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Case Report .

Meckel Gruber Syndrome: A Rare Entity

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ABSTRACT

Meckel-Gruber Syndrome (MKS) was first described by J R Meckel in 1822. It is an autosomal recessive disorder, and is caused by the failure of mesodermal induction. The typical triad of Meckel-Gruber Syndrome (MKS) involves meningo-encephalocele, polycystic kidneys and postaxial polydactyl. The diagnosis was confirmed at 20 weeks of gestation based on ultrasonographic findings of the typical triad of the disease (encephalocele, polycystic kidneys, and polydactyly) followed by autopsy and is reported here due to its rarity.

Key words: Meckel Gruber Syndrome, Autopsy.

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INTRODUCTION

MKS is a lethal, autosomal recessive, multisystemic disorder, associated with mutations affecting ciliogenesis.[1] MKS is characterized by wide variety of systemic malformations. Few abnormalities associated with MKS include cleft palate, cardiovascular diseases, hepatic ductal dysplasia, oligohydramnios, genital deformations, bowed legs, microcephaly and hydrocephalus. The worldwide incidence varies from 1 in 1.300 to 1 in 140.000 live births. The highest incidence was seen in the Gujarati Indians (1:1.300), and then in Finlands (1:9.000).[2] To date, above 200 cases of MGS have been reported in literature. Bardet–Biedl Syndrome, Alstrom Syndrome and Joubert Syndrome are other syndrome belonging to the same group of disease.[3]

CASE REPORT

A 19 year old primigravida presented with 20 weeks of gestation for routine antenatal examination with history of 3rd degree consanguinity. Routine USG showed features of occipital encephalocele, enlarged kidneys and post axial polydactyly in all the four limbs (six digits). USG diagnosis of Meckel Gruber syndrome was given. With consent of parents termination of pregnancy was planned.

All the routine investigations of the patient were within normal limits. The fetus was then send for autopsy and histopathological evaluation. Detailed anthropometric measurements were recorded. It was a female fetus of 400 gms, the crown rump length was 16cms, crown heel length was 33.5cms, head circumference was 15cms, chest circumference 16cms, and foot length was 3 cms. External examination of fetus showed well developed ear cartilage and nails with absence of palmar and plantar creases. Head and neck examination revealed a defect in occipital bone with encephalocele [fig 2] with both upper and lower limbs showing post axial polydactyly [Fig 3].The internal examination was done following virchow's technique and by giving a modified Y shaped incision starting from below the ears to symphysis pubis encircling umbilicus on the left side. Thorax and abdomen were opened. Heart was dissected out which appeared grossly normal whereas slight congestion was seen in liver.

Kidneys were bilaterally enlarged showing multiple minute cysts of different size [Fig 4 (a)(b)]. Sections were also given from thymus, adrenals, lung, brain and placenta. Sections from kidneys showed polycystic kidney disease [Fig 6 (a) (b)], while sections from liver showed hepatic fibrosis proliferation of bile ducts and hematopoitic cells (normoblasts) [Fig 5 (a) (b) (c)].

Microsections from brain revealed meningoencephalocele with congested blood vessels. Placental cord shows edematous changes and normal villi architecture. No other placental abnormalities detected. Sections from the heart, lung, adrenals and thymus were morphologically comparable to fetal organs. In view of radiological and histological findings of occipital encephalocele, post axial polydactyly, hepatic fibrosis and polycystic kidneys-diagnosis of Meckel gruber syndrome was signed out.

