PRENATAL DIAGNOSIS OF MECKEL-GRUBER SYNDROME: A CASE REPORT◆

(Meckel-Gruber Sendromu'nun Prenatal Tanısı: Olgu sunumu)

Banu Dane, Cem Dane, Salih Dural, Ahmet Çetin, Murat Yayla

Summary

Meckel-Gruber syndrome, is an autosomal recessive disorder characterized by the triad of occipital encephalocele, polycystic kidneys with cystic renal dysplasia, postaxial polydactyly, and sometimes ductal plate malformation of the liver. In our case, the pregnancy was terminated, after the fetus had demonstrated the evidence of bilateral enlarged kidneys, occipital encephalocele, polydactyly, in the sonographical evaluation at the 20th gestational week. Because the Meckel-Gruber syndrome is a recessive disease, such mothers should be warned about a 25 % risk of having an affected fetus in every pregnancy.

Key words: Meckel-Gruber syndrome, prenatal diagnosis, ultrasound

Özet

Meckel-Gruber sendromu, oksipital ensefalosel, kistik renal displaziyle birlikte polikistik böbrekler, postaksiyal polidaktili ve bazende karaciğerde duktal plate malformasyonu ile karakterize otozomal ressesif geçişli bir hastalıktır. Bizim vakamızda, gebeliğinin 20. haftasında yapılan ultrasonografide polidaktili, oksipital ensefalosel ve bilateral genişlemiş böbrekleri saptanan hastaya gebelik sonlandırılması yapılmıştır. Meckel-Gruber sendromu, ressesif geçişli hastalık olduğu için böyle çocuk doğurmuş kadınlar sonraki olası gebeliklerdeki yüksek risk (% 25) açısından uyarılmalıdır.

Anahtar kelimeler: *Meckel-Gruber sendomu, prenatal tanı, ultrasonografi*

**** Haseki Education & Research Hospital Department of Gynecology & Obstetrics Istanbul, Turkey***

◆ This study was presented in the V. International Congress of the Turkish-German Gynecological Association in May 2003, Antalya-Turkey.

BACKGROUND

Meckel-Gruber syndrome is a rare and lethal autosomal recessive disorder characterized by occipital encephalocele, postaxial polydactyly and bilateral dysplastic cystic kidneys. It can be associated with many other conditions. Meckel-Gruber syndrome may demonstrate variation in phenotypic expression. The condition is usually diagnosed ultrasonographically in the second trimester. Finding of at least two of the three features of the classical triad, in the presence of normal karyotype makes the diagnosis.

CASE REPORT

A twenty-five-year-old woman with 20 weeks amenorrhea was referred for a second trimester ultrasonogram to detect fetal anomalies. The reason for referral was the detection of encephalocele by her obstetrician. This was her first pregnancy and there wasn't history of consanguinity. The ultrasound scan revealed bilateral enlarged cystic kidneys, occipital encephalocele, six digits (Fig.1, 2). There was oligohydramnios and the fetal urinary bladder was not visualized. The pregnancy was terminated. Post-mortem examination of the fetus revealed a large abdomen, a head with occipital encephalocele, bilateral clubfeet and six digits in all the four limbs (Fig.3). Autopsy revealed bilateral large cystic dysplastic kidneys. Urinary bladder and both ureters were identified. The outer surface of the kidneys was swallowed and cut section showed multiple cysts varying in size from 0.5 to 1.5 cm involving the cortex and medulla. More than 90 % of the parenchyma was filled with cysts. The pelvicalyceal system was poorly demarcated. Histologic evaluation of the liver revealed biliary dysgenesis with elongated, elliptical bile ductules with portal fibrous septa. Portal connective tissue was increased. The liver was showing broad band of fibrous tissue encircling portal triad. In cranium examination, a dural sac covered the protruding central nervous system structures.

