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Case Report

Anatomy Section

Meckel-Gruber Syndrome with Multiple Congenital Anomalies- A Rare Lethal Case

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ABSTRACT

Meckel-Gruber Syndrome (MGS), a rare autosomal recessive malformation syndrome with incidence of one per 13,250-140,000 live birth. It is a classical triad of occipital encephalocele, infantile polycystic kidneys and postaxial polydactyly with associated multiple congenital anomalies. It leads to the death of foetus in utero or shortly after birth. Most important diagnostic tools for MGS are antenatal ultrasonography and chromosomal study. A 3.14 kg dead female foetus was delivered from 19-year-old primigravida on the first visit to hospital with full term pregnancy. Sonography revealed no cardiac activity of the foetus in utero. Termination of pregnancy was done by the decision of obstetrician and consent of patient. Gross multiple anomalies along with microanatomical changes were noticed in foetus. Typical triad of polycystic kidney resulted to oligohydramnios, protrusion of meninges with brain tissue resulted to occipital encephalocele and limb anomalies might be hereditary or due to mutational changes. Histological changes were supportive of gross anatomical changes and ultrasound scan findings. Major changes as multiple cystic lesions in kidney, non functional alveoli in lungs and fibrous tissues with deranged hepatocytes in foetal liver were noticed. Concluding through all investigations and family history might confirm the diagnosis and help in further treatment or termination of pregnancy timely and directs for further genetic and chromosomal counselling.

Keywords: Encephalocele, Multicystic kidneys, Oligohydroamnios, Postaxial polydactyly

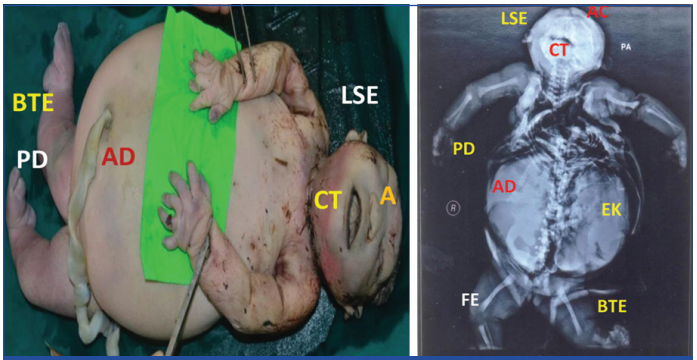
CASE REPORT

A 19-year-old pregnant female was reported first time to Obstetrics and Gynaecology Department. The patient was presented with pregnancy of around 32 weeks {as Last Menstrual Period (LMP) was not clearly recalled by patient} with no previous history of foetal anomaly, abortions, co-morbidities and family history of congenital anomalies. The patient was referred from the primary health centre to tertiary care centre for routine ultrasound. The patient was on supplements as prescribed by near primary health centre during antenatal period. No routine investigation had been done during antenatal period before due to poor background. In third trimester, the patient visited hospital for routine investigations only without any complains.

On general examination, vital parameters were stable. On abdominal examination, uterus was full term but cardiac activity was not noticed, consultant suggested for all routine investigation and an emergency ultrasound. The reports of general blood and urine test were normal however ultrasound revealed 28 weeks ±3 days pregnancy with oligohydramnios, absence of cardiac activity and multiple congenital anomalies (ultrasound showed dilated ventricles with absence of cranial vault as anencephaly, bilateral multiple cysts in kidney as infantile polycystic kidneys, abnormal spinal curvature and presence of sacro-coccygeal soft tissue mass). An informed written consent was obtained from the patient as per the hospital policies for the termination of pregnancy and foetal autopsy along with histopathological examination of the specimens. Termination was done through caesarean section by obstetrician without any complications.

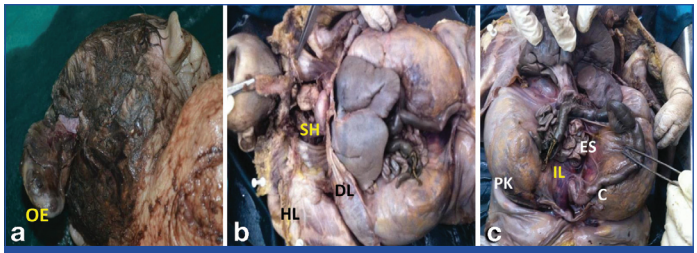
For the further study on this case, consent of the parent was taken and the research permission was granted by the Institutional Ethical Committee. 3.14 kg foetus weight, 32 cm head to heel length, 22 cm head circumference and 46 cm abdomen circumference were recorded on anthropometric measurement. The foetus was dissected and multiple gross congenital anomalies of kidney, brain, liver, umbilical cord, heart, lungs, intestine, spleen and stomach were observed and concerned tissues were collected for histological study.

