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A fetus with meckel-gruber syndrome associated with isomerism

Case Report

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Abstract: Abstract. Meckel-Gruber syndrome (MKS) is an autosomal recessive lethal malformation. As far as we know, the rate of incidence for the syndrome is 0.02 per 10,000 births. It is estimated that Meckel-Gruber syndrome accounts for 5% of all neural tube defects in Finland. Objective. The aim of this study is to present a case of a fetus with Meckel-Gruber syndrome associated with complete left isomerism. Method. The fetus was obtained after medical interruption of the pregnancy during the fifteenth gestational week. The mother was 36 years old and in a consanguineous marriage. The antenatal ultrasound examination revealed a polymalformative syndrome, leading to a postmortem examination. The fetopathological study of the fetus was conducted at the Centre for Maternity and Neonatology, Tunis, Tunisia, in 2008. Results. The female fetus had a significantly deformed ballooning abdomen, pes equinovarus, flexion of the wrist and a total posterior cleft palate. The central nervous system abnormalities were occipital encephalocele, cystic dilatation of the fourth ventricle, agenesis of corpus callosum and hydrocephalus. The study of the internal organs found dextrocardia, irregular lobulation of the lungs, left isomerism, and polysplenia. The microscopic examination revealed bilateral cystic dilation of the kidneys, fibrous proliferation of the liver and ectasic dilatation of the billiary ducts, representing a ductal plate malformation of the liver. Conclusion. The case is diagnosed with Meckel-Gruber syndrome associated with complete left isomerism, cleft palate and possibly Dandy-Walker syndrome.

Keywords: *Encephalocele • Fetus • Isomerism • Meckel-Gruber syndrome • Postmortem examination*

1. Introduction

Meckel-Gruber syndrome is an autosomal recessive lethal malformation. While not precisely known, the general rate of incidence for the syndrome is estimated to be 0.02 per 10,000 births [1]. According to one study, the rate varies from 0.07 to 0.7 per 10,000 births [2]. Meckel-Gruber syndrome is considered to be a Finnish heritage disease as its frequency is much higher in Finland, where the incidence is 1.1 per 10,000 births. The syndrome is estimated to account for 5% of all neural tube defects in Finland [3]. Meckel-Gruber syndrome belongs to a group of diseases known as ciliopathies and is caused by a mutation in the meckelin transmembrane receptor located in the ciliary transition zone, in the main cells and in the interior of the cell. Some studies emphasise the importance of the functional complex meckelin-filamin. Filamin A plays an important role in the normal ciliogenesis and in the positioning of the basal body [4]. Ciliopathies are associated with an abnormal neuronal migration and disrupted Wnt signalling.

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Meckel-Gruber syndrome is characterised by a pathognomonic triad: large polycystic kidneys, encephalocele and hexadactyly. The brain abnormalities are expressed in various degrees, the occipital encephalocele being the most common, but they may also include anencephaly or the Dandy-Walker syndrome. Hexadactyly is most often postaxial, then preaxial.

The aim of this study is to present a case of a fetus with Meckel-Gruber syndrome associated with complete left isomerism.

2. Method

The case was the result of a pregnancy interrupted during the fifteenth gestational week, after ultrasound findings of a polymalformative syndrome. The mother was 36 years old, parity two, six gestation with a history of two previous medical terminations. She was in a consanguineous marriage. A fetopathological study of the fetus was conducted at the Centre for Maternity and Neonatology, Tunis, Tunisia, in 2008.

3. Results

The weight of the fetus was above the average estimated for the gestational week (126 g) according to the reference values of Guilhard-Costa [5].

3.1. External examination

A female fetus with short and narrow rib cage and a very deformed ballooning abdomen.

- ***Head***: A brain herniation located at the occipital region with a size of one 1 cm was found. The hernial sac was formed from modified meninges and the contents were modified brain tissue. The findings were described as occipital encephalocele (Figure 1).
- ***Face***: The fetus had a distinguishable Potter's face related to early and chronic oligoamniosis. A study of the palate found complete posterior cleft palate.
- ***Limbs***: A bilateral pes equino-varus was found in the lower limbs. In the upper limbs – flexion of the wrists.

3.2. Internal examination of the cavities and organs

Upon opening the thoracic cavity, an unusual positioning of the elements was discovered. The heart was located on the right side of the thoracic cavity, and the cardiac apex was directed to the right and forward-dextrocardia. There also was irregular lobulation of the lungs. The right lung had one oblique fissure (two lobes) and the left lung had two fissures – one horizontal and one oblique (three lobes). In the left lung, the principal bronchus is the highest located in relation to the other elements of the hilus while in the right lung; the pulmonary artery was the highest. The esophagus was located to the right of the spine. The above findings suggest complete thoracic situs inversus. The diaphragm domes appeared without hernial abnormalities.