DISCUSSION

MKS is a condition characterized by ciliopathies caused by dysfunction of cilia and flagella. In 1822, Johann Friedrick Meckel described two siblings who presented with occipital meningoencephalocele, polydactyly, cleft palate, and large cystic kidneys. George B Gruber, in 1934, reported 16 similar cases and

named the disorder, 'Dysencephalia Splanchnocystica'. In 1969, Opitz and Howe re-described it as the MKS.[4]

MKS effects all races with males and females being affected equally, and it has been reported that consanguinity plays an important factor in the genetic basis of the disease. Six different loci in different chromosomes have been shown in MGS. These loci are 17q21–24 [(transmembrane protein meckelin (MKS) 1], 11q13 (MKS2), 8q21.3-q22.1 (MKS3), 12q21.31-q21.33 (MKS4), 16q12.2 (MKS5), and 4p15.32 (MKS6).[5] This variability in gene loci suggests genetic heterogeneity in MGS. The proteins produced by these genes are known to influence cell structures called primary cilia. These cilia are important for structure and function of cells, especially kidney, liver and brain cells. Mutations can cause problems in function of the cells due to problems of chemical signaling between cells. Defective cilia responsible for developmental abnormalities in kidneys and brain. MKS1 is a centrosomal protein required for ciliogenesis, and mutation in MKS1 results in defects in ciliogenesis that underlie a majority of phenotypes shown by patients.[1] Two of the three major anomalies or two other anomalies in addition to the one classical finding are sufficient for a definitive diagnosis.[6-8] The major anomalies includes the typical triad of Meckel-Gruber Syndrome (MKS) i.e meningo-encephalocele, polycystic kidneys and postaxial polydactyl. Other anomalies of MKS include CNS malformations like microcephaly, anencephaly, holoprosencephaly, hydrocephalus, polymicrogyria, Arnold-Chiari or Dandy-Walker malformation, agenesis of corpus callosum, absence of olfactory tract or lobe; and cardiac anomalies like atrial septal defect (ASD), ventricular septal defect (VSD), or a patent ductus artery (PDA). Cleft palate, microphthalmia, sloping forehead, micrognathia, short neck, and cryptorchidism are also noted.[7,9]

The most specific abnormality is encephalocele, whereas the most seen abnormality is the polycystic kidneys.[6] Oligohydramnios, and therefore, pulmonary hypoplasia occur because of nonfunctional dysplastic kidneys, which enlarge even up to 15–20 times. Because of these serious health problems infants that are born do not survive longer than a few days to weeks and die of kidney failure or respiratory problems. There are various diagnostic modalities to detect MKS.

MKS can be diagnosed by USG done at 11 to 14 weeks of gestational age and by estimation of alpha fetoprotein in the maternal serum or amniotic fluid after 12 wks of gestation help to detect encephalocele or any NTD. Sometimes, the alpha fetoprotein level is not elevated when the encephalocele contains a closed sac. Chromosome analysis by amniocentesis or chorionic villous sampling is also an important diagnostic method.[6] When available, autopsy and genetic analysis are gold standard for diagnosis.[6]

The differential diagnosis of MKS includes Bardet-Biedl syndrome (BBS), Trisomy 13, and Smith-Lemli-Opitz syndrome. CNS anomalies are not seen in BBS. The closer mimic of MKS is trisomy 13 as 30% of fetus with trisomy 13 will have enlarge cystic kidneys and many have polydactyly and neural tube defects. Karyotype analysis however will be abnormal in Trisomy 13 but is normal for MKS. In the Smith-Lemli-Opitz syndrome, there is mutations and deficiency of 7-dehydrocholesterol gama-reductase, hepatic dysfunction and cholestatic liver disease.[10,11] Smith-Lemli-Opitz syndrome can be ruled out by biochemical testing.

CONCLUSION

The prognosis of this rare entity is grim. No treatment is currently available for Meckel syndrome which has a constantly fatal outcome. It results in 100% fetal or neonatal mortality. As MKS has a high risk (25%) of recurrence; parents should be counseled to avoid consagangious marriage and explain about the outcome and prognosis of the fetus and its recurrence risk in future pregnancies.[9,10] We conclude that prenatal diagnosis based on ultrasound scan is not adequate for final and correct syndrome diagnosis . Fetal autopsy plays a significant role and should be recommended in almost all fetal deaths to establish a correct diagnosis.