The gross features observed were an anencephaly, crowding of teeth, low-set ear, disproportionately large and protuberant distended abdomen with diffuse subcutaneous oedema, bilateral postaxial polydactyly (six digits) in upper and lower limbs, bilateral talipes equinovarus [Table/Fig-1]. These external features can be seen in full body X-ray of terminated foetus. [Table/Fig-2] showed the absence of calvaria resulted to underdeveloped brain, epiphysis of lower end of femur was absent, curvature defect of spine, air inside joint cavity- as calcium is decreasing few pneumatocysts were noticed, enlarged kidney with hydronephrosis in abdominal region was evident. After autopsy [Table/Fig-3] congenital bilateral polycystic enlarged kidney, occipital encephalocele small sized heart, hypoplastic lungs, enlarged deformed thin liver, enlarged spleen (on elevation of liver), dilated colon and normal intestine loops were found. Placental weight was 480 grams and was flooded with blood.



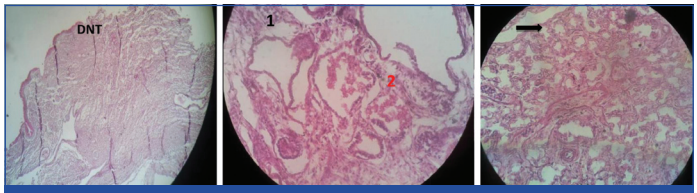
[Table/Fig-1]: Foetus showing Multiple Anomalies-anencephaly (A), postaxial polydactyly of upper and lower limb (PD), abdominal distension (AD), bilateral talipes equinovarus (BTE), crowding of teeth (CT), low set ears (LSE).
[Table/Fig-2]: Foetal X ray occipital absence of calvaria (AC), crowding of teeth (CT), low-set ear (LSE), distended abdomen (AD), bilateral postaxial polydactyly (PD) in upper and lower limb, bilateral talipes equinovarus (BTE), absence of lower end of femur epiphysis (FE), enlarged kidney (EK). (Images from left to right)

On microanatomy, brain showed marked vascular capillaries, Degenerating Neuronal Tissue (DNT) with presence of multiple

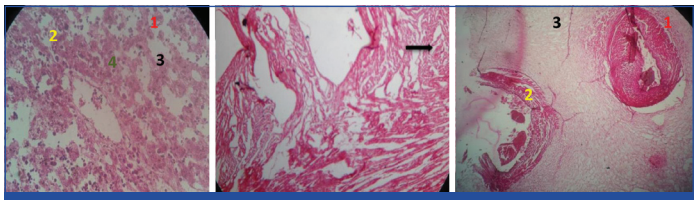


[Table/Fig-3]: Foetus showing multiple anomalies after autopsy- a) Occipital Encephalocele (OE); b) Small Heart (SH), Hypoplastic Lung (HL), Deformed Liver (DL); c) Polycystic Kidney (PK), Enlarged Spleen (ES), Colon (C) and Intestinal Loops (IL).

fibrous tissue [Table/Fig-4]. Renal histology described marked multiple dilatation of the vesicle, loss of the parenchymal tissue being replaced by cystic dilatation and with few fibrous tissues in between multiple cyst of various size [Table/Fig-5], occasionally less developed glomeruli could be seen in between dilated cyst, some were in degenerating (shrunken) state with ill-differentiated medulla. In hypoplastic lung [Table/Fig-6], cartilage was not present in bronchioles, less vascularity and cuboidal epithelium was noticed while alveolar epithelium were not clearly visible. Histological picture of liver depicts the distortion of cytoarchitecture with no clear demarcation of hepatic and portal lobule, hepatocytes are not arranged in radiating manner, reduction in the number of central vein and portal triad, sinusoid was more dilated, fibrous tissue appeared around the central vein and haematopoietic cells had been reduced considerably [Table/Fig-7]. Extensive fragmentation of cardiac muscles [Table/Fig-8] was noticed. Muscle mass appeared to be swollen and hypertrophied. In umbilical cord slide [Table/Fig-9] there was one umbilical artery and one umbilical vein, artery was highly muscular with collapsed lumen and thrombotic remnants while vein was dilated and less muscular. Irregular spaces were noticed in the wharton's jelly with reduced connective tissue cells.

