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Case report – Meckel Gruber Syndrome

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Abstract - *Meckel-Gruber syndrome is a rare and lethal autosomal recessive disorder characterized by occipital encephalocele, postaxial polydactyly and bilateral dysplastic cystic kidneys. It can be associated with many other conditions. Antenatal ultrasound examination can establish the correct diagnosis by identifying at least two of the major features described.*
In the following case report, we described a case of antenatally diagnosed Meckel – Gruber Syndrome in a woman at 18 weeks of gestation.
Keywords*: Meckel-Gruber, dysencephalia splanchnocystica, ciliopathies.*

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I. Introduction

Meckel-Gruber syndrome (MGS) is a rare, lethal autosomal recessive condition mapped to 6 different loci in different chromosomes 17q21–24 with a genetic heterogeneity. More than 200 cases have been reported. Meckel-Gruber syndrome is a condition that belongs to the ciliopathies, a category of diseases thought to be caused by dysfunction of cilia and flagella. Polycystic liver and kidney disease, Bardet-Biedl syndrome, Alstrom syndrome, and Joubert syndrome also belong to the same group.

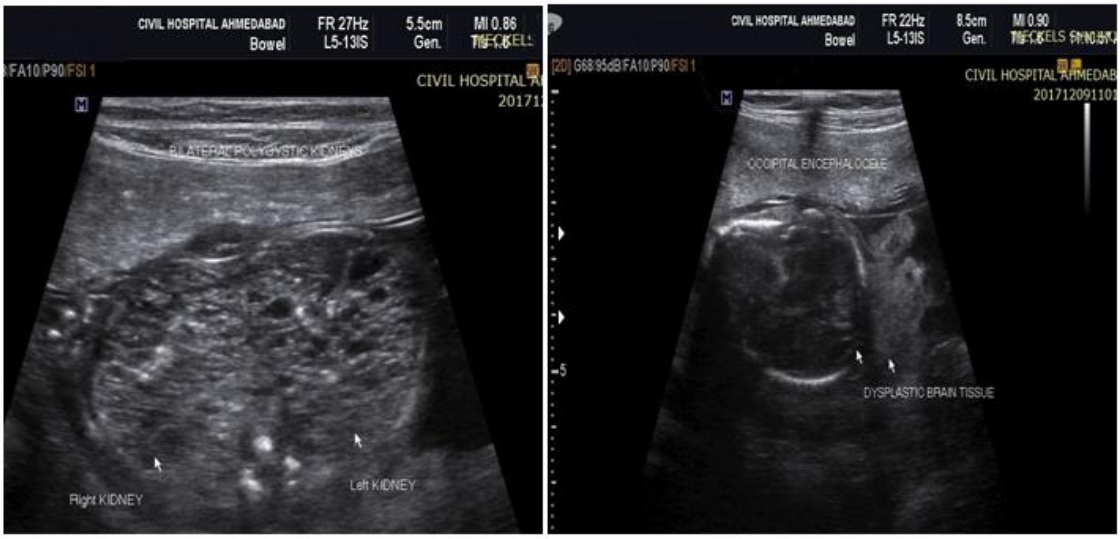
The triad of occipital encephalocele, large polycystic kidneys, and postaxial polydactyly characterizes Meckel-Gruber syndrome. Cystic dysplasia of the kidneys is the most constant and characteristic feature of Meckel-Gruber syndrome. Associated abnormalities include oral clefting, genital anomalies; CNS malformations, including Dandy-Walker, Arnold-Chiari malformation, and liver fibrosis. Cardiac lesions like atrial septal defect, coarctation of the aorta and pulmonary stenosis may be present. The mortality is 100% and most babies die in utero or shortly after birth. Pulmonary hypoplasia is the leading cause of death. Other causes include liver and renal failure.

II. Case Report

A twenty-six-year-old woman with 18 weeks amenorrhea was referred for a second trimester ultrasonogram to detect fetal anomalies. The patient gave history of a previous second trimester abortions. Records were not available and the patient stated that the abortion took place due to an abnormal baby with the abortus having an abnormal skull.

