Meckel Gruber Syndrome: Correlation Between Prenatal Diagnosis and Autopsy Findings

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OBJECTIVE: To analyze prenatal sonographic anomalies detected in fetuses with Meckel Gruber syndrome (MGS), and to correlate these anomalies with autopsy findings.
STUDY DESIGN: In a 4-year long prospective study, ultrasound findings were compared with fetal autopsy findings in eight fetuses with MGS out of 107 second-trimester termination of pregnancy (TOP) cases due to fetal malformation diagnosed by second trimester-ultrasound examination at a tertiary referral center.
RESULTS: Eight prenatally diagnosed fetuses with MGS were analyzed. Seven cases had classical clinic triad. One case had only polycystic kidneys and polydactyly. Fetal autopsy confirmed all prenatally diagnosed findings associated with MGS; fetal examination added polydactyly in two prenatally undiagnosed cases. Hepatic lesions were found in four cases which were determined during the histologic examination.
CONCLUSION: Ultrasonographic findings of MGS allow for diagnosis of the most cases. However autopsy may be valuable for confirmation of the diagnosis and to evaluate the recurrence risk in future pregnancies.

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Key Words: Meckel Gruber syndrome, Prenatal ultrasound, Fetal autopsy

Introduction

Meckel Gruber syndrome (MGS) was first described in1822 by Meckel and thereafter in 1934 by Gruber.[1,2] The worldwide incidence of MGS varies from 1/13250 to 1/140000 live births. MGS is more common in Belgian (1/3000) and Finish (1/9000) populations.[3]

The syndrome characterized by the renal cystic dysplasia, occipital encephalocel, and postaxial polydactyly. There should be at least two of three classic manifestations in most of cases.[3,4] The syndrome is generally associated with ductal plate malformations in the liver.[5] Associated abnormalities including central nervous system, incomplete development of external or internal genitalia, other genitourinary abnormalities (renal hypoplasia/aplasia, horse-shoe kidney), cleft lip/plate, and cardiac malformations may be accompanied.[3,5,6] Because the prognosis is dismal, with death in utero or shortly after the birth, prenatal diagnosis provides the option of the therapeutic abortion of many affected fetuses.[4] Prenatal sonographic screening is currently the best method available and the second trimester is the usual time of diagnosis. We report a prospective study of prenatally diagnosed cases with MGS at our tertiary referral center over a period of four years.

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Material and Methods

A total of eight fetuses with MGS, diagnosed by prenatal ultrasound at the University of Erciyes, Faculty of Medicine Hospital, Department of Obstetrics and Gynecology, between January 2003 and October 2006, were included in this prospective study. These cases with MGS were drawn out of 107 second trimester fetuses with prenatally diagnosed malformations that were reported elsewhere.[7] All targeted prenatal fetal ultrasound examinations were performed by the same experienced obstetrician (MB) using Logic 500 (GE, USA). In transabdominal use, transducers with frequencies ranging from 3.5-5.0 MHz were utilized. A vaginal probe with a frequency range of 5.0-7.5 MHz was used when necessary.

During ultrasound examinations, detailed fetal anomaly screenings as well as routine obstetric ultrasonography were performed. Gestational age, number of fetuses, localization of placenta, amnion fluid amount and cord insertion location were determined as a part of the obstetric ultrasound. Additionally, systematic anomaly screening was performed.

Termination of pregnancy (TOP) was recommended in cases with MGS. Following terminations, radiographic examinations of the fetuses were made. After couples gave informed consents, all fetuses underwent a full and standard au-

topsy that included photography, macroscopic examination, dissection and histology of fetal organs.

Results

There were eight prenatally diagnosed fetuses with MGS that were analyzed following the TOP. The mean maternal age was 25 years (range 22-40). The mean gestational age at the time of termination was 17 weeks (range 13-24). Oligohydroamnios was present in six of our cases.

Central nervous system (CNS) malformations were seen in all cases except one case during the prenatal sonographic examination and fetal autopsy (Figure 1). Occipital encephalocel was present in seven cases and in one of them there were combine anomalies with encephalocel and Dandy Walker syndrome. Prenatal ultrasonography diagnosed polydactyly in hands and feet in six cases (Figure 2). Additionally, polydactyly were found the other two cases during fetal autopsy.

