

# Meckel–Gruber Syndrome Fatal Disorder - A Rare Case Report with Review of Literature

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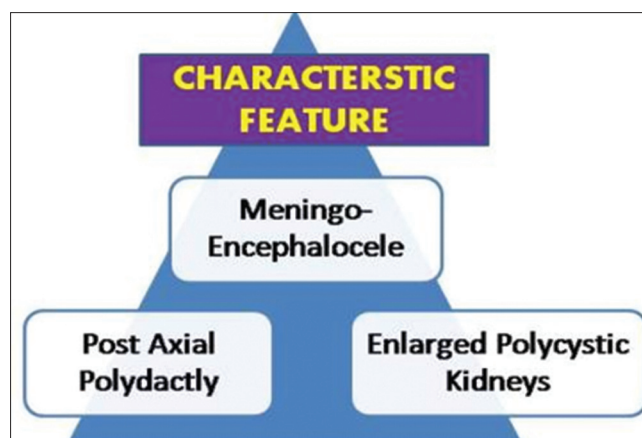
## ABSTRACT

Meckel–Gruber syndrome (MGS) is an rare lethal autosomal recessive genetic disorder, characterized by a unification of renal cysts or cystic renal dysplasia, developmental anomalies of the central nervous system, hepatic dysgenesis and postaxial polydactyly. MGS (MS) is a rare and lethal syndrome characterized by a triad of occipital cephalocele, postaxial polydactyly and dysplastic cystic kidneys. It is a rare syndrome with the highest incidence in Gujarati Indians and Finnish population. We report a case of MGS in non-Gujarati Indian, which was diagnosed on fetal autopsy. The incidence of MGS ranges from 1 in 13,250 to 1 in 40,000 live birth.


**Key words:** Meckel–Gruber syndrome, non-Gujarati Indian, rare

## INTRODUCTION

Meckel–Gruber syndrome (MGS) is a rare lethal autosomal recessive disorder with a broad range of systemic malformations mapped to 6 different loci in different chromosomes. Antenatal ultrasonography can identify significant features, but neonatal autopsy is needed to document complete anomalies. We report a female baby with typical triad of MGS. It is the result of mutation of MKS-1 gene on chromosome 17q21-24 or MKS2 gene on chromosome 11q13. Fetal death is due to pulmonary hypoplasia. It is also known as diencephalic splanchnicocystica given by Germany Anatomist Meckel in 1822. It can occur in all races and ethnicities. It is very rare disease and has been suggested to be caused by failure of the mesodermal induction.



OTHER ANOMALIES		
LIVER DYSFUNCTION	BOWED LEGS	OLIGOHYDRAMNIA
CLEFT LIP AND PALATE	MICROCEPHALY	CARDIO VASCULAR DISEASE
HYDROCEPHALY	MICROCEPHALY	GENITAL DEFORMATION

Access this article online	
Publisher	Website: www.renupublishers.com
	DOI: 10.5958/2394-4196.2015.00003.5

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**Submission:** 08 Jan 2015; **Revision:** 18 Jan 2015; **Acceptance:** 22 Feb 2015

## CASE REPORT

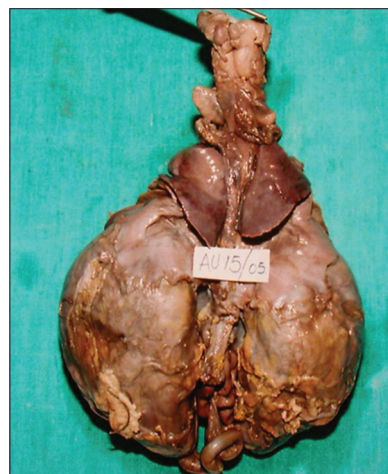
A 22-year-old primigravida (women pregnant for the first time) presented to the labor room with labor pains. On examination, she was full term with breech presentation. The fetal heart sounds were very feeble. Emergency cesarean section was done and delivered a stillborn female fetus. With the consent of the parents, the baby was sent for fetal autopsy. There was a history of second-degree consanguineous marriage. Past and family history was non-contributory. She was not on any teratogenic drugs. Routine antenatal scan during the antenatal period showed anencephaly, congenital talipo - equinovarus (club foot) and polydactyly.