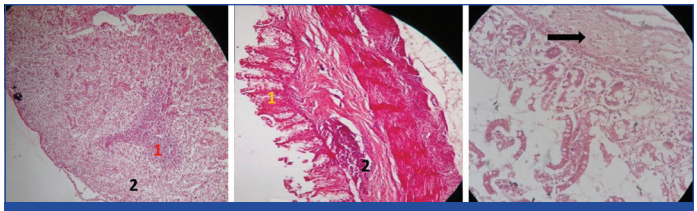


[Table/Fig-4]: Brain Degenerative Neuronal Tissue (DNT) (H&E, 600X).
[Table/Fig-5]: Kidney (1), shrunken glomeruli (2) (H&E, 600X).
[Table/Fig-6]: Lung- absence of cartilage (H&E, 600X). (Images from left to right)



[Table/Fig-7]: Liver sinusoids are more dilated (1) hepatocytes are deranged (2), presence of fibrous tissue (3), Central vein (4) (H&E, 600X).
[Table/Fig-8]: Heart Extensive fragmentation of muscles (H&E, 150X).
[Table/Fig-9]: Umbilical cord- Umbilical artery with remnants and thick muscular wall (1), thin muscular wall (2), reduced connective tissue (3) (H&E, 150X). (Images from left to right)

Splenic histology showed [Table/Fig-10] white pulp and sinusoid without proper organisation, reduction in trabeculae and haematopoietic cells with marked cellular destruction. Histological features of colon [Table/Fig-11] depicted extensive goblet cells in epithelium, collection of lymphocytes in wider area of submucosa, ill-differentiated circular and longitudinal musculature pattern. Intestinal villi [Table/Fig-12] were seen with well-differentiated goblet cells with crypts in lamina propria and musculature was in process of differentiation. This multisystem developmental malformed foetus have classical features of renal cystic dysplasia, occipital encephalocele and post axial polydactyly with abnormal multi-organ microanatomy, is diagnosed as a case of Meckel-Gruber Syndrome.



[Table/Fig-10]: Spleen white pulp (1), red pulp (2) (H&E, 150X).
[Table/Fig-11]: Colon H&E X150 Extensive goblet cell (1), collected lymphocyte (2) (H&E, 150X).
[Table/Fig-12]: Intestine musculature in process of differentiation (H&E, 150X). (Images from left to right)

DISCUSSION

Worldwide, the incidence of Meckel-Gruber Syndrome (MGS), is one per 13,250-140,000 live births. Individuals of North Africa have incidence of 1 per 140000 while Finnish have incidence of 1 per 9000 live births and Jews have 1 per 50,000. Higher incidence is noticed among Belgians and Bedouins in Kuwait with 1 per 3,500 and in the Gujarati Indians, with one affected birth per 1,300. Gene frequency of Meckel's syndrome approximately is 0.028 among Hindu parents of Gujarat State [1] in India. MGS is a rare autosomal recessive condition, belongs to the ciliopathies, a category of diseases caused by dysfunction of cilia and flagella, which might be result of mutation. MKS represents the most severe condition of this group [2]. It is found in six different loci in different chromosomes 17q21-24 (MKS1), 11q13 (MKS2), 8q21.3-q22.1 (MKS3), 12q21.31-q21.33 (MKS4), 16q12.2 (MKS5), and 4p15.3 (MKS6). Trisomy 13 carries a 1% recurrence risk, as opposed to the 25% recurrence rate for MGS [3].

In present case report, anencephaly with occipital encephalocele, crowding of teeth, low-set ear, disproportionately large and protuberant distended abdomen with diffuse subcutaneous oedema, bilateral postaxial polydactyly (six digits) in upper and lower limbs were observed while according to Kheir AEM and Imam A., and Sergi C et al., study various other associated gross internal congenital anomalies, as aniridia of the right eye, left microphthalmia, distended choledocalcyst, polycystic kidney disease with ureteric insertion on anterior surface, para ovarian cyst, genital anomalies were noticed [3,4]. The majority of the limb deformities is a result of multifactorial inheritance while abnormal spine curvature is inherited as a dominant trait. Ambiguous genitalia with absent phallus, empty scrotal sac, bilateral talipes and an 'imperforate vulva are the finding with normal karyotypes [5]. Previous study states that MGS have typical triad of large polycystic kidneys (100%), occipital encephalocele (90%), postaxial polydactyly (83.3%) and the rest exhibited other variations. Likewise, present case study, Khurana S et al., reported the X-ray showing shortening and significant bowing of the limbs, absence of calvaria and multiple cysts in kidney [6].