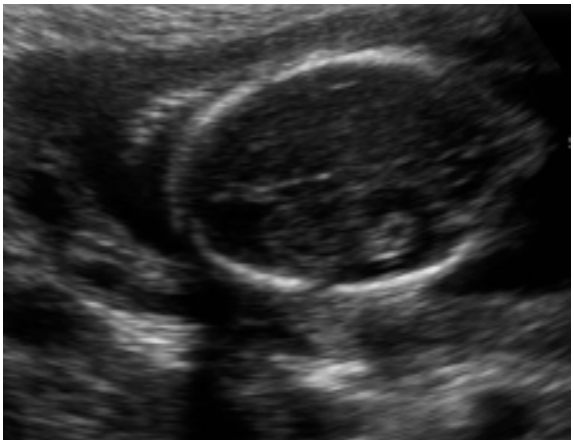

Figure 1: Axial scan through ventricles shows occiptal encephalocel

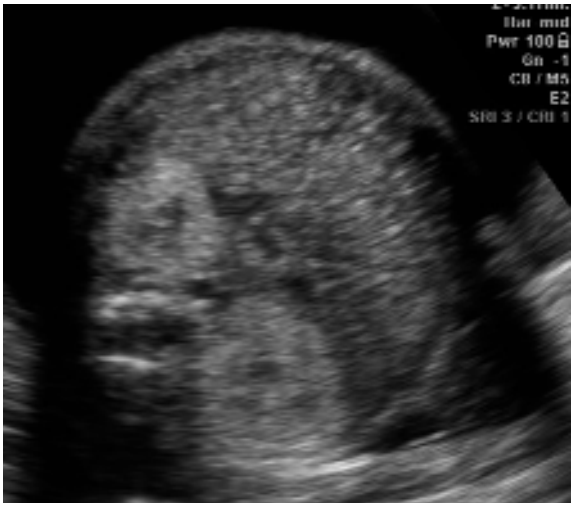

Figure 2: Sonographic image of the feet showing polydactyly

Prenatal sonography revealed cystic kidney structures, with unusual heterogeneous corticomedullary differentiation in all cases (Figure 3). The renal disease was characterized by a bilateral, symmetrical enlargement of the kidneys with abdominal distension and lung compression. The renal parenchyma was diffusely cystic throughout the cortex and the medulla. It contained small and medium-sized, thin-walled cysts that varied a great deal in diameter. Microscopic examination of the kidneys revealed thin-walled cysts appear throughout the parenchyma, a few immature glomeruli and a diffuse increase in loose connective tissue without islands of metaplastic cartilage.

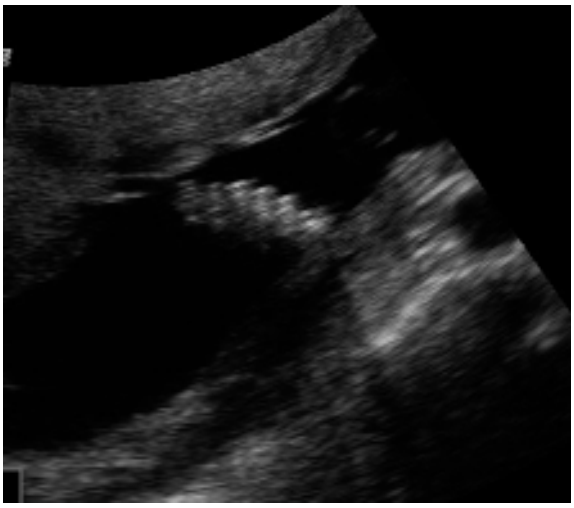

Figure 3: Transvers scan of the abdomen reveals polycystic kidneys

Hepatic lesions were found in four cases which were determined during the autopsy.

Histologically all cases showed malformation of the ductal plate of the liver with a variable degree of dilatation of the primitive biliary structures.

Additional anomalies included cleft plate (n=1), hypoplastic left ventricule (n=1), placental hemangioma (n=1), and clubfoot (n=1).