Ultrasonography was done using Samsung machine with a 4MHz Curvilinear transducer. The scan revealed bilateral enlarged hyperechoic multicystic kidneys, occipital encephalocele and six digits in all four limbs . There was evidence of oligohydramnios and the fetal urinary bladder was not visualised both in the initial scan and in all repeat scans done over a period of two days. The patient also had evidence of pericardial effusion. Rest of the organs did not reveal any gross abnormality. No further tests like karyotyping or alpha feto-protein were performed.

The pregnancy was terminated two days later. Post-mortem examination of the fetus revealed a large abdomen , a small head with a defect in the occipital region and herniated brain tissue , bilateral clubfeet and six digits in all the four limbs Autopsy revealed bilateral large cystic dysplastic kidneys and occipital cephalocele. Other visceral organs were normal.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Left KIDNEY
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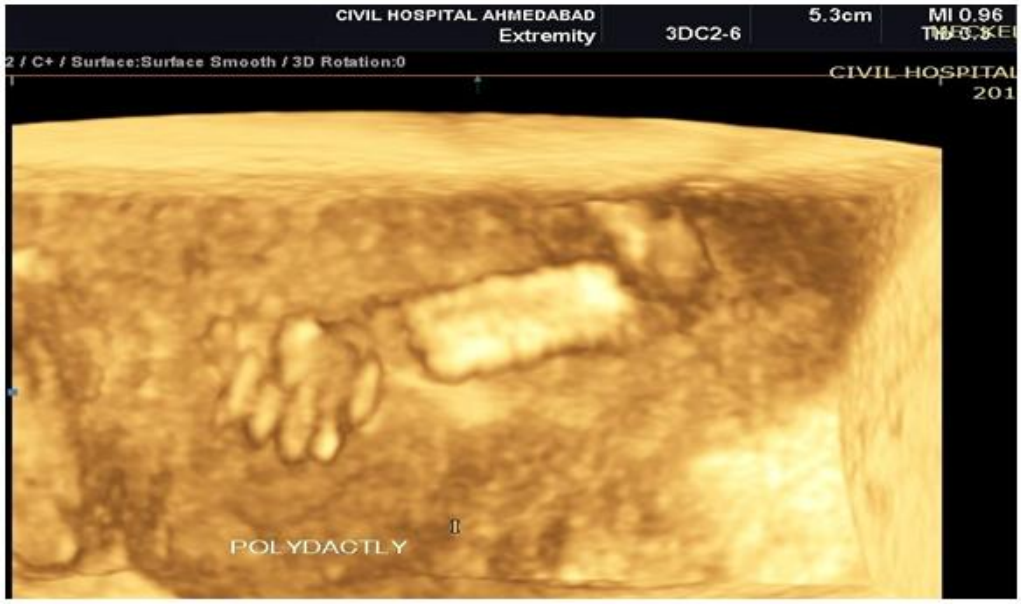
DYSPLASTIC BRAIN TISSUE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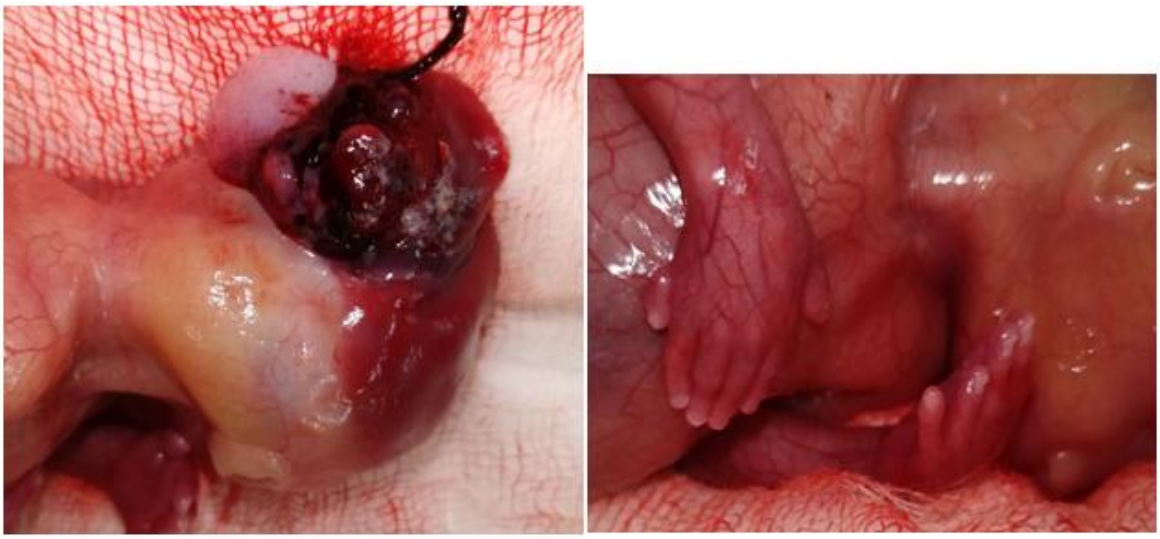

