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Embryological and Genetical Interpretations of Bilateral Polycystic Kidney Disease in a Neonate - A Case Report

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ABSTRACT

Polycystic kidney disease is a rare developmental anomaly. It is inherited autosomal dominant or autosomal recessive. Autosomal recessive polycystic kidney disease (ARPKD), previously named infantile polycystic kidney disease. Clusters of cysts develop within the kidneys and fluid filled cysts displace normal renal tubules in this disease. This is characterized by cystic dilatation of the collecting ducts and progress to renal failure. We reported a case of Autosomal recessive polycystic kidney disease (ARPKD). Earlier antenatal ultrasonography had already detected the occurrence of polycystic kidney in fetus a day before delivery and it is confirmed after the parturition by fetal autopsy. The detailed study about the congenital anomalies of kidneys are significant for medical geneticists, embryologists, anatomists, pathologists, gynecologists, clinicians, urologists, transplant surgeons and radiologists.

Keywords: Autosomal recessive polycystic kidney disease (ARPKD), Autosomal dominant polycystic kidney disease (ADPKD), Congenital Anomalies, Autopsy.

INTRODUCTION

The gross macroscopic structure of kidney will be presenting outer cortex and an inner medulla. The outer cortex is a reddish-brown and is covered by a fibrous capsule. The renal medulla consists of the proximal tubules, loops of Henle, distal tubules, collecting ducts and vasa recta. The renal medulla consists of 8-18 pyramids. They are arranged radially striated, conical structures with base adjacent to the cortex. The apex projects into renal sinus. [1] Polycystic kidney disease (PKD) is inherited as an autosomal recessive (ARPKD) or autosomal dominant (ADPKD). Based on different types of inheritance cysts present in the kidneys, which are classified into adult polycystic kidney disease and adult-onset medullary cystic disease both are autosomal dominant. Polycystic kidney disease and familial juvenile nephronophthisis are autosomal recessive inheritance which is observed in childhood. No pattern of inheritance has been described in medullary sponge kidney, simple cysts and acquired renal cystic disease. [2]

Common cause for chronic renal failure is Polycystic kidney disease (PKD) which is characterized by fluid filled cysts in the kidney and other organs. In the autosomal adult polycystic kidney disease presenting with multiple expanding cysts, which are filled with a clear serous fluid or hemorrhagic fluid. The enlargement of the fluid filled cysts will be destroying the renal parenchyma. The cysts were formed from the renal tubules throughout the nephron. In the microscopic examination, functioning nephrons are seen between the cysts. The cysts have different epithelial lining. [3] Autosomal recessive polycystic kidney

disease occurs in neonates and children. The incidence of this disease occurs approximately one in 6,000 to one in 40,000 live births. [4,5] The prevalence increase is not related to race and gender. [6] Fetal death was observed within the first year of life in 30% of cases. The survived infants develop renal failure and liver disease which leads to portal hypertension. Autosomal recessive polycystic kidney is caused due to mutations on PKD1 gene. [7] Polycystic kidney disease is associated with liver fibrosis, protein expressed by PKD1 is fibrocystin/ polyductin which is present in the thick ascending limb of Henle's loop, collecting duct, pancreatic ducts and bile ducts in the liver. [8]

CASE REPORT

A 27-year-old primigravida without prenatal care was admitted with decreased fetal movements in the maternity ward of Prathima Institute of Medical Sciences Hospital, Karimnagar, India. She is G_1 A_0. Patient vital data found to be normal and significant oligohydramnios was noted. Fetal heart rate was 155 beats/min. There is no history of consanguinity amongst the parents. There is no family history of renal diseases on the maternal or paternal side. Ultrasonographic examination revealed that fetus is having the polycystic kidney. The patient delivered a male baby which is immediately dead after the birth. On examination abdomen distention was observed in the dead fetus. During the autopsy of the fetus a larger mass in the abdomen was observed, further fine dissection exposed the bilateral Polycystic kidneys. (Figures 1 and 2) Both the kidneys were lobulated and enlarged. The kidney sectioning showed subcortical cystic dilation of collecting ducts with radial pattern. Because of the cystic transformation in medulla, the cortico-medullary junction is not distinct. The cysts in the pancreas and liver were not reported. Scarring like fibrotic feature is observed in the liver tissue associated with pulmonary hypoplasia. The blood flow in the umbilical cord is not obstructed. No other anomalies were found. The spine, face and both upper and lower limbs were normal. This case is not having any previous family history of polycystic kidney disease. Based on the gross manifestations, the mode of inheritance of this disease may be autosomal recessive type or new mutation.

