Termination of a Pregnancy for the Third Time due to Meckel-Gruber Syndrome: Case Report and Review of Literature

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Abstract

Meckel-Gruber syndrome (MGS) is a rare autosomal recessive disorder that is characterized by typical ultrasonographical (USG) findings including encephalocele, polydactyly and cystic dysplastic kidneys. In this article we report an antenatally detected MGS with a review of the literature. A 28 year-old multigravida (G7P3L3) presented with 14 weeks of gestation for routine antenatal examination. The mother had had a second degree intermarriage, and two previous pregnancies were learned to be terminated due to MGS. The USG showed occipital encephalocele, polydactyly, oligohydramnios and bilateral renal cystic dysplasia. After detecting the fetal karyotype as 46,XY, termination of pregnancy was performed. In the histopathological examination, encephalocele, polydactyly and bilateral dysplastic kidneys were observed and diagnosis of MGS was confirmed. In cases with MGS, parents should be informed about the fetal prognosis and the recurrence risk for the next pregnancies.

Key Words: Meckel Gruber Syndrome, prenatal ultrasonography, encephalocele, polydactyly

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Introduction

Meckel-Gruber Syndrome (MGS) is a rare, autosomal recessive disorder characterized by a wide range of malformations. It culminates lethal, and death occurs intrauterine or in the newborn shortly after birth. The most characteristic findings are occipital encephalocele, multicystic renal dysplasia, postaxial polydactyly, and cystic and fibrotic changes in the liver [1]. The worldwide incidence is 1/13,250- 1/140,000 live births, and it affects males and females equally [2]. Observing the characteristic findings as early as 14 weeks of gestation by ultrasonography (USG) should bring MGS to mind, but a neonatal autopsy is needed to document complete anomalies and exact diagnosis [3]. The parents should be informed about the fetal prognosis and the recurrence risk for the next pregnancies. They should be given genetic counseling, and early prenatal diagnosis should be obtained in subsequent pregnancies.

Case

A 28 year-old multigravida (G7P3L3) with 14 weeks of gestation applied to the clinic for routine antenatal examination. She had a history of a second-degree intermarriage, and two previous pregnancies were terminated due to MGS, one in the 18th and the other in the 16th weeks. Her previous obstetric history is shown in Table 1. She did not have a history of using teratogenic drugs or any acute or chronic diseases. She was supplemented with a regular folic acid regimen since the beginning of conception. The obstetric USG revealed a 26x20 mm encephalocele in the occipital area, polydactyly in both hands and feet, bilateral renal cystic dysplasia, and oligohydramnios (Figure 1). Combining these features, we suspected of MGS, and the possible outcomes were explained to the parents.

The parents agreed to terminate the pregnancy after fetal karyotyping (46,XY). Extra-amniotic balloon was administered, and a 14 week-old fetus was delivered intact. The autopsy revealed a male fetus weighing 120 grams, and a defect in the occipital bone with encephalocele through the posterior fontanelle was detected (Figure 2). Post-axial polydactyly was present in all four limbs. Biliary duct hyperplasia and fibrosis in the liver were also observed. The microscopic examination of the kidneys showed multiple cysts of different sizes, lined by flattened epithelium. Other visceral organs were observed to be normal. Based on these features, pathological diagnosis of MGS was confirmed. A proper genetic analysis

could not be done, as the parents were unable to afford it. We informed them about the fetal prognosis and the recurrence risk for the next pregnancies.

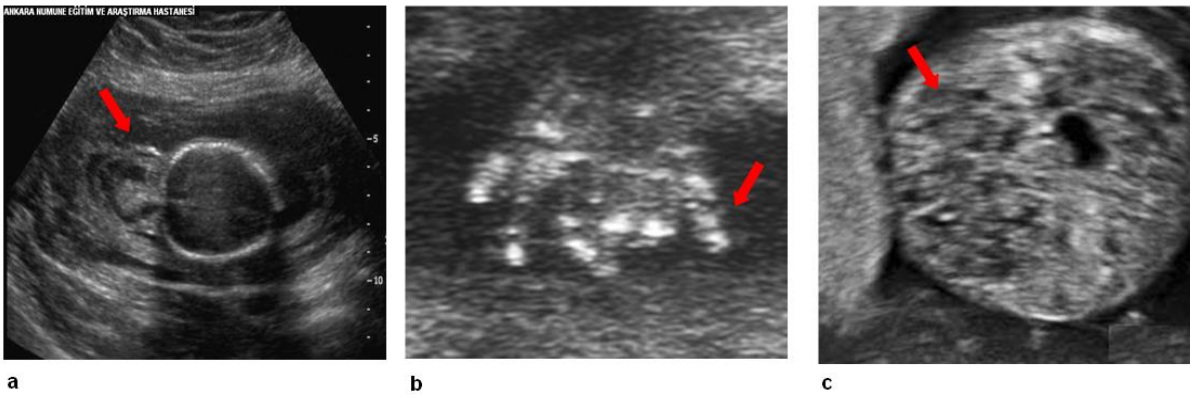

Figure 1. Ultrasonography showed occipital encephalocele (a), polydactyly (b) and bilateral enlarged cystic kidneys (c)