Figure 1. *Ultrasonography revealed bilateral enlarged cystic kidneys*

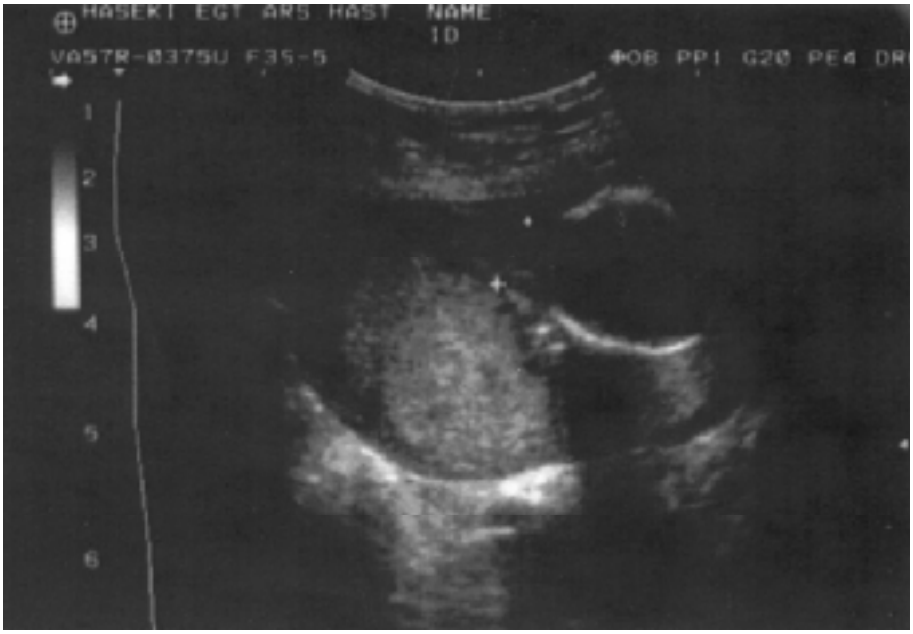


Figure 2. Ultrasonography showed occipital encephalocele

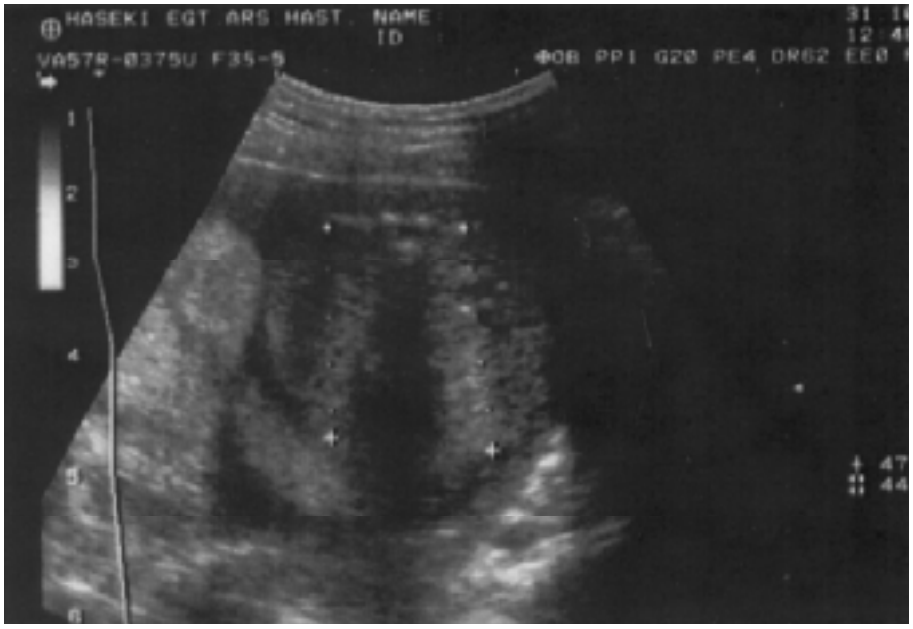
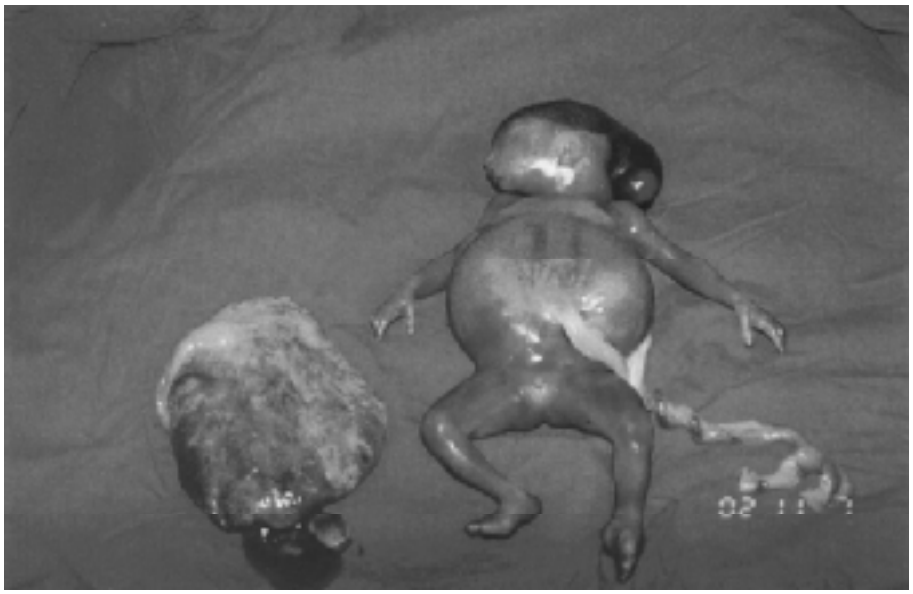