Seven cases had classical clinic triad (encephalocele, polycystic kidneys and polydactyly). One case had only polycystic kidneys and polydactyly. Fetal autopsy confirmed all prenatally diagnosed MGS; fetal examination added polydactyly in two prenatally undiagnosed cases (Figure 4) (Table 1).

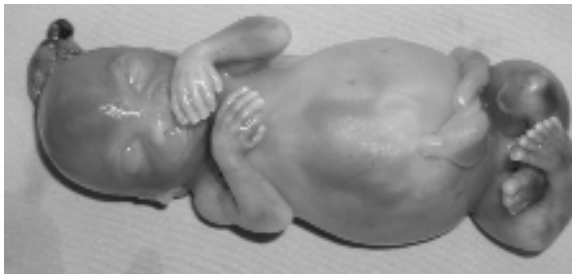

Figure 4: Fetus after termination. Note that polydactyly in hands and feet, occiptal encephalocel and abdominal distantion due to polycystic kidneys are present

Table 1: Characteristics of the cases of Meckel Gruber syndrome

Case	Encephalocele	Polycystic kidney	Polydactyly	Ductal plate malformation in liver	Additional anomaly
1	+	+	+		
2	+	+	+	+	
3	+	+	+ (added during the autopsy)	+	Hypoplastic left ventricule
4	+	+	+	+	Chorangioma
5	-	+	+	+	
6	+	+	+ (added during the autopsy)		
7	+	+	+		
8	+	+	+		Dandy walker Cleft palate Pes equine varus

Discussion

MGS is a rare and lethal disorder. Diagnosis of MGS is very important due to the recurrence risk in subsequent pregnancies resulting from autosomal recessive inheritance. This condition is usually diagnosed by ultrasonography in the second trimester and earlier diagnosis has been made possible to those women with a previously affected fetus.[8] Our cases showed typical sonographic features of MGS before 20 weeks, including the occipital encephalocele, multicystic kidneys and polydactyly in five cases.

The diagnosis of MGS may be difficult. Ickowitz et al.[4] reported a series of 30 cases with prenatally suspected fetuses with MGS but they were able to confirm the diagnosis in only 17 (57%) cases. We confirmed the sonographic findings of all cases with prenatally diagnosed MGS during fetal autopsy. Several minor and major criteria have been proposed to the diagnosis of MGS.[3,4,9] As has been done previously, we based the final diagnosis of MGS on the association of renal cystic involvement (where the cysts are located in the medulla), CNS anomaly and polydactyly. During prenatal sonography, cystic renal dysplasia, occipital encephalocele, and postaxial polydactyly were detected in 100%, 87.5 %, and 83.3% of the fetuses, respectively. Polydactyly is a minor criterion for MGS [4] Moreover, we diagnosed six cases with polydactyly during prenatal sonography and fetal autopsy detected the remaining two fetuses with polydactyly.

Occipital encephalocele was the most common CNS anomaly, encountered in 87.5% of our cases and we detected a fetus with Dandy Walker malformation in our series. Diagnosis of Dandy-Walker malformation in MGS has been reported more frequently in recent years.[10,11,12] Duzcan et al.[11] presented a stillborn fetus with Dandy-Walker malformation and MGS. Yapar et al.[12] reported two cases of MGS with Dandy-Walker malformation diagnosed by prenatal sonography. The relationship between Dandy-Walker malformation and MGS confirms a disturbance in rhombencephalon development in the pathogenesis of MGS, and it should be included among the central nervous anomalies representative of the syndrome.[13] Other CNS anomalies including anencephaly, hydrocephalus, aquaductal stenosis, Arnold Chiari malformation, arachnoid cysts, cerebellar hypoplasia and polymicrogyria without encephalocele have been reported in fetuses with MGS.[3]

