal vein thrombosis. These conditions do have some unique findings, however can present with "similar" fetal renal abnormalities, making a specific diagnosis very difficult, in particular if family history is negative.

In some families, severe fetal expression of ADPKD seems to cluster and so far, all DNA analyses performed in families with subjects presenting during the fetal or neonatal period have been consistent with linkage to the PKD1 locus.

2. CASES

We report two cases of fetal Autosomal polycystic kidney disease from Sanjay Gandhi Post Graduate Institute of Medical Sciences.

Case 1 – A 22 years old women, third gravida with previous one baby affected with anenecephaly and one missed abortion presented to the outpatient department at 15 weeks 3 days for antenatal check-up in view of her previous history of neural tube defect. In routine evaluation she was diagnosed as having chronic hypertension. In view of her early onset chronic hypertension, maternal renal sonography was done which was suggestive of Autosomal dominant kidney disease (Figs. 1a & 1b).

Obstetric Ultrasound at 15 weeks 4 days was normal. With high index of suspicion, patient was kept on regular follow up. At 18 weeks 5 days, fetus showed hyper echoic kidneys with renal size less than 95th centile for that gestational age. A repeat ultrasound at 21 weeks 4 days pregnancy (Fig. 2) showed bilateral hyper echoic kidneys with renal size increased to more than 95th centile with normal amniotic fluid. There were no cysts seen.

Follow up USG were done till 34 weeks which showed that the kidney increased in size with loss of corticomedullary differentiation and normal liquor. She had a preterm vaginal delivery at 35 weeks gestation of 2.3 kg female baby. Baby had bilateral enlarged kidneys. On follow up with pediatricians and till age of three, she is having normal renal function and is normotensive with some cystic changes in enlarged kidneys. A certain diagnosis was made by imaging of cysts larger than 0.5 cm diameter with postnatal ultrasound and 0.2 cm by postnatal MRI.

Case 2: A 28 years old women, primigravida was referred to us at 18 weeks 2 days with echogenic fetal kidneys. Both fetal kidneys were enlarged with poor corticomedullary differentiation with normal amniotic fluid. Follow up scans were done every 2 weeks. Keeping the possibility of ADPKD, parental renal sonography was done. Maternal USG was normal and paternal USG showed bilateral enlarged cystic kidney. He was asymptomatic with normal blood pressure. The couple were explained about the future risk and consequences of both the fetus and father as well. Fetal kidney disease gradually progressed and at 25 weeks 4 days (Fig. 3) both the kidneys were enlarged with size more than 95th centile, echogenic with attenuated corticomedullary differentiation (Fig. 3).

There was associated oligohydramnious, renal cysts were not seen. Bilateral kidneys increased in size till 36 weeks when the patient went into labour at 36 weeks 5 days. She had vaginal delivery giving birth to a female child weighing 2.5 kg with an uneventful neonatal period. On follow up, the child at 3 years of age had normal blood pressure, renal function and ultrasound showing kidney size to be at 95th centile without any cyst development till yet.

3. DISCUSSION

Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary kidney disease, with 1/1000 people carrying the gene. Although the age of clinical onset of this disorder is typically in the third to fifth decade of life, early manifestations during childhood or during the prenatal period have been reported [2,3]

ADPDK in fetal life brings with a huge challenge to the clinician and to the parents as well. If pregnancy is continued what would be the course of renal affection in the baby, the development of other disease components and finally the end stage renal disease, makes a lot of uncertainty.

Till date there are only small series or cases reported in literature and no large study to predict exact outcome of the fetus in antenatally diagnosed ADPKD. Of 83 such reported cases, 43% died before 1 year. Of the remaining patients 67% developed hypertension over next 5 yrs and 3% had end stage renal failure by age 3 [3].