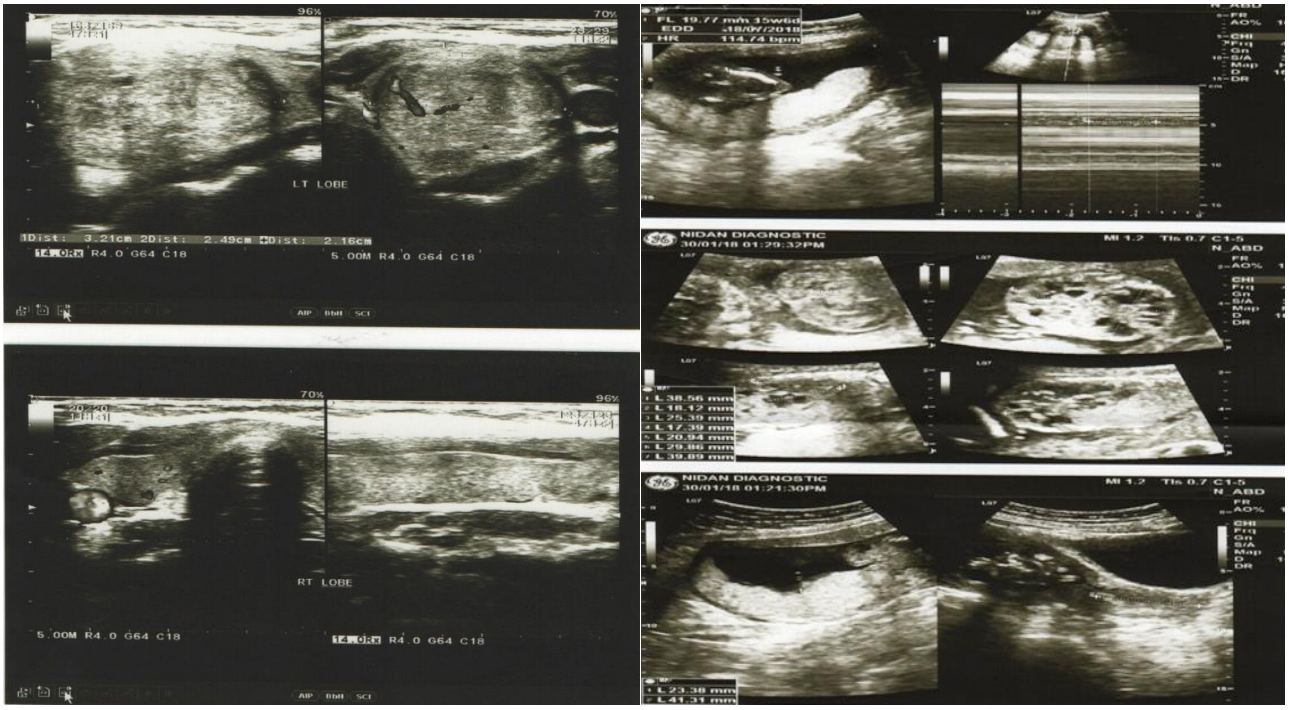

Fig 1 (a, b): USG scan showing the fetal anomaly.