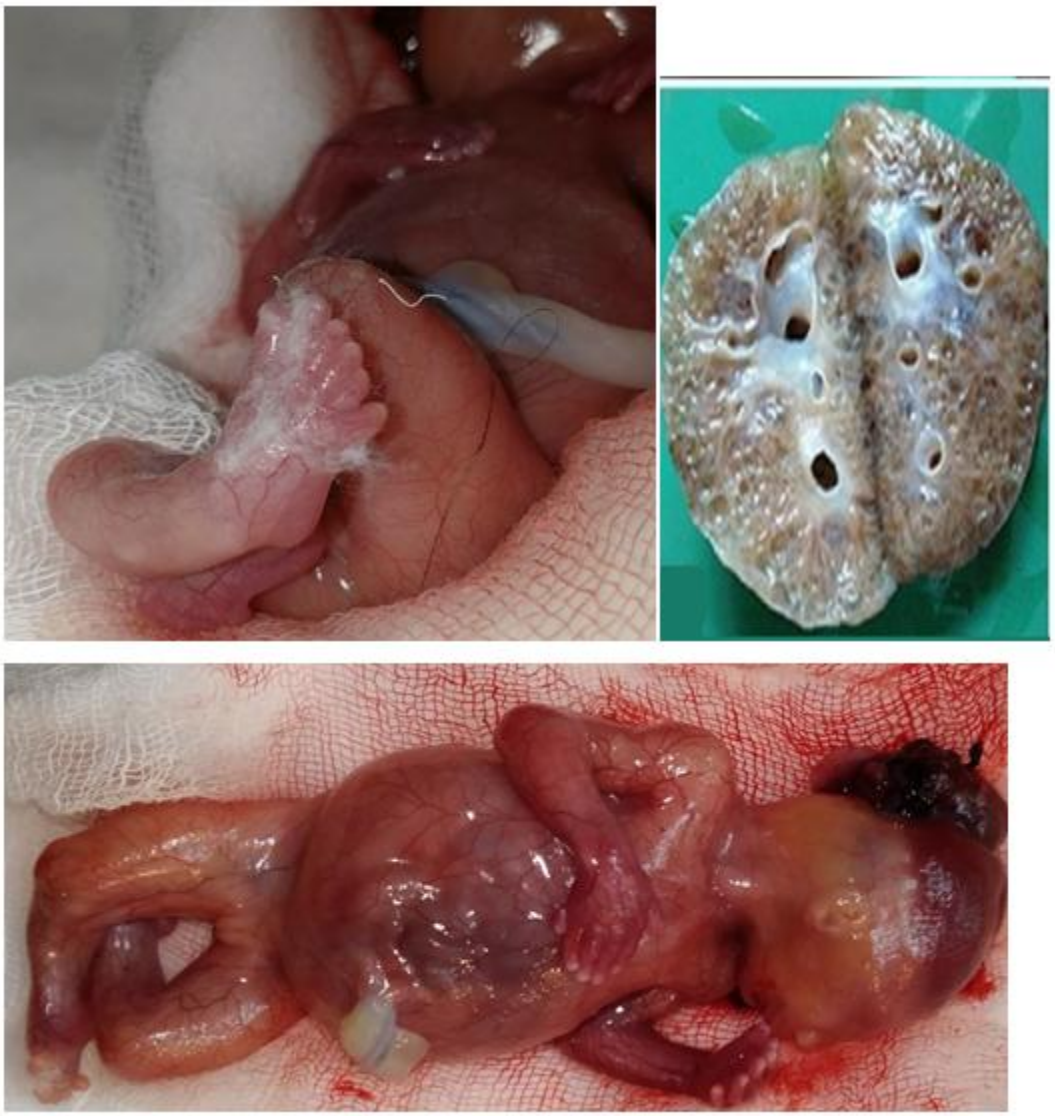

III. Discussion

MKS was first described by Johann Friedrich Meckel in 1822 in two siblings who died of identical malformations of occipital encephalocele, polycystic kidneys, and polydactyly. George B Gruber, in 1934, reported many familial cases with similar features and coined the term "dysencephalia splanchnocystica". In 2006, Opitz *et al* gave the detailed review of developmental pathology of Meckel syndrome.

The incidence of this rare syndrome is 1 per 1 300 live births in Gujarati Indian families, 1 per 3000 in Belgium, and 1 in 9000 in Finland. The disease affects all races with males and females being equally affected. Once diagnosed, the chances of MKS in subsequent pregnancy are 1 in 4 (25%). The diagnostic criteria for MKS is presence of at least two of the three classic features like cystic renal dysplasia, occipital encephalocele, and polydactyly, which are observed in 100%, 90%, and 83.3%, respectively.

Meckel-Gruber syndrome is a lethal disorder. Most infants are stillborn or die in hours or days after birth. A few patients sometimes survive a few months with poor quality of life. According to Ramadani, there is one report of a long survivor who died at the age of 28 months. In 1995, Paavola reported another atypical case of a long survivor who died at 18 months of life.