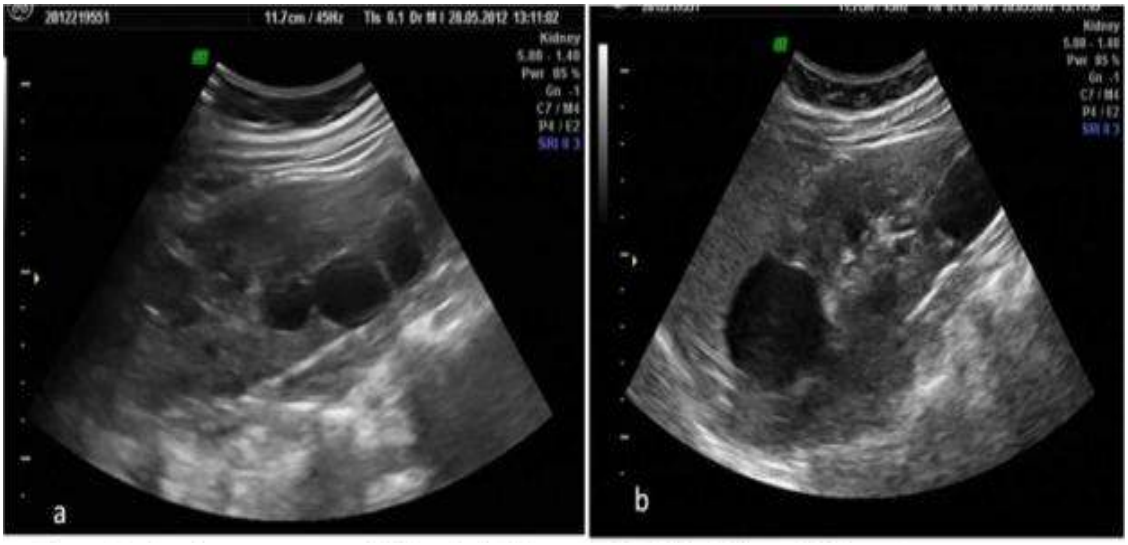

Fig. 1a. and 1b. Shows maternal Kideny left (a) and right (b) with multiple cysts

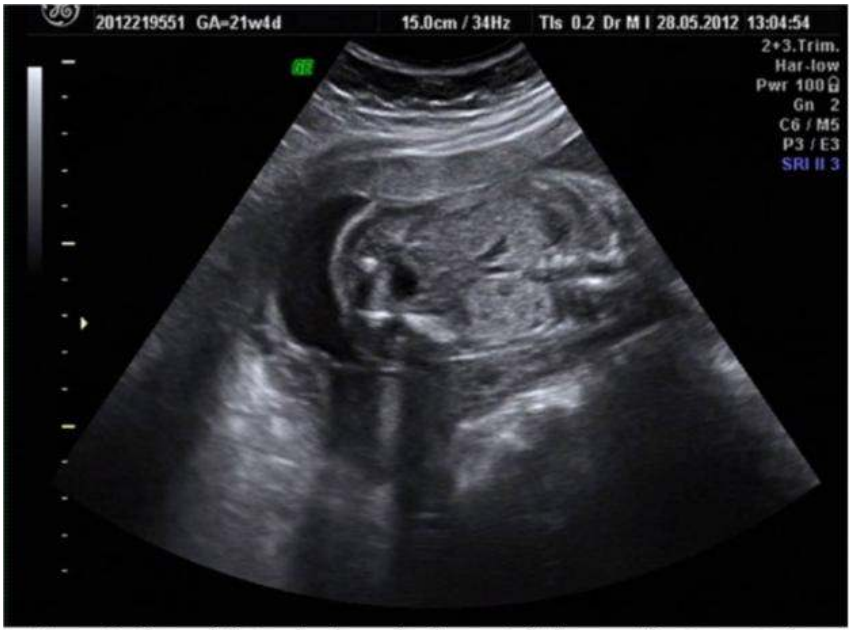

Fig. 2. Shows bilateral enlarged echogenic kidneys with attenuated corticomedullary differentiation

