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Meckel-Gruber Syndrome: A Report of Three Cases

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Abstract

Objective: We aimed to present three rare cases of MeckelGruber syndrome, the diagnosis of which was made prenatally by ultrasonographic examination of the fetuses.

Case: Three pregnancies which were diagnosed prenatally to have occipital encephalocele, postaxial polydactily and bilateral multicystic dysplastic kidney were terminated. In autopsy, they were identified as MeckelGruber syndrome.

Conclusion: MeckelGruber syndrome is a rare, lethal, autosomal recessive multisystemic disorder. This syndrome is characterized by central nervous system defects, cystic renal dysplasia, and ductal proliferation in the portal area of the liver and postaxial polydactily. The signs of the syndrome can be detected during the routine ultrasonographic examination between 1114th weeks of the pregnancy. Because of high rate of recurrence risk (25), patients should be closely followed in future pregrancies.

Keywords: Fetal anomaly, Meckel Syndrome, prenatal diagnosis.

Meckel-Gruber Sendromu: üç olgunun sunumu

Amaç: Seyrek görülen üç MeckelGruber Sendromu olgusunu yeni bilgiler ışığında sunmak.

Olgu: Prenatal dönemde ensefalosel, bilateral polikistik böbrek ve polidaktili saptanan üç olguda gebelik sonlandırıldı. Otopsi sonucu MeckelGruber Sendromu tanısı kondu.

Sonuç: MeckelGruber sendromu otozomal resesif geçiş gösteren letal multisistemik bir hastalıktır. Santral sinir sisteminin gelişimsel anomalileri, kistik displastik böbrekler, hepatobilier duktal plate malformasyonu ve postaksiyal polidaktili gibi bozukluklarla karakterizedir. Gebeliğin 11-14. haftalarında yapılan rutin ultrasonografik tarama ile MKS tanısı konulabilir. 25 tekrarlama riski nedeni ile olgular sonraki gebeliklerinde yakın takip gereklidir.

Anahtar Sözcükler: Fetal anomali, Meckel Sendromu, prenatal tanı.

Introduction

Meckel-Gruber syndrome (MKS) is a lethal, autosomal recessive multi-systemic disorder. Cystic renal dysplasia, and ductal plate malformation characterized by ductal proliferation and fibrosis in the portal area of the liver are classical findings. In fetuses, occipital meningoencephalocele and postaxial polydactily are found by 90% and 80% respectively.[1] From 2005 to September 2010, 233 fetuses were evaluated at Department of Pathology and 3 of these fetuses were diagnosed as MKS.

Case

All the cases were fetuses with abnormal prenatal findings detected and terminated during the routine ultrasonographic examination.

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Gestational age was between 16 to 18 weeks. In two cases, there was first and in one case third degree consanguinity. There were occipital encephalocele, postaxial polydactily and bilateral multi-cystic dysplastic kidney in the all the cases (Figure 1A, 1B, 2A, 2B). In one case, micrognathia (Figure 1A) and in another one bowing of long tubular bones (Figure 2C) were observed. Kidney and liver findings were similar. In kidney sections of fetuses, cysts of various sizes were found (Figure 3A). A stroma of loose mesenchyme was located between the cystic lesions. The epithelial lining of the cysts wall was cubical or flattened. Primitive glomerular structures were detected in the renal cortex (Figure 3B). In the liver section, fibrosis and proliferation of the bile ducts in the portal area were noted (Figure 3C). In encephalocele sac section, immature neuroglia tissues were detected. Detailed findings are shown in Table 1.

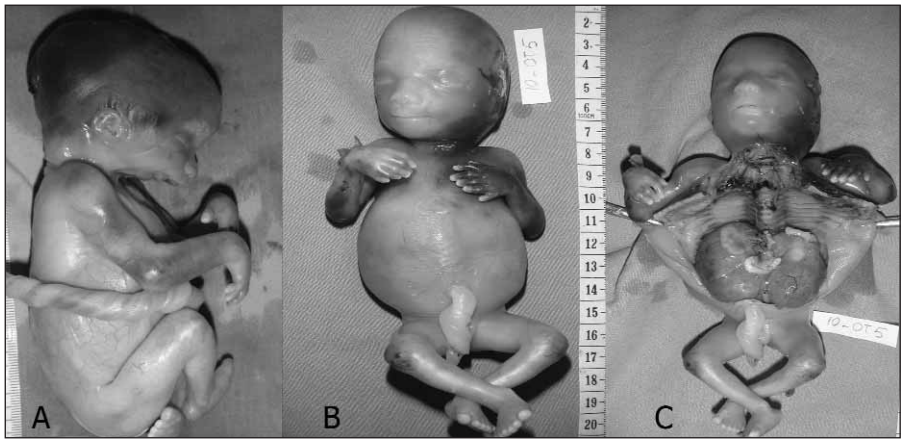

Figure 1. **A**; Case 1; Meckel Gruber Syndrome, Polydactyly, micrognathia, encephalocele sac, abdominal distantion. **B**; Case 2; Meckel Gruber Syndrome, Polydactyly, abdominal distantion. **C**; Case 2; Bilateral large, multicyctic kidneys.