Figure 3. Post-mortem examination of the fetus



DISCUSSION

This syndrome is also known as dysencephalia splanchnocystica, Meckel syndrome (used in English literature), and Gruber syndrome (used in the European literature), Meckel-Gruber syndrome [1,2]. The incidence is not precisely known. According to different authors, the incidence of Meckel Gruber syndrome varies between 0.07-1.1:10,000 live births [3]. It is also estimated that this syndrome corresponds to 5% of all neural tube defects [4]. It is an autosomal recessive disorder with a recurrence risk of twenty-five percent. Locus heterogenecity has been demonstrated by the mapping of the MKS1 locus to 17q21-24 in Finnish kindred's, MKS2 to 11q13 in North African-Middle Eastern cohorts, and a third MKS locus (MKS3) to chromosome 8q24. Comparison of the clinical features of MKS3-linked cases with reports of MKS1 - and MKS2-linked kindred suggests that polydactyly (and possibly encephalocele) appear less common in MKS3-linked families [5]. Although some cases of Meckel syndrome have normal amniotic fluid, the first sonographic finding in most cases is oligohydramnios, due to renal dysfunction, and it develops early in the second trimester. The concurrence of oligohydramnios and bilateral severe renal anomalies should initiate a search for other anomalies indicative of the Meckel-Gruber syndrome. The reported incidence of renal disorder in this syndrome varies from 95% to 100%. The kidneys have initially microscopic cysts that develop destroying the parenchyma and enlarging the organ up to 10 or 20 times. The primary renal abnormality appears to be failure of the metanephric duct and renal blastema to interact. The kidneys, therefore, show little corticomedullary differentiation and the nephrons are severely deficient, causing enlargement of the kidneys. Thin-walled cysts appear throughout the parenchyma. An early normal sonogram in a family at risk for recurrence, does not exclude Meckel syndrome. A follow-up scan at 20 weeks of gestation is recommended. Occipital encephalocele is present in 60% to 80%. Maternal serum or amniotic fluid a-fetoprotein level may be normal, as a membrane may cover the cephalocele. Post-axial polydactyly is present in 55% to 75% [6]. Other limb anomalies such as bowing and shortening may also be present. Various possible anomalies associated with this syndrome are described by different authors. In some situations, such a wide phenotypic variation makes the recognition of the disease more difficult. In a review of the pathologic findings in 9 cases, Blankenberg concluded that a hepatic lesion is a consistent feature: arrested development of the intrahepatic biliary system at the stage of biliary cylinders with varying degrees of reactive bile duct proliferation, bile duct dilatation, portal fibrosis, and portal fibrous vascular obliteration [7]. Hepatic lesions can be considered one of the hidden abnormalities of MKS since they are visible only during postmortem examination. An arrest of development occurs at the stage of bilaminar plates, which atrophies during normal development. In MKS, the plates do not atrophy and prevent reorganization by the remaining biliary cells to form tubular ducts. The resultant fibrosis can be so severe as to occlude portal veins. Dandy-Walker malformation was detected by several cases. Al-Gazali et al. suggested that Dandy-Walker malformation should be added to the list of brain defects in Meckel syndrome [8]. Meckel syndrome is a lethal disorder. Most infants are stillborn or die in hours or days after birth. A few sometimes survive a few months with poor quality of life. According to Ramadani, there is one report of a long survivor who died at the age of 28 months [9]. In 1995, Paavola reported another atypical case of a long survivor who died at 18 months of life [10].