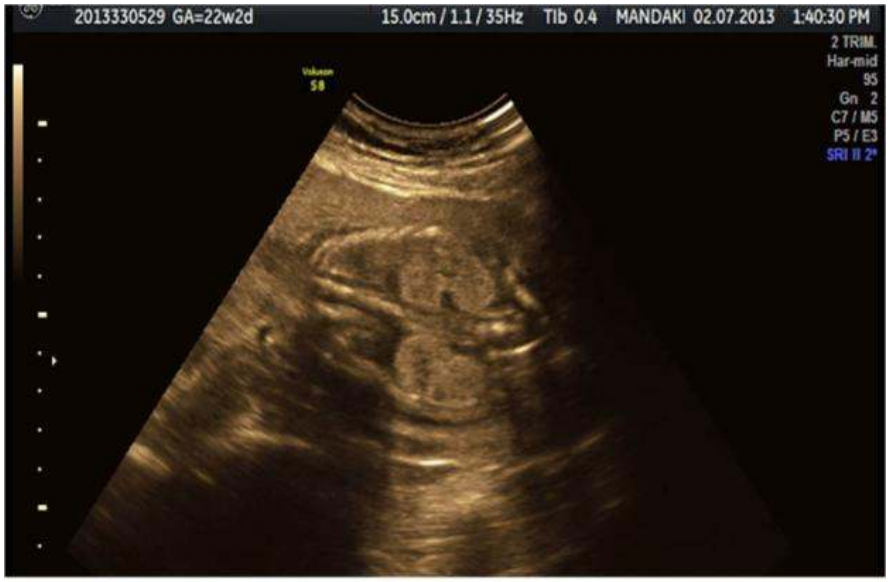

Fig. 3. Shows bilateral enlarged echogenic kidneys

Chapman et al. [4] demonstrated the impact of birth weight on the mean age of end-stage renal disease (ESRD) in a large Danish ADPKD cohort. Each kilogram of birth weight extended the mean age of ESRD onset by 1.7 years. Placental insufficiency, activation of the renin-angiotensin-aldosterone system, increased fetal vasopressin levels, compensatory increases in insulin like growth factor-I, and a reduction in total nephron number may all contribute to this observation. Collectively, these changes result in an accelerated pace of cyst formation and expansion, and an inability to maintain glomerular hyperfiltration during kidney expansion which results in a more rapid progression to ESRD. Therefore the intrauterine

environment may play a critical role in disease severity in ADPKD.

Being autosomal dominant, family history is extremely important. Even when there is no evidence of disease, detailed evaluation has led to diagnosis of affected often asymptomatic individual in the family. Jezova et al. [5] reported an unusual case of fetal polycystic kidney disease where oligohydramnios and enlarged hyperechogenic kidneys were found at 21 weeks. The pregnancy was terminated and fetal autopsy performed. The histopathological pattern of fetal kidneys was consistent with glomerulocystic disease and this raised suspicion of ADPKD. Initially, the family history seemed to be negative for ADPKD. The mother's diagnosis was established only after the abortion of the affected fetus. She had no symptoms of renal disease. Multigenerational involvement was revealed on the mother's side.

We report our experience with two cases; Case 1 was a known case of ADPKD where fetus showed affection of the disease. However in case 2, we see that fetal disease led to the diagnosis of disease in father. It is believed that ADPKD in fetal life are rarely seen to present, but it might not be so.

Brun M, et al. [6] did a multicenter study of prenatal sonographic patterns in autosomal dominant polycystic kidney disease amongst 25 had hyperechogenic renal cortex, 20 had hypoechogenic medulla resulting in increased cortico medullary differentiation (CMD). In six cases the medulla was hyperechogenic leading to absent or decreased CMD. One patient had normal cortical echogenicity and CMD. Renal cysts were present during the prenatal period in four patients (at 22 weeks in one case and after 30 weeks in three cases). In 12 patients, cysts appeared after birth (within the first 6 months of postnatal life in 10 cases and by the age of 1 year in two cases). Elevated blood pressure was observed in only two cases, moderate chronic renal failure in one case of moderately enlarged hyperechogenic kidneys with increased CMD.