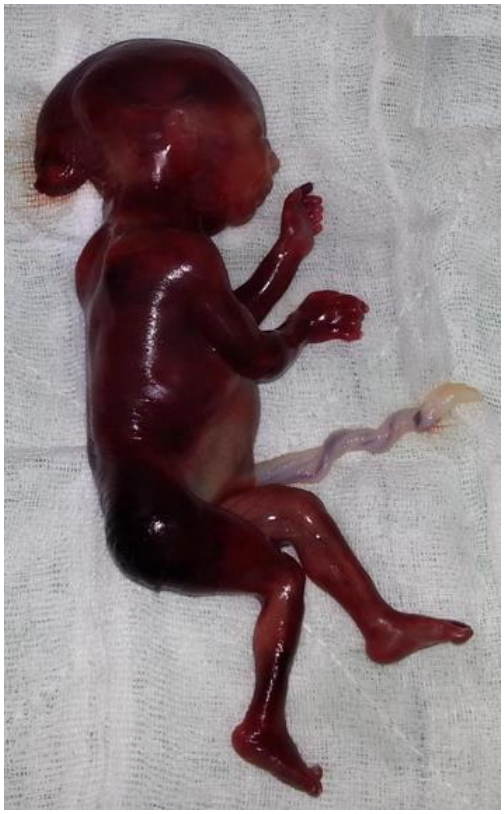

Figure 2. Fetus after delivery with encephalocele and polydactyly.

Table 1. Previous obstetric history

Pregnancy	Sex of the fetus	Pregnancy outcome	Prenatal findings	Autopsy findings
1. pregnancy	Female	Pregnancy terminated at 18th week of gestation due to MGS	Occipital encephalocele, polydactyly, renal cystic dysplasia, oligohydramnios, cleft lip	Occipital encephalocele, polydactyly, hepatic fibrosis, bilateral dysplastic kidneys, cleft lip
2. pregnancy	Male	Healthy birth at term	-	-
3. pregnancy	Male	Healthy birth at term	Cleft Lip/Palate	-
4. pregnancy	Female	Pregnancy terminated at 16th week of gestation due to MGS	Occipital encephalocele, polydactyly, renal cystic dysplasia, oligohydramnios, single umbilical artery	Occipital encephalocele, polydactyly, hepatic fibrosis, bilateral dysplastic kidneys
5. pregnancy	Female	Spontaneous abortus at 14 weeks of gestation	-	-
6. pregnancy	Male	Healthy birth at term	-	-
7. pregnancy	Male	Our case	Occipital encephalocele, polydactyly, renal cystic dysplasia, oligohydramnios	Occipital encephalocele, polydactyly, biliary duct hyperplasia, hepatic fibrosis, bilateral dysplastic kidneys

Table 2: Most frequent manifestations in Meckel-Gruber Syndrome

System	Anomalies
Central nervous system	Occipital encephalocele, microcephaly with sloping forehead, cerebral and cerebellar hypoplasia, anencephaly, hydrocephaly with or without Arnold-Chiari malformation, Dandy-Walker malformation, craniosynostosis, absence of olfactory lobes, olfactory tract, corpus callosum, or septum pellucidum.
Face/neck	Microphthalmia, cleft palate, micrognathia, ear anomalies, coloboma of iris, hypoplastic optic nerve, hypoplastic philtrum and/or nasal septum, hypertelorism, midline cleft lip, short neck, webbed neck
Skeletal	Postaxial polydactyly, talipes, relatively short-boned limbs, syndactyly, simian creases, clinodactyly
Urinary system	Renal dysplasia with varying degrees of cystic formation, absent or hypoplastic urinary bladder
Liver	Bile duct proliferation, hepatic fibrosis and cysts
Genitalia	Cryptorchidism, and incomplete development of external and/or internal genitalia, missing or duplicated ureters
Mouth	Lobulated tongue, cleft epiglottis, neonatal teeth
Cardiovascular system	Cardiac septal defects, patent ductus arteriosus, coarctation of aorta, pulmonary stenosis, pulmonary hypoplasia
Abdomen	Patent urachus, omphalocele, intestinal malrotation, spleen abnormalities, laterality defects, adrenal hypoplasia, imperforate anus
Others	Enlarged placenta, single umbilical artery

Discussion

Meckel-Gruber syndrome (MGS) was first described by Johann Friedrich Meckel in 1822 after he observed two siblings succumb to similar malformations including occipital encephalocele, polycystic kidneys and polydactyly [4]. About a century later, in 1934 George B. Gruber reported more cases with identical features and brought up the term of 'dysencephalia splanchnocystica' [5]. The name 'Meckel syndrome' was proposed by Opitz and friends in 1969 [6].