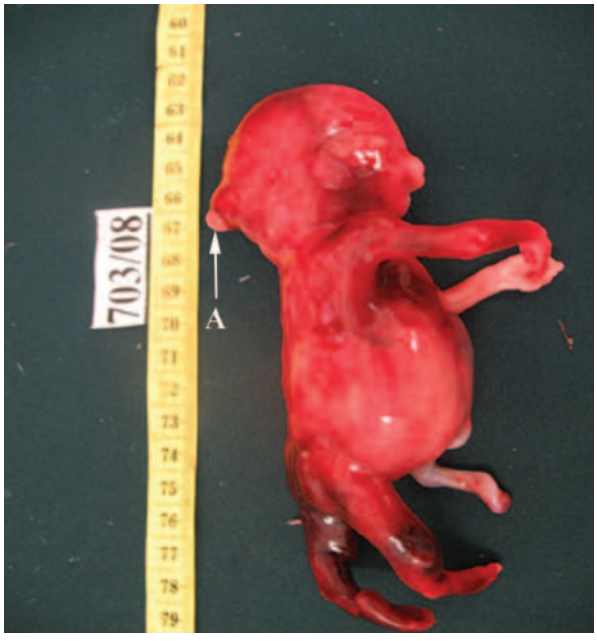

Figure 1. Occipital encephalocele. A – Occipital encephalocele

The observation of the abdominal cavity found the stomach to be located in the supracolic compartment, in the right hypochondriac region. The spleen, along with a few additional spleens, was located under the right dome of the diaphragm. The retroperitoneal organs demonstrated abnormally large kidneys, giving a balloon-like configuration of the abdomen. The ureters were very thin and filiforme, coming out of each kidney. The right lobe of the liver was situated under the left dome of the diaphragm. The examination of the abdominal cavity confirmed abdominal situs inversus (Figure 2).

The pelvic cavity: the bladder was situated between the two umbilical arteries and was tubular in shape. Both filiform ureters opened in the bladder wall. The internal reproductive organs (ovaries, fallopian tubes and uterus) correspond to the external genitalia.

The study of the brain was carried out in a second stage – after conservation with 40% formaldehyde for several months. The findings were: Occipital encephalocele with a large bone defect, prolapse of brain tissue, abnormal gyrification and hydrocephalus, an absence of the corpus callosum and cystic dilatation of the fourth ventricle.

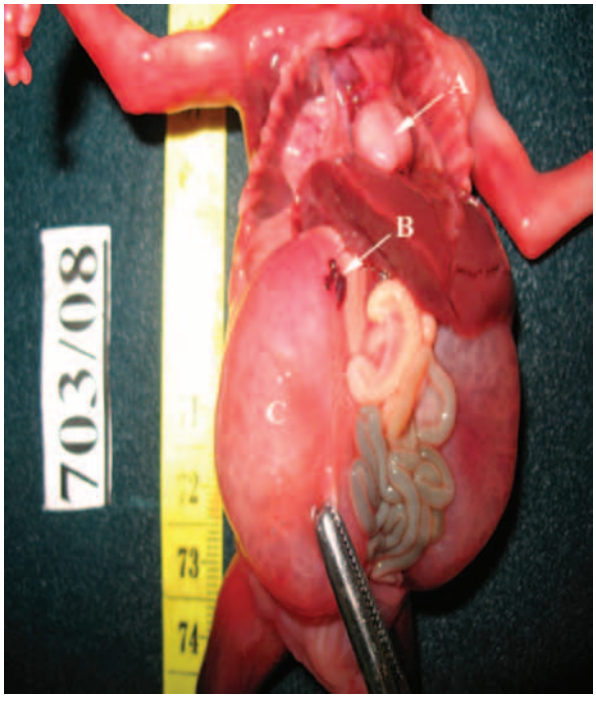

Figure 2. Dextrocardia, polysplenia, nephromegaly. A – Dextrocardia; B – Polysplenia; C – Nephromegaly

Microscopic examination**:** The microscopic examination found bilateral cystic dilation of the kidneys (cysts located throughout the parenchyma; no glomerulus between the cysts). In the cortical part of the kidney, the cysts were smaller in size while in the medulla they were larger. The liver parenchyma had fibrous proliferation and ectasic dilatation of the billiary ducts-ductal plate malformation of the liver (Figure 3).

The dextrocardia, polysplenia, polycystic kidneys, ductal plate malformation of the liver, occipital encephalocele, and cleft palate led the fetopathological diagnosis: Meckel-Gruber syndrome associated with left isomerism, cleft palate and Dandy-Walker malformation.