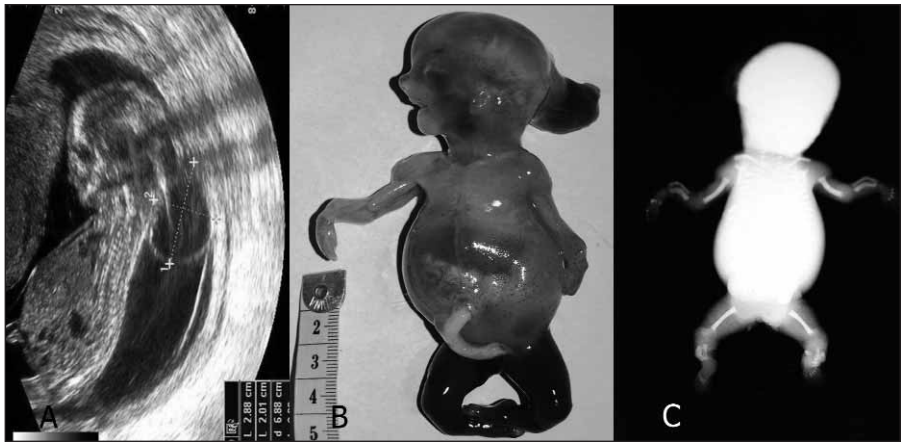

Figure 2. **A**; Case 3; Meckel Gruber Syndrome, USG findigs. **B**; Case 3; Polydactyly, abdominal distantion, bowing of long tubular bones. **C**; Case 3; X-Ray findings.

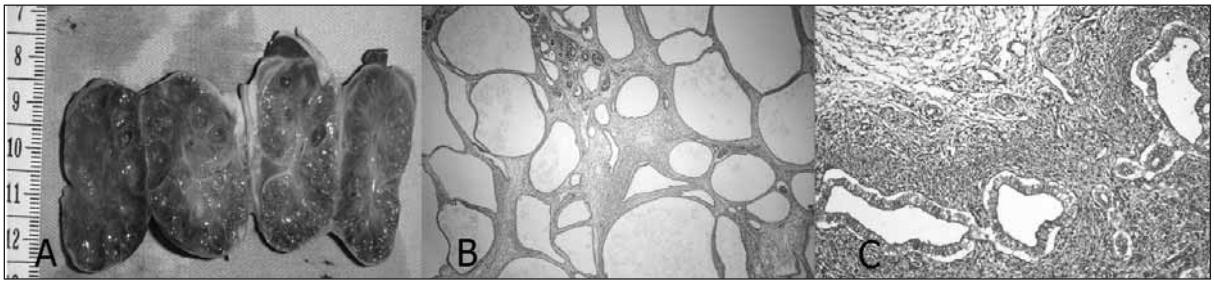

Figure 3. **A**; Gross appearance of bilateral multi-cystic dysplastic kidneys. **B**; Microskopic appearance of multi-cystic dysplastic kidneys. **C**; Microskopic appearance of bile duct proliferation and hepatic fibrosis (ductal plate malformation) in the liver.

Table 1. Findings about three Meckel-Gruber syndrome cases detected during prenatal period.

	Age of mother	Consanguinity	Sex of fetus	Prenatal findings	Autopsy findings
Case 1	21	3st degree	Male 1st pregnancy	18 week fetus, Bilateral cystic kidney and oligohydramnios	17 week fetus, Polydactily, micrognathia, bilateral multi-cystic dysplastic kidney, encephalocele, and ductal plate malformation of the liver
Case 2	26	1st degree	Female 1st pregnancy	16 week fetus, Growth retardation, Bilateral cystic kidney and encephalocele	15 week fetus, Polydactily, bilateral multi-cystic dysplastic kidney, encephalocele, and ductal plate malformation of the liver
Case 1	29	1st degree	Male 3rd pregnancy 1 abortion 1 alive	18 week fetus, Bilateral cystic kidney and encephalocele	18 week fetus, Polydactily, bowing of long tubular bones, bilateral multi-cystic dysplastic kidney, encephalocele, and ductal plate malformation of the liver

Discussion

In Meckel-Gruber syndrome, in addition to classical findings, various anomalies have also been reported. These anomalies include such central nervous system as microcephaly, cerebellar hypoplasia, and ventriculomegaly; heart malformations such as patent ductus arteriosus and atrial septal defect; internal and external genital anomalies like ovarian agenesis, bicornuate uterus, and genital ambiguity; urinary system anomalies such as horse-shoe kidney, missing ureters, and hypoplastic urinary bladder; and other anomalies like simian line, shortening and bowing of long tubular bones, cleft lip/palate, papillomatosis and fissure of tongue, atypical face with short nose and low-set ears.[1-5] The findings obtained as regards MKS are presented in Table 2. MKS is precisely diagnosed with the presence of two classical findings or two other anomalies in addition to one classical finding. Classical findings were detected in all of our cases. In the diagnosis of MKS cases, fibrosis and bile duct proliferation in the portal area of the liver are of high importance. Compared to healthy fetus liver, in MKS cases, increased microfibroblastic cells around bile ductules in the portal area were also identified. In experimental animals, fibroblastic cells around bile ducts in the portal area are trans-

Table 2. Most frequent manifestations in Meckel-Gruber syndrome.