Arrest of the development of intrahepatic bile ducts at the stage of the bilaminar plate formation or ductal plate malformation is considered of high diagnostic value in Meckel syndrome, but there is no complete agreement in the literature about its occurrence. Sergi at al.[5] described two distinct pattern of hepatic lesions: type I, characterized by an evident cystic dilatation of the primitive biliary structures with little portal fibrosis, and type II, characterized by rings of interrupted curved lumina of the primitive biliary structures around a central fibrovascular axis and pronounced portal fibrosis. In some portal tracts with type II ductal malformation, an abnormal pattern of the portal vein with too many, too small, and too closely spaced branches of the portal vein may occur.[5] Ductal plate malformations were found four (50%) of our eight cases. All of our cases showed mainly a cystic dilatation of primitive biliary structures with little portal fibrosis. Ductal plate malformation of the liver is found in association with autosomal dominant or autosomal recessive polycystic kidney diseases. The Smith-Lemli-Opitz syndrome may have a pattern of anomalies similar to that of the MGS and it may overlap with

the MGS.[14] Casamassima et al.[15] described a syndrome in which features suggesting Smith-Lemli-Opitz syndrome and those suggesting MGS were combined.

The sonographic characteristics of MGS depend on gestational age. The classic triad was solely seen in cases diagnosed before the 14th week of gestation.[16] Later in the pregnancy, severe oligohydramnios makes it more difficult to establish the diagnosis by ultrasound alone.[3,16] We performed amnioinfusion in four of the cases to reach the diagnosis. Amnioinfusion may be valuable to screen fetal anatomy in cases with severe oligohydramnios. Moreover, a meticulous autopsy is necessary to establish the diagnosis of MGS, when amnioinfusion is declined.[3,4]

Genetic heterogeneity of MGS has been established by three reported MKS loci, i.e., MKS1 on 17q23, MKS2 on 11q13, and MKS3 on 8q21.13-q22.1. MKS1 encodes a component of flagellar apparatus basal body proteome, which is associated with ciliary function. MKS3 encodes a seven-transmembrane receptor protein, meckelin.[6,17] We performed karyotype analysis in all cases, and there were not detect any chromosomal anomalies.

The differential diagnosis of MGS should include trisomy 13, Zellweger syndrome, Smith Lemli-Opitz Syndrome, Agostino syndrome and Jeune syndrome.[3,4,17] In each of these syndromes, additionally investigations, in particular morphological, karyotypic and genetic analyses, are necessary. Amniotic fluid volume generally remains normal in all these conditions and this is in contrast to MGS, in which oligohydramnios occurs earlier in the pregnancy. If histologic examination of the kidneys and liver are performed, the diagnosis of MGS can be made. Autosomal recessive polycystic disease is another differential diagnosis to be discussed, but medullary lesions are very unusual, especially during the first trimester.[4]

In conclusion, Meckel-Gruber syndrome is characterized by a triad of characteristic gross and histologic features, including central nervous system malformations (in particular occipital encephalocele), cystic dysplasia of the kidneys, and postaxial polydactyly. In addition, ductal plate malformation of the liver occurs in most cases. Autopsy provides valuable differential diagnostic information and can be used to validate obstetric management and to evaluate the recurrence risk in future pregnancies.

Meckel Gruber Sendromu: Prenatal Tanı ve Otopsi Bulgularının Korelasyonu

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Prenatal ultrasonografik incelemede Meckel Gruber Sendromu (MGS) tespit edilen fetuslarda ultrason ve otopsi bulgularının korelasyonun değerlendirilmesi. Dört yıl süren bu prospektif çalışmada, merkezimizde ikinci trimester ultrason incelemelerinde fetal malformasyon tespit edilen ve bu nedenle termine edilen 107 ikinci trimester fetus arasında MGS tespit edilen sekiz fetusun ultrason bulguları fetal otopsi bulguları ile karşılaştırıldı. Prenatal incelemede MGS tanısı alan sekiz fetusa otopsi yapıldı. Olguların yedisinde klasik klinik triad vardı. Bir olguda yalnızca polikistik böbrek ve polidaktili görüldü. Fetal otopside MGS'nin prenatal olarak tespit edilen bulgularının tamamı tespit edildi, iki olguda ek olarak polidaktili görüldü. Dört olguda histolojik inceleme sırasında hepatic lezyonlar bulundu. MGS'nin ultrason bulguları pek çok olguda tanının kolaylıkla konulmasını sağlar. Ancak otopsi tanının doğrulanması ve annenin daha sonraki gebeliklerinde rekürrens riskinin belirlenmesinde yardımcı olabilir.

Anahtar Kelimeler: Meckel gruber sendromu, Prenatal ultrason, Fetal otopsi

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