Histological features of many organs are found distorted and underdeveloped in present case. As per lungs histology they are underdeveloped as per gestational age of case, absence of cartilage and alveolar bronchus represents a canalicular stage of lungs suggestive of 16 to 22 week gestational age while at 24 weeks alveolar histology is similar like an adult [7]. In both polycystic kidneys foetal glomeruli were present while cortico-medullary junction was not distinct due to cystic dilation of the tubules at medulla causing distortion of renal columns and it is corresponding with the micro cysts on gross morphology [8], spherical cyst with single layered cuboidal epithelium, absence of glomeruli and prominent interstitial fibrosis are also noticed by some author [7]. Functional activity of kidney cannot be described whole this process might be implication of gene mutation and faulty signalling [2]. Microscopy of liver showed evidence of foetal haematopoiesis [8]. In the normal liver histology of 27-31-week foetus have clear demarcation of hepatic and portal lobule with reduced haematopoietic activity, arrangement of hepatocytes in radiating pattern that is arising from distinct central vein. Kupffer cells and increased capsule thickness was also present

[9]. Chen IY et al., has found the congenital hepatic fibrosis is a rare inherited form of ductal plate malformation which is associated with autosomal recessive polycystic kidney disease [10].

The mortality of MGS is 100% and most foetal death occurs in utero or shortly after birth. Pulmonary hypoplasia is the leading cause of death along with liver and renal failure. Few babies survive for few months with poor quality of life [2]. Ramadani HM and Nasrat HA, noticed the longest survival case of age 28 months with poor quality of life [11]. A female foetus is reported with hydrocephalus, cleft lip and palate during ultrasonography, soon after birth, baby developed convulsions and required phenobarbitone, phenytoin and calcium supplements but died due to apnoea.

However, difficulty may be encountered in differentiating mild MGS from severe Smith-Lemli-Opitz syndrome (microcephaly, mental retardation and polydactyly), Potters' sequelae, Dandy-walker, Arnold-Chiari malformation, hydrolethalus syndrome (duplicated big toe, micrognathia, hydrocephaly with absent midline structures of the brain), trisomy 13 (holoprosencephaly, cleft lip/palate, congenital heart diseases), trisomy 18 (choroid plexus cyst, congenital heart/kidney disease, rocker bottom feet and polydactyly), liver fibrosis, gastrointestinal anomalies like omphalocele, highly variable phenotype, extreme genetic heterogeneity, Joubert syndrome (hypoplasia/dysplasia of vermis, facial abnormalities, cleft palate), Bardet-Biedl syndrome (vision loss, mental retardation, renal diseases, polydactyly and cleft palate), and Ivemark syndrome (cardiac anomalies with asplenia) [7,12-15].

Clinical diagnosis is suggested on the basis of the presence of classical clinical features and when the syndrome recurs in subsequent pregnancies [16]. Investigative tool of choice is ultrasound, but in severe oligohydramnios Magnetic Resonance Imaging (MRI) is valuable compliment to ultrasound, as polydactyly might be missed during ultrasound due to the marked oligohydramnios in later pregnancy. Two other signs encephalocele and polycystic kidney are clearly visible in ultrasound [12]. To diagnose earliest at 11-14 weeks alpha-fetoprotein and chorionic villous sampling might be done for genetic association. Colour doppler can assess lung perfusion in the last trimester, detects the presence of renal arteries in oligohydramnios and detect the flow in umbilical artery [17]. In a study done by Jondhale P et al., following findings are found in CT scan-extremely dialated urinary bladder, pericardial effusion, choroid plexus cysts on right-side, bilateral multiple dysplastic kidneys, gall bladder sludge, multiple cysts in liver and enlargement of ventricles [16]. Recent advances in genetic technology, with the widespread use of multi-gene panels for molecular testing, have significantly improved diagnosis, genetic counselling, and the clinical management of MGS families [14,15]. Unfortunately, there is no effective treatment for MGS [18].

CONCLUSION(S)

In the present case report, MGS had reported with typical triad of large polycystic kidneys, occipital encephalocele, postaxial polydactyly along with multiple congenital anomalies like anencephaly, crowding of teeth, low-set ear, disproportionately large and protuberant distended abdomen with diffuse subcutaneous oedema, bilateral talipes equinovarus. The MGS is lethal and rare syndrome with autosomal recessive condition occurs in cases of consanguinity occasions with 100% mortality. Diagnosis is confirmed by the autopsy but early diagnosis of MGS at 11-14 weeks by transvaginal ultrasound is vital for obstetric management. The patient should be counselled regarding the termination of this pregnancy as earliest due to poor prognosis and incompatibility with life. Parents must be informed to undergo genetic counselling for healthy pregnancies in future.

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