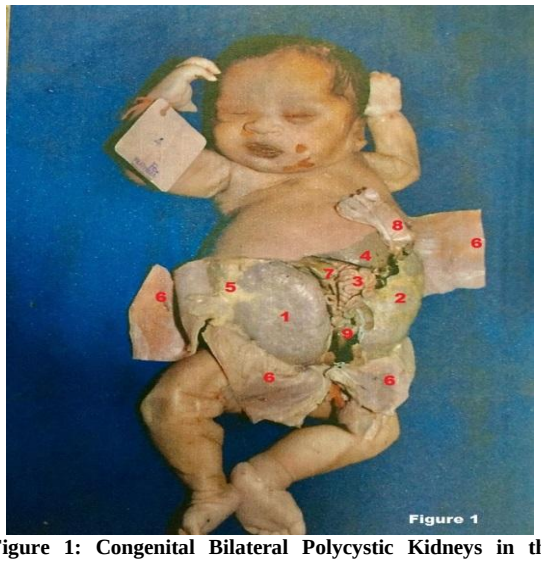

Figure 1: Congenital Bilateral Polycystic Kidneys in the newborn

1.Enlarged Polycystic kidney – Right Side 2.Enlarged polycystic kidney – Left Side 3.Coils of Small intestine 4.Left lobe of the liver –Exposed 5.Paranephric fat 6.Anterior abdominal wall with parietal peritoneum - Exposed inner surface 7.Caecum with vermiform appendix 8.Visceral Peritoneum 9.Descending colon

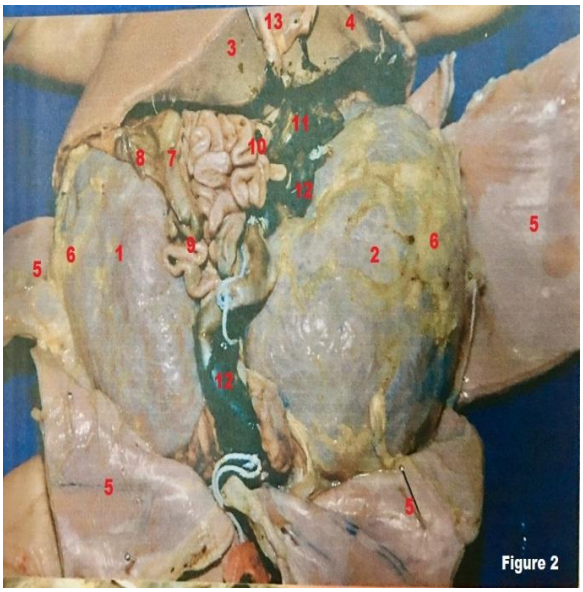

Figure 2: Congenital Bilateral Polycystic Kidneys in the newborn – Dissected

1.Polycystic kidney – Right Side, 2. Polycystic Kidney – Left Side, 3. Inferior surface of Liver (Right lobe) – Exposed, 4. Liver – Left lobe, 5.Anterior abdominal wall with parietal peritoneum - Exposed inner surface, 6.Paranephric fat, 7. Caecum, 8.Vermiform Appendix, 9. Coils of Ileum , 10. Coils of Jejunum, 11.Transverse colon, 12. Descending colon, 13.Falciform ligament.