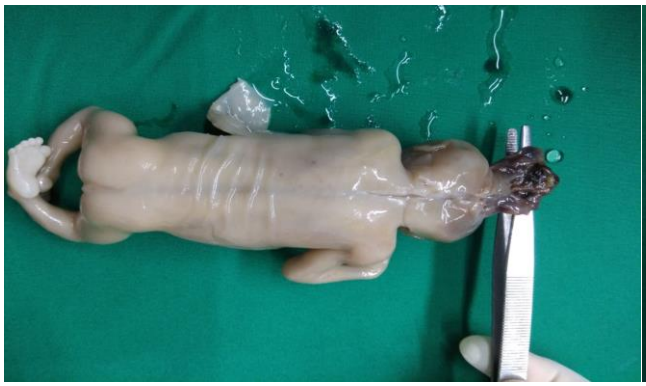

Fig 2: Showing fetus with meningoencephalocele

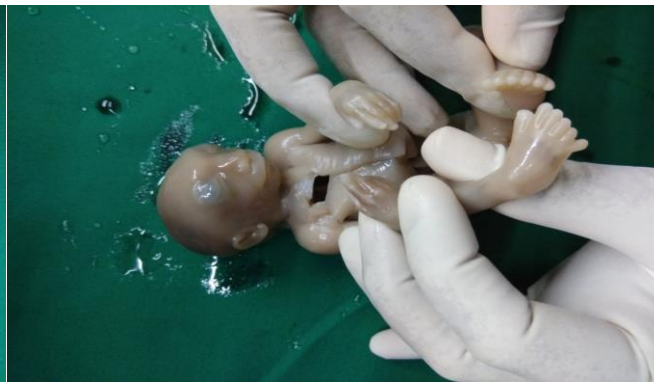

Fig 3: Showing post axial polydactyl (Six digits in each limb).

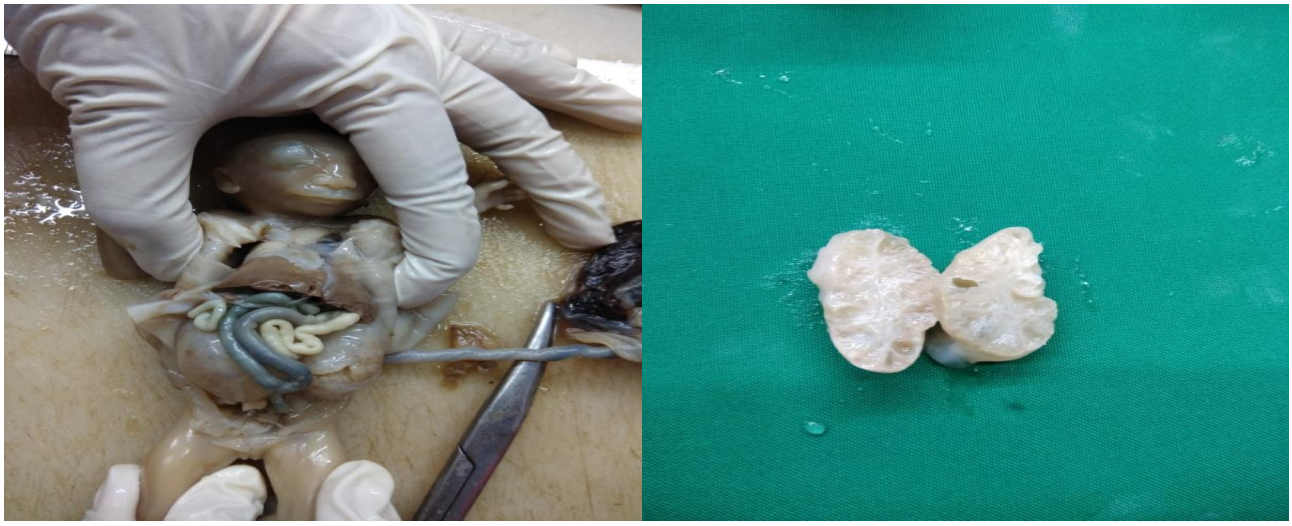

Fig 4 (a, b): Showing polycystic kidneys

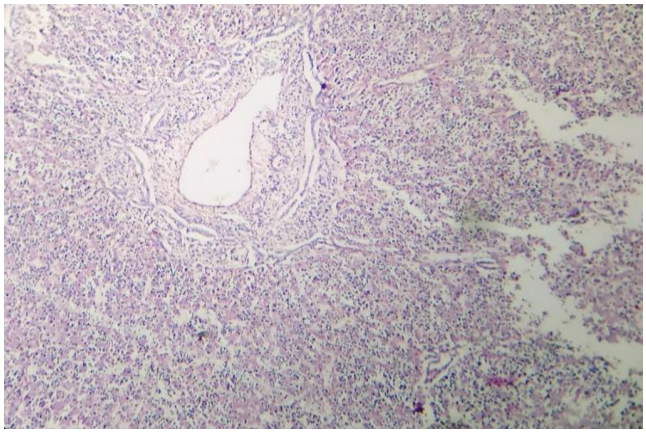

Fig 5 (a): Scanner 40X-HP study of liver –Showing portal triad fibrosis.

