A rare case of Meckel–Gruber syndrome

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Abstract
Meckel–Gruber syndrome (MKS) is a lethal, autosomal recessive transmitted anomaly, characterized by the ultrasound triad: occipital meningoencephalocele, bilateral polycystic kidney, postaxial polydactyly. The incidence is between 1/13 250 and 1/140 000 live births, being a rare anomaly. We report a MKS case of feminine gender diagnosed on two ultrasound findings (bilateral polycystic kidney, occipital meningoencephalocele). This case highlights the presence of MKS in a young female without family history.

Keywords: Meckel–Gruber syndrome, ultrasound, polycystic kidney, meningoencephalocele, postaxial polydactyly.

Introduction
Meckel–Gruber syndrome (MKS), is a lethal, autosomal recessive disorder characterized by central nervous system (CNS) malformations (typically occipital meningoencephalocele), bilateral renal cystic dysplasia, hepatic ductal proliferation, fibrosis and cysts, and polydactyly [1, 2].

MKS is characterized by the following ultrasound (US) triad: polycystic kidneys (present in 95–100% of the US examinations), occipital encephalocele (60–80%) and postaxial polydactyly (55–75%) [3, 4].

The worldwide incidence of the disease varies from 1/1304 in Gujarati Indians [5] to 1/140 000 in Great Britain [6]. High rates were found in Belgium and Finland (1/9000 births) [1]. There is evidence that prevalence is higher in populations with higher consanguinity rates, as India [5, 7], Pakistan [8], Kuwait and other Arabian countries [9, 10]. Genetically, MKS is known to be a heterogeneous disease with linkage to five loci and four genes identified so far. All the genes are associated with ciliary functions. Mutations in ciliary genes are known to cause a number of human monogenic disorders that are collectively known as ciliopathies, disorders with overlapping clinical features. An especially interesting aspect of ciliary diseases is that they range from embryonically lethal Meckel syndrome to less severe multisystem disorders, such as Bardet–Biedl syndrome, where the patients suffer from obesity, retinal degeneration, polydactyly, mental retardation, and cystic kidneys, for example.

In 1822, the German anatomist Johann Friedrich Meckel (1781–1833) first described two newborn siblings, a female and a male, that died of identical malformations of occipital meningoencephalocele, polycystic kidneys, polydactyly, and cleft palate. In 1934, Georg Benno Gruber (1884–1977) reported several familial cases with encephalocele, polycystic kidneys, and polydactyly using a disease name “dyencephalia splanchnocystica”, and suggested a genetic origin of the disease. In 1969, Opitz & Howe delineated the clinical features and proposed a disease name “Meckel syndrome” [11].

MKS is classified based on the chromosome were the gene mutation is placed: MKS type I (gene mutation on chromosome 17), MKS type II (gene mutation on chromosome 11), MKS type III (gene mutation on chromosome 8) [12].

MKS was frequently reported in consanguineous marriages, affecting both sexes equally.

Case presentation
A 15-year-old primigravida, 29 weeks of gestation, with unremarkable family history was admitted in our Hospital with the diagnosis of oligohydramnios. She was previously diagnosed with oligohydramnios in a level I center, then transferred to our Unit.

US examination revealed: severe oligohydramnios (amniotic fluid index 2 cm) bilateral polycystic kidneys (occupying the entire fetal abdomen) (Figure 1, A and B). Skull US revealed: normal parenchyma, moderate unilateral ventriculomegaly, interhemispheric cyst, and bone defect in the posterior region of the calvarium with herniation of the brain (approximate 3/3 cm occipital encephalocele) (Figure 2, A and B). Fetal profile revealed micrognathia (Figure 3).
Based on the two characteristic ultrasound elements (polycystic kidneys and occipital encephalocele), we suspected the presence of MKS. We searched for the third element (postaxial polydactyly), but we could not reveal that due to severe oligohydramnios.

For differential diagnosis with trisomy 13, we performed cordocentesis with assessment of the fetal karyotype (that turned out to be normal 46XX) (Figure 4).

The patient was informed that the US findings are incompatible with life and might indicate the consequence of recessively inherited gene mutations (e.g., Meckel–Gruber syndrome). In order to detect the gene mutation, prenatal genetic counseling is paramount for future pregnancies. Given the fact that this syndrome has a mortality rate of 100%, with most fetuses surviving only a few days to weeks, we advise termination of the pregnancy with the signed consent of the legal guardians of the mother. She elected immediate termination of pregnancy. We induced labor using Prostaglandin E2. The patient gave birth to a female fetus weighing 2000 g that died in the first hour after birth.