Chromosome analysis is essential to exclude trisomy 13, which mimics Meckel-Gruber syndrome. Trisomy 13 carries a 1% recurrence risk, as opposed to the 25% recurrence rate for Meckel-Gruber syndrome. Linkage or mutation analysis is not yet available. The mortality is 100% and most babies die in utero or shortly after birth. Pulmonary hypoplasia is the leading cause of death. Other causes include liver and renal failure.

Renal cystic dysplasia is the most characteristic feature of MKS, but differs from those typical of polycystic kidney disease. The degree of cyst formation varies between individuals with MKS, but the kidneys

will often be grossly enlarged, causing massive swelling of the abdomen). Large, fluid-filled cysts are visible by eye in most affected individuals. However, in other small cysts, cystic changes of the proximal tubules and the absence of normal renal parenchyma are visible by microscopic investigation. Cysts develop first in the glomeruli in the cortex, and cystogenesis progresses along the tubules and collecting ducts in the medulla. Abnormal fetal renal function is a frequent cause of oligohydramnios or anhydramnios, a common complication of an MKS pregnancy. Potter's sequence is frequent (pulmonary hypoplasia, growth restriction, club feet, and contractures) with a distinctive facies (comprising slanting forehead, flattened nose, and low-set ears), and is secondary to oligohydramnios or anhydramnios during pregnancy. In addition to cystic kidney dysplasia, hepatic involvement is an obligate feature of MKS. The typical histology shows bile duct proliferation and dilation, associated with excess collagenous connective tissues, which are thought to arise from the incomplete development of the hepatic biliary system.