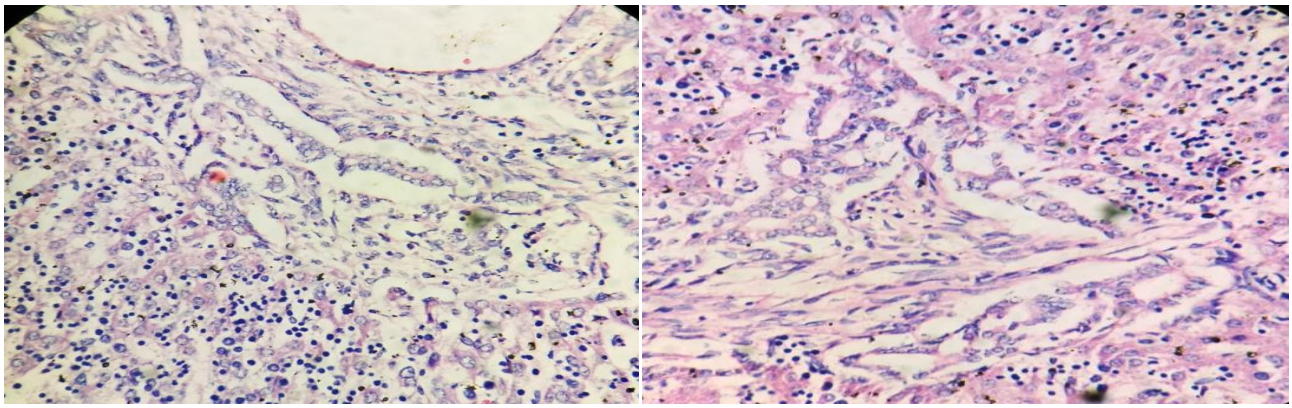

Fig 5 (b)(c): LP 100X-HP showing hepatic fibrosis and bile duct proliferation

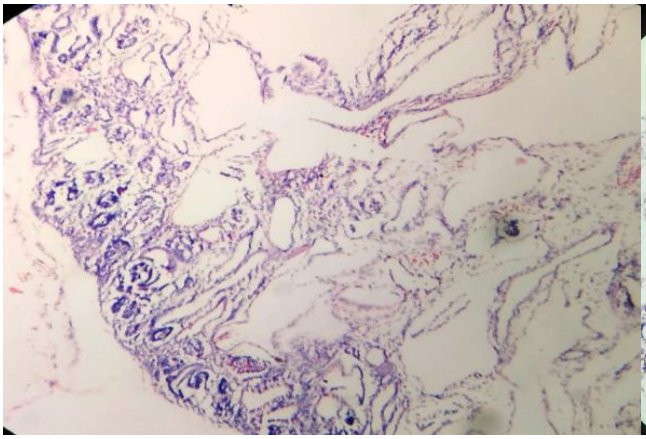

Fig 6 (a): Scanner view 40X –Kidney tissue HP Study.

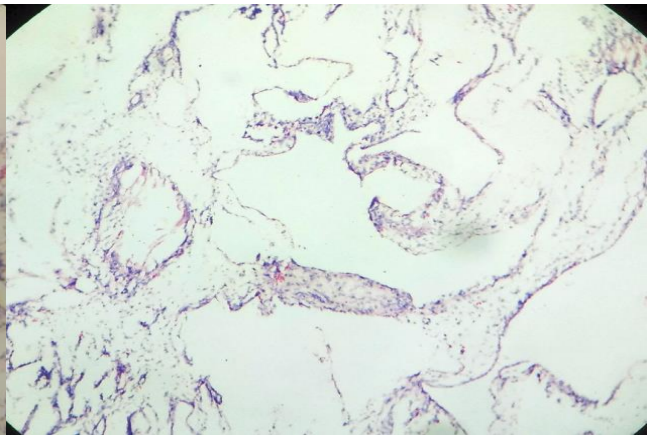

Fig 6(b): LP 100X- Showing polycystic kidneys

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