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RESEARCH ARTICLE

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE ABOUT A NEW CASE REPORT

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Abstract

We present the case of a 25-year-old woman gravida 2, para 01 who presented for childbirth at 40 weeks of gestation. Which Fetal Anatomy Ultrasound showed enlarged, hyperechoic fetal kidneys and a normal amniotic fluid index. Karyotyping was done on umbilical cord blood to look for mutations in the PKHD1 gene for the presumptive diagnosis of autosomal recessive polycystic kidney disease (ARPKD). In our patient, a previously reported pathogenic missense mutation in the PKHD1 gene, c.10444C>T, was found to be maternally inherited. A second previously unknown de novo mutation, c.5909-2delA, was discovered. This mutation is likely pathogenic because it affects the canonical splice site. Our case emphasizes PKHD1 allelic heterogeneity and the importance of prenatal genetic testing in a setting where many other genetic etiologies can phenocopy ARPKD.

Introduction:

ARPKD (autosomal recessive polycystic kidney disease) is one of the most common pediatric renal cystic diseases, with a 1/20,000 incidence. Mutations in the PKHD1 gene on chromosome 6p12 cause it. The clinical spectrum is highly variable, ranging from milder forms that appear later in life to severe perinatal manifestations. The management of newborns with severe pulmonary insufficiency is difficult, and the most common causes of death are sepsis or respiratory failure. We present a case of ARPKD diagnosed prenatally before labor in a poorly followed consanguineous marriage pregnancy.

Case presentation

We report the case of Mrs. H B , 25 years old , married , gravida 2 para 1 , currently pregnant with a first degree consanguineous marriage estimated at 40sa (pregnancy badly followed), and denied exposure to any teratogens. A three-generation pedigree did not reveal significant history of renal disease. Her obstetric history was significant for a previous pregnancy with loss of a fetus with an omphalocele at 18 weeks of gestational age and normal chromosomal microarray. admitted in our formation for childbirth, Clinical examination on admission found a stable conscious patient

Observation: HU=30cm, BCF +, vaginal touch showing central cervix effaced at 80% dilated to 3cm,intact water pocket

Obstetrical Ultrasound found normal fetal biometry with an estimated fetal weight at 3400g, normal amniotic fluid, with a suspicion of ARPKD since we found hyperechoic enlarged kidneys with loss of cortico-medullary differentiation **(FIGURE1)**

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The patient was counseled regarding the suspicion for ARPKD and given options for genetic testing of the blood cord

The labor took place in an eutocique way giving birth to a girl Apgar 10/10 then the newborn installed at H1 of life a severe DR SS at 6/10 which required a hospitalization in neonatology on the other hand the patient presented sexual ambiguity with low ears insertion **(FIGURE2)**. Genetic study made from umbilical cord blood and parents blood revealed a normal Karyotype 46, XX. Mutation analysis of the PKHD1 gene revealed a maternally inherited and previously reported c.10444C>T (p.Arg3482Cys) missense mutation and a novel, previously unreported de novo splice site mutation, c.5909-2delA.

The newborn required intubation for respiratory distress and continued to have persistent hypoxemia and hypercarbia despite aggressive mechanical ventilation. Chest X-rays done after birth revealed low lung volumes with bilateral pneumothorax. The family elected for palliative care and the newborn was extubated approximately three hours following delivery and died soon thereafter. An autopsywasoffered, which the familydeclined.

Figure 1:- Hyperechoic enlarged kidneys with loss of cortico-medullary differentiation.

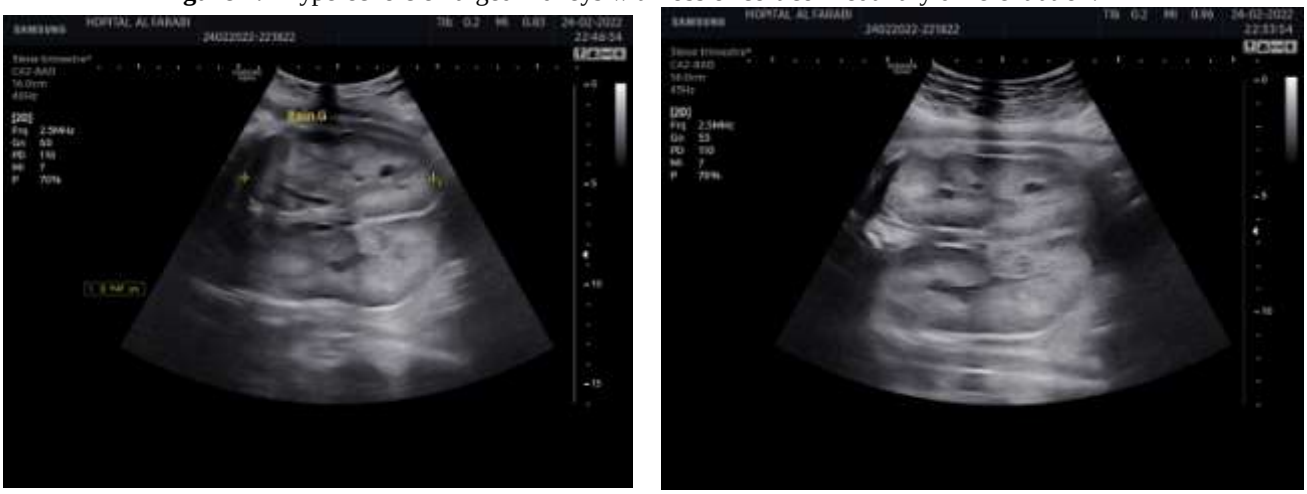

Figure 2:-Picture of fetal sexual ambiguity and low ear insertion.