Review of literature shows presence of renal cysts [7] but we identified cysts prenatally, in only one out of two cases. The cysts appeared in one case during the first year of postnatal life. Hence, cyst might not a unanimous finding just like oligohydamnious in prenatal life. The amniotic fluid volume was normal in two cases of ADPKD we saw, as observed in majority of cases by Brun et al. Thus, the presence of severe oligohydramnios might have little prognostic value. In a study by Mashiach et al over a period of 7 years, there were. three live-born infants with autosomal dominant polycystic kidney disease. Increased renal echogenicity with normal amniotic fluid volume was seen in all three fetuses without other anomalies. It is a difficult diagnostic dilemma. Although oligohydramnious is usually indicative of renal parenchymal disease with possible renal failure after birth or in early childhood, in some cases, it represents a normal variant. In contrary, our patient with oligohydramnious did well postnatally. Sonographic diagnosis was made in the late second trimester with a mean of 21 weeks in our population. Some cases of earlier sonographic diagnosis have been reported but mostly in cases with known family history and majority are reported in third trimester.

The disease was unknown to the family in one of the parents at the time of obstetric ultrasound. Also, prenatal onset of ADPKD has been reported to be more frequently associated with maternal transmission [8] we had two cases one with maternal and one with paternal transmission.

Associated malformations appear to be uncommon in ADPKD. In all two cases there were no associated malformations noticed.

The benefit of prenatal diagnosis of ADPKD even if the disease remains dormant for several decades is to keep more than normal vigilance at later ages when patient can land up in life threatening complications like ruptured intracranial aneurysm or renal failure.

In diseases like ADPKD it is vice versa, that is, recognition in either parents or fetus can be considered as an indicator to search for disease in the other. There are could be an example [9] where paternal disease led to diagnosis of ADPKD in a case of a six-month-old infant who was a full term baby delivered by uncomplicated vaginal delivery without forceps or fetal distress with an uneventful pre and postnatal period. Father had few symptoms and was diagnosed with APKD with creatinine clearance around 25%-30%. Sonography of the baby revealed normal sized and shaped kidneys, but with multiple bilateral cysts in the renal cortices, each measuring about 5 mm- 7 mm in diameter. Subsequent DNA analysis showed presence of PKD1 gene, present on chromosome 16. Renal

function of the baby was within normal range but because we know the presence of disease the baby needs to be regularly followed-up for the most common complications of APKD, including hypertension and renal insufficiency.

On the other hand there could be situation [10] where fetal sonographic findings suggestive of ADPKD can lead to additional evaluation and identification of likely maternal ADPKD as well.

It is important point to keep a high index of suspicion whenever we encounter enlarged echogenic kidneys in a prenatal ultrasound and also to keep possibility of ADPKD in early onset renal disease and hypertension in adults of reproductive age group.

4. CONCLUSION

Most common sonographic presentation in fetuses with ADPKD is moderately enlarged hyperechogenic kidneys with poor corticomedullary differentiation with or without cysts. Other prenatal sonographic characteristics, such as detection of cortical cysts and reduced liquor can be observed at a later gestational age.

The clue to diagnosis is the family history or affection of parents or sibling and search for any other malformations. If no malformation is found and parent found to have renal cysts, the main diagnosis remains autosomal dominant polycystic kidney disease.

ADPKD is a highly penetrant disease but due to its varied clinical expression and typical late onset of symptoms, reproductive aged people may not be aware of their carrier status. Recognition of fetal ADPKD can not only help to better ascertain fetal diagnosis and future consequences to parents but will also help to screen a dormant disease in parents who can then become more vigilant and can undergo regular screening or prophylaxis before onset of a major disease complication like renal failure or ruptured aneurysm.

Follow up study is required to predict whether the course of the disease is different in early onset fetal disease as compared to adult onset disease.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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