At autopsy, the fetal weight was 2.650 g, head circumference 26 cm, abdominal circumference 40 cm, chest circumference 33 cm, crown-rump length 25 cm and crown-heel length of 32 cm. External examination showed anencephaly, bilateral club feet, postaxial polydactyly of all four limbs, distended abdomen and encephalocele [Figure 1]. On dissection, only squamous portion of the occipital bone was present. Cerebral hemispheres were not identified. Spinal cord could be traced to the thoracic spine. Meningeal layer was continuous with the sac in the occipital region. Internal examination showed enlarged thymus gland, hypoplastic lung, healthy liver, both kidneys enlarged with absence of adrenal glands. Other visceral organs were normal [Figure 2].

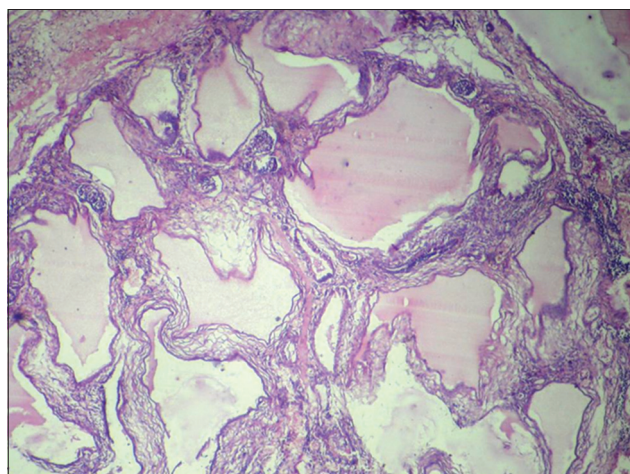
On gross examination of both the kidneys, each weighed 250 g, cut section showing indistinct corticomedullary differentiation with a spongy appearance. Sections from the kidney showed dilated tubules with focal hamartomatous change and epithelial hyperplasia. Most of the glomeruli were standard with some showing glomerular cysts. Bundles of connective tissue, neural tissue and adipose tissue were seen around the dilated tubules. The interstitium showed focal areas of extramedullary hemopoiesis. Histological features were in favor of multicystic renal dysplasia [Figure 3]. Sections from the liver showed bile duct hyperplasia, foci of extramedullary hematopoiesis and portal fibrosis suggesting the diagnosis of hepatic dysgenesis [Figure 4]. Sections from the encephalocele showed choroid plexus and oligodendroglia favoring the diagnosis of encephalocele [Figure 5a and b]. Based on the above features the diagnosis of MGS was



**Figure 1:** External examination - Female baby with bilateral club feet and distended abdomen. Anencephaly with occipital encephalocele, polydactyly of one upper limb, polydactyly of other upper limb



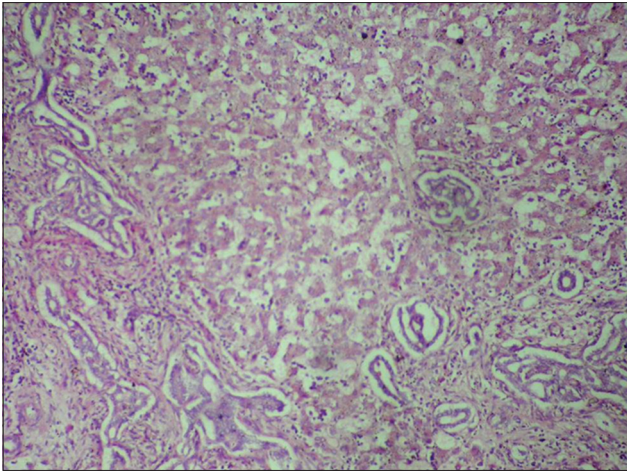
**Figure 2:** Internal examination - Hypoplastic lungs, bilateral enlarged kidneys and absence of adrenal glands



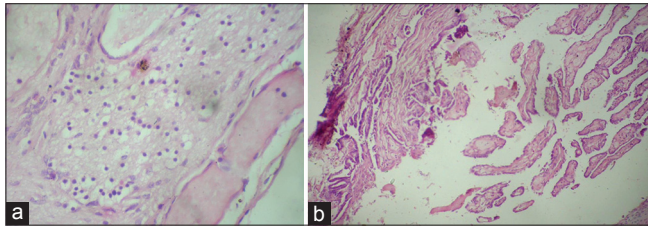
**Figure 3:** Cystic renal dysplasia - Microscopy showing dilated tubules

made. Both the parents did not give consent for genetic analysis.