4. Discussion

In 1882, Meckel first described the Meckel-Gruber syndrome on two newborn babies**.** In 1934, Gruber described the syndrome of encephalocele**,** cystic kidneys and polydactyly as “dysencephalia splanchnocystica”. In 2006, Opitz detailed the pathogenetic mechanism of the syndrome. Six different mutations causing the syndrome are known today: MKS1-17q21-q24, FlJ 20345/MKS1, MKS2-11q13, MKS3-8q24, MKS4-12q21, MKS5-16q12 [6].

In the 1960s, the Meckel-Gruber syndrome was described as Trisomy 13 but with normal chromosomes. Currently, it is known that the common brain abnormality

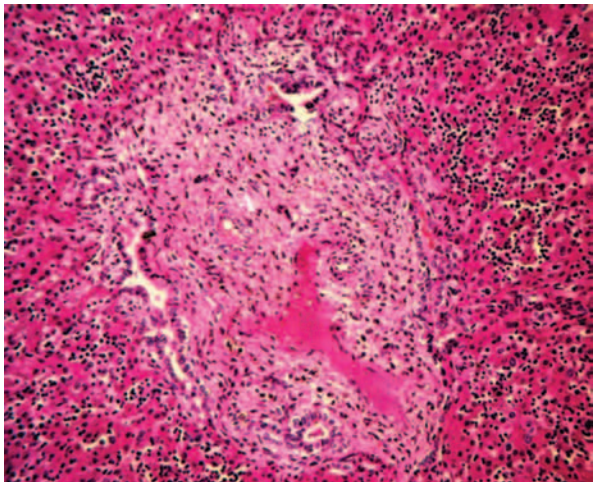

Figure 3. Microscopy of the fibrous proliferation of the liver (Hematoxylin eosin stain x100). A – Fibrous proliferation of the liver

in Trisomy 13 is holoprosencephaly rather than occipital encephalocele. Unfortunately, the presented case was not karyotyped. The clinical picture of hexadactyly, pancreatic and polycystic kidney disease and cleft palate could be diagnosed as Trisomy 13, but isomerism has not been recognised as a commonly associated feature of the syndrome. Also, Trisomy 13 is often associated with cyclopia or probosis [7]. Karyotyping is very useful in distinguishing between the two [8].

The renohepatopancreatic dysplasia, also known as syndrome Ivemerk type II, is associated with greatly enlarged kidneys, irregularly located cysts and fibroadenomatosis of the billiary duct. The presented case could also be mistaken for isomerism (Ivemerk type I) [9], but in contrast to it, the fetus had encephalocele. Ivemerk type II syndrome on the other hand, is associated with pancreatic fibrosis, unlike this case.

Trisomy 18 is another possible differential diagnosis. The syndrome is often accompanied by curved feet and pes planus, cardiac abnormalities (often septal defects), anomalies of the ear and encephalocele. It is important to remember that Trisomy 18 is not associated with polycystic kidneys or liver fibrosis.

Another possible differential diagnosis could be the Bardet-Biedl syndrome, which is an autosomal recessive disease expressed with polycystic kidneys, postaxial polydactyly, oligoamniosis, hypogonadism, obesity and liver abnormalities. In this syndrome however, no encephalocele is present. Encephalocele is also not present in the Smith-Lemli-Opitz syndrome which is also an autosomal recessive syndrome associated polydactyly, anomalies affecting the gender, central nervous system, liver and kidneys.

The diagnosed Meckel-Gruber syndrome with Dandy-Walker malformation is different from the Jubert

syndrome, which is an autosomal recessive syndrome characterised by meningocele, hypoplasia of the vermis, polydactyly, low placed earlobes, polycystic kidney disease, abnormalities of the liver and tumor of the tongue.

Transvaginal ultrasound examination around the twelfth week of gestation is crucial for antenatal screening and the possible diagnosis of the Meckel-Gruber syndrome, particularly in high risk families [10].

Deviation of the heart from the medial axis as well as abnormality in the position of the liver and spleen are simple ultrasound features to look for in the early diagnosis of an abnormality such as isomerism. Amniotic fluid examination and measurement of the head circumference are essential for the search of oligoamniosis. The combination of isomerism with large kidneys occupying the whole abdominal cavity, an abnormal cranial diameter and hexadactyly are pathognomonic features of the Meckel-Gruber syndrome. If the Meckel-Gruber syndrome is suspected, genetic testing and DNA analysis should be recommended in order to clarify genotype-phenotype correlations.

Conflict of interest statement

Authors state no conflict of interest.

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