The Case of Recurrent Lethal Fetal Syndrome: Meckel–Gruber Syndrome

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ABSTRACT
Meckel–Gruber syndrome (MGS), a rare lethal syndrome, is characterized phenotypically by polycystic kidneys, occipital encephalocele, and postaxial polydactyly. This entity with 100% fatality has autosomal recessive transmission with multiple gene loci. Mutation analysis is the confirmatory test to label a case as MGS. However, two of the three above-mentioned anomalies are sufficient to arrive at a working diagnosis of MGS. We report a case of MGS in a family with a history suggestive of multiple affected fetuses previously. Early diagnosis at 13 weeks gestation was made on antenatal ultrasound examination and the findings were confirmed on postabortal autopsy.

Keywords: Autosomal recessive, Consanguinity, Meckel–Gruber syndrome, Occipital encephalocele, Polycystic kidneys, Postaxial polydactyly.

CASE REPORT
A 25-year-old second gravida with a history of pregnancy termination at 22 weeks of gestation in view of multiple congenital malformations in the fetus, which included occipital encephalocele, microcephaly, bilateral multicystic dysplastic kidneys, and anhydramnios, visited antenatal clinic at 7 weeks of gestation. In view of the above history, an early anomaly scan was done. The scan showed a single viable 13 weeks fetus with multiple malformations similar to those seen in the first pregnancy, i.e., occipital encephalocele (Figs 1 to 3), microcephaly, and enlarged, hyperechoic polycystic kidneys (Fig. 4). Liquor was adequate, but fetal urinary bladder was not visualized. Polydactyly was not appreciated in hands and feet. The mother denied having taken any medications other than folic acid.

These phenotypic abnormalities prompted the diagnosis of MGS. Because of the condition being incompatible with life, patient opted for discontinuation of pregnancy and consent for a 2nd trimester medical termination of pregnancy using mifepristone–misoprostol regimen was sought. The aborted fetus weighed 60 gm, and a defect in the occipital bone with outpouching of
meninges and part of brain parenchyma forming occipital encephalocele was seen. Examination of the spine revealed no obvious malformation. Autopsy revealed bilateral multicystic enlarged kidneys and so the diagnosis was almost certain.

History revealed that patient’s sister underwent pregnancy termination at 26 weeks gestation for similar fetal anomalies 10 months back. Diagnosis was not arrived at in that pregnancy because of the malformation being considered sporadic. Both the sisters have first-degree consanguineous marriage, married to their paternal first cousins.

Pedigree analysis (Fig. 5) further revealed that paternal uncle’s wife also had two 3rd-trimester abortions with gross occipital encephalocele in the fetuses. No medical attention was sought and autopsy was not performed, so the status of the kidneys stayed undiscovered; nonetheless, the diagnosis of MGS cannot be ruled out.

DISCUSSION

Meckel–Gruber syndrome is a rare genetic autosomal recessive disorder with both genders being equally affected; it has an incidence varying from 1 in 13,250 to 1 in 140,000 live births,\(^2\) with Belgian (1 in 3,500) and Finnish population (1 in 9,000)\(^3\) being worst affected. Young et al\(^4\) reported an incidence of 1 in 1,300 live births in Leicestershire Gujarati Indians, though not supported by any Indian study. So far only 200 cases of the syndrome have been reported in medical literature.

Genetic heterogeneity with at least 12 different gene loci mapped over different chromosomes (MKS1–MKS12) typifies the condition. MKS1 (17q21–q24) is
more prevalent in Finnish and European population, whereas MKS2 (11q13) runs in Middle East and Northern African families. MKS3 (8q22.1) is common in Asian population. Polydactyly is less common in MKS3 compared with MKS1.5

Diagnostic triad of MGS includes cystic kidneys (100%), a central nervous system (CNS) malformation; most commonly occipital encephalocele (90%) and polydactyly, mostly postaxial (60–80%).6 Presence of two of these three phenotypic anomalies is sufficient to label the case as MGS.

Renal cysts probably originate from collecting ducts and lead to gross enlargement of the kidneys (may be 10–20 times the normal size). Deranged renal function leads to oligoamnios and pulmonary hypoplasia, which has been proposed as the main cause of death in this syndrome.

Microcephaly with a sloping forehead and occipital meningoencephalocele is the typical CNS malformation. The encephalocele is not a neural tube closure defect but results from an apical defect of the occipital bone through which varying volume of brain parenchyma and meninges herniate.

Fibrocystic change of the liver is another constant finding seen as portal fibrosis, bile duct dilatation, reactive bile duct proliferation, hepatic cysts, and portal fibrous vascular obliteration.1 Multitude of anomalies that may be associated with MGS include cleft lip and palate, ambiguous genitalia, cardiac septal defects, gastrointestinal anomalies like omphalocle, and CNS abnormalities like agenesis of corpus callosum, Dandy–Walker cyst, and Arnold–Chiari malformations.2

The role of early prenatal diagnosis lies in the fact that the condition being 100% fatal needs termination of pregnancy. However, there is one report of survival up to 28 months.8 Since the syndrome has been reported mostly in the 2nd and 3rd trimester of pregnancy, it makes the 11 to 14 weeks ultrasonography a potential diagnostic tool for early diagnosis, provided a thorough systemic evaluation is performed routinely.9 Virtually, the diagnosis of MGS is easier at this gestation before the oligoamnios sets in due to the renal malformation when the encephalocele and polydactyly can be difficult to recognize in the setting of oligohydroamnios. Role of chorionic villi sampling or cordocentesis is only to make molecular diagnosis.

Meckel–Gruber syndrome needs to be differentiated from trisomy 13, autosomal dominant polycystic kidney disease, and autosomal recessive Smith–Lemli–Opitz syndrome.2 Chromosomal analysis will help establish the diagnosis when in doubt.

Unfortunately, the diagnosis was not made in the previously affected fetuses that were just terminated in view of lethal anomalies. Had the diagnosis been arrived at, genetic counseling regarding recurrence risk and early diagnosis could have been done. The option of in vitro fertilization and (PGD) could also have been provided.

Although the risk of having an affected fetus with MGS is only 25%, the present family we report has been unfortunate to have three affected fetuses in the same family within a span of 1 year.

Future options for the family include waiting for that 75% chance of having an unaffected child. Preimplantation genetic diagnosis is another option that has recently been used for primary prevention of MGS.10 However, to make use of PGD, it is important to first identify the locus of the gene mutation at the DNA level in the index case. Also, it is a costly option and not readily available in low-resource settings. Because of lack of facilities, we were not able to perform mutation analysis in our patient.

CONCLUSION
Prenatal diagnosis of bilateral enlarged multicystic kidneys should alert us for MKS and prompt a thorough investigation of CNS malformations and polydactyly. A detailed family history and thorough prenatal ultrasonographic evaluation are essential in diagnosing MGS. In pregnancy complicated by MGS, counseling forms an integral part of the management, especially about the fetal prognosis and recurrence risk in subsequent pregnancies.

Though neonatal autopsy and genetic studies are the diagnostic gold standards, detecting two of the above-mentioned three major anomalies in the fetus is also sufficient to arrive at the diagnosis in the clinical setup.

REFERENCES