DISCUSSION

In kidney, heterogeneous cysts are localized structures filled with fluid which may be hereditary, developmental or acquired. The similar pattern of cysts can be developed in ovaries, liver, spleen, brain etc. The congenital anomalies in kidney and urinary tract present in 20% to 30% of antenatal cases in developed countries. [9]

Embryological and genetical basis of the PKD

During organogenesis of the excretory system, the primitive kidneys (Pronephros, mesonephros, metanephros) appearing in between cervical and sacral regions of the developing embryo. [10, 11] They originates from the lateral part genito-urinary ridge, which belongs to the intermediate mesoderm. At the initial phase of the IVth week of the intra-uterine life the Pronephros starts to appear and it constitutes of nearly seven to ten cell groups in the cervical part. At the terminal phase of IVth week, the pronephros disintegrates. During regression of the pronephros in the fourth week, excretory tubules of the mesonephros appears, tubules elongates and form an Spiral shaped curve and obtain a clump of capillaries, which is known as the glomerulus. [11-13] Bowman's capsule is developed surrounding the glomerulus by the tubule itself. The mesonephros performs the function of kidney from the IVth to VIIIth weeks of intraembryonic life. At the stage of the Vth week the metanephros (sacral part of nephrogenic cord) starts to develop and function, it will become the chief kidney in adult life. The excretory units were formed in the similar pattern of the mesonephros. There will be differences in the formation of the ductal system. The ureteric bud develops as an out pocketing from the mesonephric duct close to the cloaca (hindgut) forms the collecting ducts. There is an epithelial interaction between the ureteric bud with mesenchyme of metanephric blastema. [11, 12, 14] The bud invaginates into the metanephric tissue and further dilation leads to the formation of the initial renal pelvis, the major calyces develops from further branching of the pelvis. [12, 15, 16] The calyces shows 2 buds during the invagination of metanephric blastema, further division of the buds by 12 or more generations forms the minor calyces. The renal pyramids develop from the collecting tubules of Vth generations which dilatates and merges over the minor calyces. [13, 15, 17] The elongation ureteric bud gives rise to the ureters, renal pelvises, major and minor calyces with nearly 3 million collecting tubules. [13, 16, 17] The epithelial tissue induction between the ureteric bud and the metanephric tissue is under the influence of reciprocal control system. [18] The metanephric blastema produces the gonadal derived neurotrophic factor (GDNF), which is needed for the binding of the Ret receptor over the ureteric bud that further divides, consolidates and differentiates as renal pelvis, major calyces, minor calyces and the ductal system. The breakdown in induction, defects in the formation of nephrons and collecting ducts leads to the PKD. The metanephric blastema expresses transcription factors that makes this tissue compatible and respond to the induction of ureteric bud. [18, 19]

Congenital Types of PKD

Autosomal Recessive Polycystic Kidney Disease (ARPKD):

In this condition cysts were seen in the collecting ducts. The cell adhesion molecules especially syndecan, E-catherin which are significant for the condensation of mesenchyme to epithelium, lack of these molecules or lack of response in cell adhesion leads to PKD of collecting ducts. [20]

The gene PKHD1, on short arm of chromosome 6p21 responsible for ARPKD. [20-23] The ARPKD presents as bilateral enlargement of kidneys with severe renal failure observed that histologically kidney showed simple cysts lined by a single layer of epithelial cells. [20] In the present gross anatomical study we confirmed the bilaterally enlarged PKD. Consanguinity will be the etiological factor main diagnostic criteria of patients with PKD. [20, 24] Parents

of a child with ARPKD should be informed that each child or new fetus would have a one in four (25%) chance of developing the disease (although the expression of the disease may be different from that in other siblings) and a one in two chance (50%) of being a carrier. [22] Perinatal, neonatal, infantile, and juvenile types have been identified based on the time of presentation. The first two are most common serious manifestations usually present at birth. [25] Children born with ARPKD may develop kidney failure before reaching adulthood. Severity of the condition varies. Severe cases can be detected after 24 weeks of gestation by antenatal ultrasound. The prognosis of these antenatally detected cases is more prone to death that occurs within first two months as a result of uremia or respiratory failure. The impairment in renal function leads to oligohydramnios, characterized along with pulmonary hypoplasia. Liver scarring is a common feature seen in all patients with ARPKD and worsens with advancement of age. [26] In the present study bilateral enlarged kidneys manifesting with scarring of liver tissue and pulmonary hypoplasia were recorded and this kind mostly exhibits the features of ARPKD.