Physical examination of the fetus revealed: occipital encephalocele, micrognathia and postaxial polydactyly of the upper and lower limbs (Figures 5–8).

The autopsy was not performed because the legal conditions were not meet.
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**Discussion**

MKS is a recessive condition, most commonly characterized by cystic kidneys, posterior encephalocele, polydactyly and hepatic fibrosis.

The largest study regarding the prevalence of MKS, conducted between 1990–2011, based on 34 EUROCAT (European Registration of Congenital Anomalies and Twins) reported 191 cases of MKS per 5 483 380 births [13]. According with National Organization for Rare Disorders (NORD), until 2016 only 200 cases of MKS have been reported in the literature [11, 12].

Recent advances in molecular genetic diagnosis have shown that MKS can be caused by mutations in thirteen genes [12, 14]. Importantly, it is now clear that all of the genes involved in MKS affect the structure or function of the cilium, a hair-like organelle present on the surface of most cell types. Recently, diseases due to disorders of the structure and/or function of the cilium have been termed ‘ciliopathies’. Therefore, MKS is best thought of as being part of the large spectrum of ‘ciliopathies’ disorders that includes MKS, Joubert syndrome, COACH (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, hepatic fibrosis) syndrome, nephronophthisis, Senior–Løken syndrome and others [15].

Among the ciliopathies, MKS manifests with the most striking fetal malformations, making it amenable to diagnosis by prenatal imaging. Ultrasonographic prenatal diagnosis of MKS was first accomplished in 1982. Over the ensuing years most reported prenatal diagnoses have been in the second trimester, although first-trimester diagnoses have been described as well [16]. In general, confirmation of the diagnosis of MKS has been based on pathological findings and family history.

MKS can be suspected from 14 weeks of gestation due to the presence of oligohydramnios. Determination of AFP (alpha-fetoprotein) in the amniotic fluid at 12 weeks of gestation can be useful to detect neural tube abnormalities (encephalocele) [3].

Besides the classical US triad, which is almost consistently present, other malformations can be found:

- **CNS**: microcephaly, anencephaly, holoprosencephaly, hydrocephaly, polymicrogyria, agenesis of the corpus callosum;
- **face**: micrognathia, cleft palate, hypertelorism, microphthalmia;
- **heart**: atrial septal defect, ventricular septal defect, patent ductus arteriosus.

MKS may be associated with Dandy–Walker and Arnold–Chiari malformations [16, 17]. The differential diagnosis should be made with the following conditions: trisomy 13 (requires karyotyping – which was performed in our case report), Larsen syndrome, Smith–Lemli–Opitz syndrome (caused by deficiency of the enzyme 7-dehydrocholesterol-Δ7-reductase), Bardet–Biedl syndrome (no CNS abnormalities) [1, 14, 18], Joubert syndrome – the last two syndromes are part of the same ciliopathies as MKS [19]. It is an autosomal recessive (AR) disease with 25% chance of recurrence at each pregnancy [1, 11].
With a mortality of 100%, once the diagnosis is certain, termination of the pregnancy is recommended and genetic counseling due to the risk of recurrence [1, 11].

It is a lethal anomaly – most fetuses are born dead or die within the first hours of life due to kidney dysfunction and pulmonary hypoplasia.

**Psychological counseling**

The patient received counseling during 14 sessions in order to reduce the level of anxiety and emotional distress and to prevent depression. The whole intervention should be in an ethical, non-stigmatizing frame, taking into account the fact that the patient is still an adolescent [21–23]. Cognitive restructuring techniques, breathing and relaxation control techniques (Schultz’s autogenous training) were applied [24].

During therapy, the patient completed a personal diary in which she described daily personal experiences, results of exercises and themes.

**Conclusions**

The case we present is unusual, because it occurred in a low-risk patient with no prior history. Autopsy and genetic analysis (when available) represents the gold standard for the diagnosis. Unfortunately, in our case the autopsy could not be performed due to failure to meet the legal criteria.

**Conflict of interests**

The authors declare no conflict of interests.

**Author contribution**

Ana Cristina Bredicean has equal contribution and thus shares first authorship.

**References**


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