Discussion:-

Mutations in the PKHD1 gene, which maps to chromosome 6p21.1-p12, cause ARPKD. With 66 coding exons [1,] PKHD1 is one of the largest genes in humans, encoding a 4074-amino acid protein called fibrocystin/polyductin (FC/PD). FC/PD can be found in the kidneys, adrenal glands, liver, and pancreas. FC/PD is a protein with a single transmembrane domain, a short intracellular carboxy terminus, and a large extracellular amino terminus [1]. FC/PD has been shown to be localized to the primary cilia with basal body concentrations [3, 4]. Mutations in FC/PD cause abnormal epithelial differentiation, which is followed by increased apoptosis and fluid secretion, resulting in clinically detectable cyst formation [2, 5].

Because of the high prevalence of private mutations, the clinical outcome cannot be predicted using molecular genetic data. The reported mutation detection rate for the entire clinical spectrum of ARPKD patients is around 80% [6, 7]. The remaining mutations are most likely in regulatory regions that are not covered by current sequencing methods.

In our case, PKHD1 gene mutation analysis revealed a maternally inherited c.10444C>T (p.Arg3482Cys) missense mutation in the PKHD1 gene, which has been reported several times in the literature and is always pathogenic.

A second previously unknown de novo c.5909-2delA splicing mutation was discovered and inherited paternally. The exome variant server, dbSNP135, and HGMD do not contain the c.5909-2delA variant. The exon 37 splice acceptor canonical site is disrupted by the c.5909-2delA mutation. In frogs and other vertebrates, the exon 37 splice acceptor site is conserved. The next predicted splice acceptor site is a 25-nucleotide downstream location that results in premature stop codon insertion. As a result, the mutation is likely to result in a truncated protein product. Carrying two truncating mutations is usually fatal, whereas carrying at least one missense mutation allows for survival due to residual functional fibrocystin protein [2].

In our case, one of the mutations is a previously reported missense mutation, while the other is predicted to be a novel splice mutation. Previously, a homozygous p.Arg3482Cys missense mutation was linked to a perinatal lethal phenotype in two consanguineous Israel-Arab families [3]. It's not surprising that missense p.Arg3482Cys and splicing c.5909-2delA mutations caused perinatal death.

On routine fetal anatomy ultrasound, the fetus in our case was suspected of having ARPKD. It is important to note, however, that other genetic etiologies can mimic ARPKD renal findings.

HNF1B and the diverse group of ciliopathies, such as nephronophthisis, Bardet Biedl, and Joubert syndrome, are among these disorders. Serial ultrasound assessment of the fetus is the preferred antenatal imaging modality for monitoring disease progression. MRI has also been used to improve renal anatomy phenotyping. In ARPKD patients, MRI will reveal enlarged kidneys with hyperintense T2-weighted signals [8]. Although MRI may be more sensitive than ultrasound in distinguishing cysts, normal parenchyma, and fibrosis, its higher cost limits its use in prenatal imaging.

Follow-up ultrasounds at 2-week intervals revealed progressively declining amniotic fluid in the current case, with oligohydramnios beginning at 29 weeks and anhydramnios by 35 weeks of gestation.

Thirty percent of newborns with ARPKD die during the neonatal period as a result of pulmonary hypoplasia. The use of a ventilator has been proposed as a prognostic marker for poor survival [7, 9]. After the baby is born, resuscitation is critical, as is a thorough physical examination to rule out other structural birth defects that could indicate etiologies other than ARPKD. At the time of delivery, our patient was in severe respiratory distress.

Following intubation, the newborn required high ventilator settings but experienced persistent hypoxemia and hypercarbia, as well as bilateral pneumothoraces, all of which were caused by underlying pulmonary hypoplasia. Survival after the neonatal period has a better outcome, with a 10-year survival rate of around 82 percent [10].

Given the poor prognosis and severity of ARPKD, couples who are known to be carriers of ARPKD mutations should consider prenatal testing during pregnancy and preimplantation genetic diagnosis (PGD) in any subsequent pregnancies. For known mutations, PGD using a single embryo genome amplification with multiple displacement

amplification (MDA) and haplotype analysis with novel short tandem repeat (STR) markers from the PKHD1 gene have previously been successful [11, 12].

ARPKD has a variable clinical spectrum, but patients in the same family usually have comparable phenotypes. In our case, the affected newborn was the family's first victim. With more cases of ARPKD being diagnosed prenatally, research for therapies to halt disease progression in the future is ongoing, but none are currently available.

Conclusion:-

Our case emphasizes the importance of routine fetal anatomic ultrasound for prenatal diagnosis of renal abnormalities, as well as genetic testing for ARPKD. Because other diseases can mimic ARPKD, genetic panels are likely to become the preferred method of genetic testing. Our findings show a detailed change in fetal biometry during the prenatal course of perinatal ARPKD caused by a novel splice mutation.

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