Introduction

Meckel Gruber syndrome (MKS) is a lethal, autosomal, recessive, multisystemic disorder, associated with mutations affecting ciliogenesis. In 1822, Johann Friedrich 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. Since the time it was first reported; only 200 cases have been reported. From January 2004 to December 2010, we evaluated 268 fetal autopsies in our institute in the Department of Pathology; two of these fetuses were diagnosed as MKS.

Case History

In the first case, a 26-year-old patient, with 17 weeks of gestation, decided to terminate the pregnancy after ultrasonography (USG) revealed a single fetus with microcephaly and occipital meningoencephalocele and occipital meningoencephalocele [Figures 1a and b]. There was second-degree consanguinity. She was not on teratogenic drugs. The female fetus weighing 95 g was sent for autopsy. On examination the fetus showed occipital meningoencephalocele [Figures 2a], along with low set ears, microcephaly, absence of forehead, hypertelorism, large protruding eyes, a large nose, and a short neck. There was postaxial polydactyly [Figure 3a].

The second case was of a 35-year-old female patient, with 20 weeks of gestation. Ultrasonographic examination revealed a single intrauterine pregnancy, with meningoencephalocele and polycystic kidneys with reduced liquor. There was no history of consanguinity or teratogenic drugs. The pregnancy was terminated and a female fetus delivered, weighing 540 g, which was sent for autopsy. On examination, the fetus showed occipital meningoencephalocele [Figure 2b] measuring $3 \times 2.5 \times 2$ cm. The bilateral kidneys were large lobulated and cystic [Figure 3b]. Both lungs were hypoplastic. Microscopically, the kidneys showed features of cystic renal dysplasia and the liver showed perportal fibrosis [Figures 4a and b].

In both cases, the diagnosis of MKS was confirmed after autopsy. In both cases the parents did not give consent for molecular analysis, but were re-counseled for future pregnancies.

Discussion

MKS is characterized by occipital meningoencephalocele, cystic kidneys, postaxial polydactyly, and fibrosis in the liver. The worldwide incidence of MKS varies from 1/140,000 (Great Britain) to 1/3500 (North Africa) in live births. A higher incidence is recorded in Gujarati Indians.

Address for correspondence: Dr. Aneel Myageri, Department of Pathology, SDM College of Medical Sciences and Hospital, Sattur, Dharwad, Karnataka, India. E-mail: leenamyageri@gmail.com
Belgians, Bedonins. The male-to-female ratio is equal. MKS shows genetic heterogeneity. Six genetic loci were identified
for MKS. They are MKS1, on 17q21-24, in Finnish and Caucasian people; MKS2, on 11q13, in the Middle East and North African families and MKS3, on 8q24, in Pakistan and Northern India.[6,7]

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.[4-7] In our first case occipital meningoencephalocele with polydactyly and other associated anomalies were present, but the kidneys were normal. In the second case there were occipital meningoencephalocele, bilateral polycystic kidneys, and fibrotic changes in the liver, but polydactyly was absent. Although postaxial polydactyly is a feature described in MKS, it is seen only in 80% of the cases.[9]

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.[2,9]

The differential diagnosis of MKS includes Bardet-Biedl syndrome (BBS), Trisomy 13, and Smith-Lemli-Opitz syndrome. CNS anomalies are not seen in BBS, whereas, karyotype analysis will be abnormal in Trisomy 13. In MKS cases the karyotype is normal. In the Smith-Lemli-Opitz syndrome, due to mutations and deficiency of 7-dehydrocholesterol reductase, hepatic dysfunction and cholestatic liver disease are seen.[3,10]

The 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. Sometimes, the alpha fetoprotein level is not elevated when the encephalocele contains a closed sac. When available, autopsy and genetic analysis are gold standard for diagnosis.[9]

The MKS results in 100% fetal or neonatal mortality. As MKS has a high risk (25%) of recurrence; parents should be counseled for future pregnancies.[4-9]

Birth defects often pose a diagnostic and management challenge. So, preventive measures should start at the primary health care (PHC) level. PHC providers should give preconception care, to ensure the optimal physical and mental well-being of women, to increase the likelihood of a normal pregnancy. The timely identification of a family risk of birth defects is necessary. Such services include prenatal screening and diagnosis for birth defects, selective termination of pregnancy, and the availability of counseling services. Care and support should always be given by the primary health care provider, with assistance from the medical genetic specialist or other specialists, when needed.

**Conclusion**

The MKS has a high recurrence risk. PHC providers should use a methodical approach for birth defects, to allow accurate diagnostic and recurrence risk counseling, informed management decisions, and the apt provision of medical resources. Although improved prenatal testing has increased the detection of fetal abnormalities, an autopsy remains valuable, as it provides morphological confirmation.

**References**

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