A karyotype study should be obtained when Meckel syndrome is suspected, to exclude chromosomal disorders. The differential diagnosis will depend on the type of the associated anomalies. Due to several sonographic similarities between these conditions, trisomy 13 must be excluded by karyotype. Another possible differential diagnosis is autosomal dominant polycystic kidney disease. If the diagnosis is made before viability, termination can be offered. When the family decides to continue the pregnancy, or if the diagnosis is made after viability, the standard obstetrical management is not altered.

REFERENCES

1. Buyse ML. Birth Defects Encyclopedia, 1st.edn. Massachusetts. USA; Blackwell Scientific Publication, 1990: 1541-1542.

2. Altmann P, Wagenbichler P, Schaller A. A casuistic report on the Gruber or Meckel syndrome. ***Hum Genet*** 1977; 38: 357-62.

3. Salonen R, Norio R. The Meckel syndrome in Finland: epidemiologic and genetic aspects. ***Am J Med Genet*** 1984; 18: 691-8.

4. Nyberg DA, Hallesy D, Mahony BS. Meckel - Gruber syndrome; importance of prenatal diagnosis. ***J Ultrasound Med*** 1990; 9: 691-6.

5. Morgan NV, Gissen P, Sharif SM. A novel locus for Meckel-Gruber syndrome, MKS3, maps to chromosome 8q24. ***Hum Genet*** 2002; 111: 456-61.

6. Weinstein BJ, Benacerraf BR. Meckel syndrome, first trimester diagnosis. ***Fetus,*** 1994; 5: 4.

7. Blankenberg TA, Ruebner BH, Ellis WG, Bernstein J, Dimmick JE. Pathology of renal and hepatic anomalies in Meckel syndrome. ***Am J Med Genet*** (Suppl) 1987; 3: 395-10.

8. Al-Gazali LI, Abdel Raziq A, Al-Shather W, Shahzadi R, Azhar N. Meckel syndrome and Dandy Walker malformation. ***Clin Dysmorph*** 1996; 5: 73-6.

9. Ramadani HM, Nasrat HA. Prenatal diagnosis of recurrent Meckel syndrome. ***Int J Gynecol Obstet*** 1992; 39: 327-32.

10. Paavola P, Salonen R, Weissenbach J, Peltonen L. The locus for Meckel syndrome with multiple congenital anomalies maps to chromosome 17q21-q24. ***Nat Genet*** 1995; 11: 213-5.