Genitourinary	**Cystic kidney dysplasia** (100%) External/internal genital and ureter anomalies
Hepatobiliary	**Bile duct proliferation, hepatic fibrosis and cysts** (ductal plate malformation) (100%)
CNS	**Occipital meningo-encephalocele** (90%) Dandy-Walker malformation Arnold-Chiari malformation Agenesis of the corpus callosum Anencephaly Cerebral/cerebellar hypoplasia
Skeletal	**Postaxial polydactily** (80%) Shortening and bowing of long tubular bones
Other	Heart malformations Cleft lip/palate Micrognathia Microphtalmia

formed into myofibroblastic cells, causing bile duct ligation. The distribution of the myofibroblastic cells in the tissue remodeling MKS partially resembles that of bile duct ligation or unusual liver damage.[6] The worldwide incidence of the disease varies from 1/140,000 (Great Britain) to 1/3500 (North Africa) in live births.[1] In our province, the average annual birth rate is 29.584.[7] In our 5-year study, 3 MKS cases were diagnosed. The prevalence of MKS in our province is 1/49,300 births. Most of pregnancies with MKS fetuses end with death. It is possible to detect and diagnose MKS by ultrasound examination at 11th to 14th weeks of gestation. In later pregnancies, oligohydramnios might make it increasingly more difficult to establish the diagnosis by ultrasound only.[8] The earliest diagnose was made at 12th gestational week.[9] However there are few cases who lived 7 and 9 months after a term delivery.[4,10] Pregnancies with MKS fetuses may be associated with an elevated maternal serum α-fetoprotein level and an abnormal screening test. In some MKS cases, fetal serum α-fetoprotein levels might increase.[11] MKS show genetic heterogeneity. Recently, many genes have been established to be associated with the formation of MKS. Three of these reported genes are loci, i.e., MKS1 on 17q21-q24, MKS2 on11q13 and MKS3 on 8q24.[1] Whereas MKS1 is identified in Finnish and Caucasian people, MKS2 is found in families from the Middle East and North Africa, and MKS 3 in families from Pakistan and Northern India.[1,12] In a study carried out by Frank et al, 25 MKS cases were evaluated from different countries, including 9 cases from Turkey. MKS1 mutated gene was identified in 4 of the 9 cases from our country, and the other 5 cases were found to have no connection with gene defects.[1] In some studies on genotype-phenotype correlation, compared to MKS1, in MKS3, postaxial polydactily is rarer.[1] MKS1 gene is associated with ciliated function in the cell. Ciliary dysfunction is associated with MKS1.[1] Differential diagnosis for MKS includes Bardet-Biedl syndrome (BBS), trisomy 13, and Smith-Lemli-Opitz syndrome. BBS is characterized by obesity, hypogonadism, learning difficulty, progressive retinal dystrophy, and postaxial polydactily. Renal pathologies are similar in MKS and BBS, but CNS anomalies and proliferation of the bile ducts in the portal area are not observed in BBS.[1,8] In trisomy 13, polycystic kidneys (15-30%), hydronephrosis, horseshoe kidneys, and duplicated ureters can be observed. Trisomy 13 can be diagnosed through central system abnormalities such as holoprosencephaly. In addition, cardiovascular malformations, ocular anomalies, heterotopic pancreatic or splenic tissues, and postaxial polydactily can also be identified, but trisomy 13 does not have hepatic fibrosis. Karyotype analysis is important in differential diagnosis of MKS cases from trisomy 13.[8] In MKS cases, karyotype is normal.[3] In our case, abnormal karyotype was not detected. The final diagnosis was made through autopsy. In differential diagnosis, another pathology to be considered is Smith-Lemli-Opitz syndrome, an autosomal recessive disorder, which is characterized by such central nervous system anomalies as microcephaly, cerebellar hypoplasia, and ventriculomegaly; genito-urinary system anomalies such as genital

ambiguity, hydronephrosis, renal cystic dysplasia, adrenal duplication; and postaxial polydactily of hands but less often of feet. In this syndrome, there are mutations and deficiency of 7-dehydrocholesterol gama-reductase (DHRC7). Hepatic dysfunction and cholestatic liver disease are found in this syndrome.[8]

Conclusion

MKS has a high risk of recurrence (25%). It is important to examine pregnancies with anomaly fetus histories. For certain diagnosis, autopsy must certainly be done and families should be informed about the possible risks. Early (11-14th weeks) ultrasonographic examination must be suggested for the following pregnancies.

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