Other associated anomalies include :

System	Anomalies
CNS	Occipital encephalocele, hydrocephalus, microcephaly, anencephaly, absence of olfactory lobes and tract, holoprosencephaly, cerebellar hypoplasia, Dandy-Walker malformation, Arnold-Chiari malformation, schizencephaly, and agenesis of corpus callosum
Face	Cleft lip and cleft palate, microphthalmia, micrognathia, epicanthal folds, hypo/hypertelorism, nasal anomalies
Mouth	Lobulated tongue, cleft epiglottis, neonatal teeth
Skeletal	Polydactyly, short limbs, talipes, bell-shaped thorax, syndactyly, club foot, clinodactyly
CVS	Atrial septal defect, coarctation of aorta, pulmonary stenosis
RS	Hypoplasia of lungs
Renal	Polycystic kidneys, cystic dysplasia, renal hypoplasia, horseshoe kidney, double ureter
Liver	Hepatic fibrosis, ductal agenesis, portal fibrosis
Genitalia	Hypoplasia, ambiguous genitalia, hermaphroditism, cryptorchidism
Abdomen	Malrotation of the gut, accessory spleen, omphalocele, imperforate anus, adrenal agenesis
Others	Enlarged placenta, single umbilical artery

(Dahiya *et al.*[8] 2001), CNS- Central nervous system

Transabdominal ultrasonography, performed at 10–14 weeks gestation, has been shown to successfully detect several of the fetal anomalies associated with MKS, including polycystic kidneys (from 9 weeks gestation), occipital encephalocele (from 13 weeks), and polydactyly (from 11 weeks), in both high-risk and low-risk pregnancies. Visualization can be compromised by oligohydramnios , but this is less problematic when performed in the first trimester of pregnancy. Further investigation of anomalies is possible by transvaginal scanning. Enlargement of the fetal trunk can give an early indication of multicystic renal dysplasia, in addition to unusually heterogeneous corticomedullary differentiation, reduced echogenicity of the medulla, increased echogenicity of the cortex, and the visualization of small medullary cysts. The fetal bladder can also be visualized by ultrasonography from 11 weeks, and the absence of a visible fetal bladder is often indicative of renal dysfunction.

Fetal MRI is an alternative if ultrasonography findings are inconclusive or lack of amniotic fluid prevents clear imaging. MRI offers better soft-tissue resolution than ultrasonography, and can provide clearer images of intracranial structures to enable an accurate diagnosis of CNS malformations, but is rarely performed before 18 weeks gestation. Fetal movement and maternal aortic pulsation do not preclude a successful diagnosis of MKS using MRI , since imaging artifacts caused by fetal movement can be minimized by a fetal neuromuscular blockade or general anesthesia of the mother. Transabdominal or vaginal endoscopy in the first trimester of pregnancy allows diagnosis of MKS by visualization of the surface anatomy of the embryo. Fetoscopy enables the direct observation of polydactyly and occipital encephalocele from 11 weeks gestational age. Prenatal diagnosis is also possible by using a combination of these imaging techniques, α-fetoprotein testing of amniotic fluid, and DNA testing of fetus and parents. For example, elevated levels of maternal α-fetoprotein during antenatal screening may be associated with MKS.

Since MKS has an AR inheritance pattern, couples with a previously affected child should have the opportunity for genetic counseling with a medical professional in order to discuss the nature, inheritance, and implications of an MKS diagnosis. The possibility of prenatal testing needs appropriate counseling of parents if it is being considered for the purpose of pregnancy termination in addition to early diagnosis. With consanguineous MKS families, geneticists will encourage disclosure to at-risk relatives. The fact that these individuals often do not seek carrier testing suggests that many families are not sharing this information. In families with an AR disorder who practice consanguinity, the concern that their children's carrier status would affect their marriage prospects can contribute to non-disclosure of this important information to their wider family.

IV. Conclusion

In conclusion, Meckel-Gruber syndrome is a rare autosomal recessive condition that has 100% mortality; the diagnosis should be made possible antenatally with modern ultrasound techniques and the parents should be fully counselled regarding the recurrence risk in future pregnancies.

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