Meckel-Gruber syndrome is inherited autosomal recessively, and there is a 25% chance of recurrence in each subsequent pregnancy. Although MGS has been reported to occur in intermarriages more commonly, it may also be seen in non-intermarried couples. The prevalence is not known exactly because it causes early fatality and is similar to many other diseases. The worldwide incidence is 1/13,250- 1/140,000 live births [2]. Although this syndrome may occur in all ethnic groups, the incidence in Finnish population is approximately 1/9000, making the carrier rate about 1/50.7. It is also more common in Belgian, Kuwaiti, and Israeli Jewish individuals [7].

Meckel-Gruber syndrome shows genetic heterogeneity and six genes have been found to be related to it (MGS1 on 17q21-24, MGS2 on 11q13, MGS3 on 8q21.3-q22.1, MGS4 on 12q21.31-q21.33, MGS5 on 16q12.2, and MGS6 on 4p15.3). Mutations in these genes disrupt ciliary development and epithelial morphogenesis, therefore MGS is considered as a ciliopathy. [7]. These genes were identified from different ethnic groups, and were found to be functionary in various parts and systems of the body, including brain, spinal cord, lungs, liver, kidneys, adrenal glands, and cartilages. They may also be present in other disorders like Joubert syndrome, Leber congenital amaurosis, Senior-Loken syndrome, nephronophthisis and Bardet-Biedl syndrome, and the clinical features may be overlapping [8].

Diagnosis of MGS is made through at least 2 of the 3 major features of cystic renal dysplasia, occipital encephalocele or other central nervous system anomalies, and polydactylyd. These features are found in 100%, 90%, and 83.3% of the fetuses, respectively. [9]. Microcephaly, Dandy-Walker malformation, agenesis of the corpus callosum, rhombic roof or prosencephalic dysgenesis are other central nervous system abnormalities associated with MGS. Ahdab-Barmada et al. suggested that a triad of prosencephalic dysgenesis, occipital

encephalocele and rhombic roof dysgenesis should also be included in the diagnostic criteria of MGS [10]. Another constant finding in MGS is hepatic fibrocystic changes, appearing as an impaired development of the intrahepatic biliary system, and ductal plate malformation, with histopathologically increased number of microfibroblasts surrounding bile ductules [11]. These microfibroblasts were shown to cause bile duct ligation in animal studies [12]. Minor criteria for MGS diagnosis are cleft palate/lip, atrial septal defect, omphalocele, ambiguous genitalia, urethral atresia, and other facial, cardiac, gastrointestinal or urologic anomalies (Table 2) [11,13-14].

Meckel-Gruber syndrome may be diagnosed perinatally by routine USG between 11th and 14th weeks of gestation. In proceeding weeks, diagnosis by USG becomes harder due to possible oligohydramnios [3]. After 12th week of gestation, measurement of alpha fetoprotein (AFP) levels in the maternal serum or amniotic fluid may also help to detect the presence of encephalocele as well as neural tube defects [15]. Molecular genetic testing and pathologic examination may be required, and fetal autopsy is also advised for the accurate diagnosis [16].

Meckel-Gruber syndrome should be differentiated from some of the previously stated genetic disorders. Trisomy 13 (holoprosencephaly, polydactyly, cleft lip/palate, congenital heart diseases), trisomy 18 (choroid plexus cysts, polydactyly, congenital heart and kidney diseases, rocker bottom feet), Joubert Syndrome (hypoplasia or dysplasia of vermis, facial abnormalities, cystic renal diseases, polydactyly, cleft palate), Bardet-Biedl syndrome (loss of vision, mental retardation, renal diseases, polydactyly, cleft palate), and Smith-Lemli-Opitz syndrome (microcephaly, mental retardation, polydactyly) share some of the characteristic findings of MGS. As trisomy 13 has the most similar findings, it is important to confirm the karyotype to be normal for the exact diagnosis of MGS [17].

Meckel-Gruber syndrome is a lethal disorder. As the kidneys are dysplastic, oligohydramnios occurs and this leads to pulmonary hypoplasia. As a result of these, most infants are stillborn and the others die within hours or days after birth. Therefore, termination of the pregnancy is offered once the diagnosis is made, yet there is no available prenatal treatment [18].

Parents should be informed about the outcome and prognosis of the fetus, and the high recurrence risk for subsequent pregnancies. In case of a following pregnancy, first trimester

USG should be performed, and a chorionic villus biopsy or amniocentesis should be obtained if necessary.

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