**Figure 4:** Hepatic dysgenesis - Microscopy showing bile duct hyperplasia with portal fibrosis



**Figure 5:** (a) Encephalocele - Microscopy showing oligodendroglia, (b) encephalocele - microscopy showing choroid plexus

## DISCUSSION

MGS (MKS) was first described by Johann Friedrich Meckel in 1822 in two siblings who died of identical malformations of occipital encephalocele, polycystic kidney and polydactyly. George Gruber in 1934 reported many familial cases with similar features and coined the term “diencephalic splanchnocystica.”<sup>[1]</sup> Opitz *et al.* gave the detailed review of developmental pathology of Meckel syndrome.<sup>[2]</sup>

DIFFERENTIAL DIAGNOSIS	
Bardet- Biedl Syndrome	Senior-Loken Syndrome
Trisomy-13	Alstrom Syndrome
Smith- Lemli- Opitz Syndrome	Zellweger Syndrome
7-Dehydrochlesterol Gama-Reductase	Hepatic Dysfunction
Cholestatic Liver	Joubert Syndrome Nephronophthisis (NPHP)

The incidence of this rare syndrome is 1 per 1300 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. Chances of MGS in subsequent pregnancies are 1 in 4 (25%).<sup>[3]</sup>

MGS is an extremely heterogenous syndrome; six different loci have been identified. MKS 1 was mapped to chromosome 17q21-q24, in Finnish population. The tissue expression of this gene was reported mainly in the brain, liver, kidney and cartilage of the developing digits. MKS2 is mapped to chromosome 11q13. This locus is commonly observed in North Africa and Middle East. MKS3 is mapped to 8q 24, which is having expression in the adrenal gland, brain, kidney, lung and spinal cord explaining the rarity of polydactyly in MKS3.<sup>[4]</sup>

The diagnostic criteria for MGS (MKS) are the presence of at least two of the classic features of cystic renal dysplasia, occipital encephalocele and polydactyly, which is 100%, 90% and 83.3% respectively.<sup>[5,6]</sup> MGS is a condition characterized by ciliopathies caused by dysfunction of cilia.

The anomalies observed in MGS are as follows; in central nervous system: Occipital encephalocele, hydrocephalus, microcephaly, anencephaly, absence of olfactory lobes and tract, holoprosencephaly, cerebellar hypoplasia, Dandy–Walker malformation or Arnold–Chiari malformation, schizencephalic and agenesis of corpus callosum.

Face: Cleft lip and cleft palate, microphthalmia, micrognathia, epicanthic folds, hypo/hypertelorism nasal anomalies, mouth: Lobulated tongue, cleft epiglottis, neonatal teeth.

Skeletal: Polydactyly, short limbs, talipes, bell-shaped thorax, syndactyly, club foot, clinodactyly.

Cardiovascular system: Atrial septal defect, coarctation of an aorta, pulmonary stenosis, Respiratory system: Hypoplasia of lungs, ventricular septal defects, patent ductus artery, microphthalmia, short neck and cryptorchidism.

Renal system: Polycystic kidneys, cystic dysplasia, renal hypoplasia, horseshoe kidney, double ureter, liver: Hepatic fibrosis, ductal agenesis, portal fibrosis, genital system: Hypoplasia, ambiguous genitalia, hermaphroditism, cryptorchidism.

Others: Malrotation of the gut, accessory spleen, omphalocele, imperforate anus, adrenal agenesis, enlarged placenta and single umbilical artery.<sup>[7]</sup>

In MGS, most infants are stillborn or die within few hours or days after birth. Review of literature reveals only ten neonates surviving beyond birth.<sup>[8]</sup> According

to Ramadan, there is one report of a long survivor who died at the age of 28 months.

The MKS can be diagnosed by ultrasonography (USG) done at 11-14 weeks of gestational age and by estimation of  $\alpha$ -fetal protein in maternal serum (MSAFP also known as  $\alpha$ -1 fetoglobulin or  $\alpha$ -fetal protein). USG diagnosis of MKS can be done as early as the first trimester at 10-11 week's gestation with demonstration of polydactyl and an encephalocele. Although in many cases of MKS oligohydramnios (secondary to renal abnormality) may complicate the diagnosis. It is the protein that is encoded by AFP gene located on the q-arm of chromosome in humans. It is produced by the yolk sac and liver during fetal development.

## CONCLUSION

MGS is a rare autosomal recessive condition and is mostly results in neonatal death or intrauterine death within few hours of life lethal. Counseling forms an integral part of the management especially about the recurrence risk of subsequent pregnancies. Our aim of this review is to enhance the knowledge and spread awareness about this rare and lethal anomaly.

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**How to cite this article:** Uma P, Usha P, Sushma J, Sarkar RN. Meckel-Gruber Syndrome Fatal Disorder - A Rare Case Report with Review of Literature. *Int J Dent Med Spec* 2015;2(1):14-17.

**Source of Support:** None; **Conflict of Interest:** None