Autosomal Dominant Polycystic Kidney Disease (ADPKD):

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder manifested by the growth of numerous cysts in the kidneys. Symptoms usually develop between the ages of 30 and 40. [27, 28] ADPKD will be progressive disease and symptoms will be worsening when the age advances. ADPKD is most often caused by changes in the *PKD1* and *PKD2* genes, and less often by changes in the *GANAB and* DNAJB*11* genes. [28, 29]

Both ARPKD and ADPKD are conditions presenting severe rates of morbidity and mortality. Recent advances in the understanding of the gross anatomical, embryological, genetic and molecular pathogenesis of both ARPKD and ADPKD have resulted in new, targeted therapies designed to disrupt cell signaling pathways responsible for the abnormal cell proliferation, dedifferentiation, apoptosis, and fluid secretion characteristic of the disease. Various surgical, gross anatomical, ultrasonic and histological studies were done and recorded by many authors as follows, Eswari et al. tubular and glomerular microcysts were recorded in initial 12 weeks of gestation and concluded the particular period in the formation of cysts is not known. [25] Adrian S.Woolf *et al*. have explained about the mechanism of obstruction in which normal glomeruli can become cystic after birth. The Bowman's capsule is dilated after collapse of glomerular tufts as a result of conditions such as glomerulosclerosis, mesangiolysis and hemolytic uremic syndrome. When cysts form in the kidney they are filled with fluid. Cysts can enlarge in the kidneys while replaces the normal structure, resulting in diminished kidney function that leads to renal failure. [30] Sathialakshmi V *et al.* during their study of cysts of multiple organs, they recorded bilateral polycystic kidney in a male cadaver. [31] Sujatha *et al*. cadaveric kidneys with cysts were observed in various age groups of both sexes. The cysts are predominant in male cadavers. The size and number of cysts was also variable and though the cause of death of the individual cadavers was not recorded in their study, the chance finding of cysts in adult kidneys indicate that an autosomal dominant disease manifests itself late in adult life and does not involve in the disturbance of other organs. Most probably the cysts were formed due to obstruction in the glomeruli and did not go as far as renal failure for manifestation clinically. [32] This kind of pattern indicates the ADPKD, which is different from our present study of neonatal kidneys. Shroff Gautam *et al.* studied the gestation of kidney development between 25-29 weeks by means of ultrasound. They found unilateral multi cystic dysplastic left kidney, right hypoplastic kidney with left lobulated kidney, right kidney agenesis & left kidney

enlarged with cystic mass, according to their opinion the failure of the ureteric bud to elongate and invaginating into the metanephric blastema results in multicystic kidney disease. In the present study the cysts formed in the intra-uterine life itself and tend to enlarge till the birth, changes were seen in the other adjacent organs such as hepatomegaly and pulmonary aplasia. [33] Vinnakota Sunitha *et al.* studied various stages of development from 10 weeks to 40 weeks in the still born fetus. They observed that lobulation is seen at 12th week. They observed juxta glomerular apparatus at 14 weeks of gestation and changes in the histological feature of tubules by 16 weeks and major development of kidney happens between 20-22 weeks. In 32 weeks of still born male fetus, bilateral polycystic kidneys with hepatic fibrosis and hypoplastic lung are reported. [34] This can be compared and similar to the present case report.

CONCLUSION

The congenital anomalies develop commonly in the urinary system. Most of the abnormalities are asymptomatic and diagnosed by prenatal ultrasound or during systematic evaluation for other congenital anomalies. In the present study, the polycystic kidneys were observed incidentally during routine antenatal ultrasonography and exposed during autopsy with respect to anatomical dissection. This knowledge about the congenital anomalies of kidneys is helpful for pediatricians, urologists, nephrologist, surgeons, radiologists, embryologists, anatomists, pathologists and gynecologists.

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