Meckel syndrome

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Abstract
Meckel syndrome (MKS) is a lethal syndrome with a central nervous system malformation, usually occipital meningoencephalocele, bilaterally large multicystic kidneys with fibrotic changes of the liver, and polydactyly in most cases. Additional anomalies are frequent. A common characteristic of the parenchymal changes of many organs is a proliferation of the stromal connective tissue and increase and dilatation of the associated epithelial ducts.

Autosomal recessive inheritance is well confirmed and the gene locus has been mapped to chromosome 17q21-24 by genome wide linkage study. The locus was later refined to within a less than 1 cM region (17q22), in which most of the Finnish MKS patients share a common chromosomal haplotype suggesting one major and relatively old mutation. However, in most of the non-Finnish MKS families studied, this linkage could not be confirmed. The linkage studies provide evidence that more than one locus is involved in bringing about the combination of CNS malformations, cystic kidneys, and polydactyly, maybe even in typical cases of MKS.

Prenatal diagnosis of MKS by vaginal ultrasound scan is possible from 11-12 weeks of pregnancy, especially in families where there is a known risk. In those families where linkage to 17q22 is established, prenatal diagnosis by DNA analysis is possible.

Keywords: Meckel syndrome

In 1822, Meckel published a detailed pathological description of two newborn sibs, a female and male, who died with identical malformations. They both had microcephaly with occipital encephalocele, polydactyly, cleft palate, and large cystic kidneys. The male child had cryptorchidism. In 1934, Gruber added a few similar cases of his own to those he had collected from published reports and reported these 16 non-viable newborn children with encephalocele, polycystic disturbance of the kidneys, often of the liver, and sometimes of the pancreas, and polydactyly in eight cases. He named the disorder “dysencephalia splanchnocystica” and assumed it to be of genetic origin because of the many familial cases. For some time after that, the existence of this syndrome seems to have been forgotten. In the 1960s, when trisomies were recognised through the development of cytogenetics, there were reports of “cases of trisomy 13 with normal chromosomes”, which obviously represented Meckel syndrome (MKS). Opitz and Howe reintroduced MKS in their review published in 1969. Delineation of the clinical picture continued through the 1970s and 1980s with reports from North America, Europe, and Israel. MKS has also been reported from different parts of Asia, for example, Indonesia, India, Kuwait, and Japan. Since the very first reports, broader diagnostic criteria have been accepted and the process of defining them continues.

Clinical features
It is probably safe to say that Meckel syndrome is lethal with very limited survival in the most typical cases. The main anomalies are a severe central nervous system (CNS) malformation, with occipital meningoencephalocele in 90% of the cases, bilaterally large kidneys with multicystic dysplasia, and fibrotic changes of the liver probably in 100%, and polydactyly in 80% (fig 1).

THE CENTRAL NERVOUS SYSTEM
The most typical CNS malformation is microcephaly with a sloping forehead and occipital meningoencephalocele. Hydrocephalus is seen in 10-20% of cases. The spectrum of the CNS malformations ranges from total craniarachnoidis and cerebrospinal fluid in the corpus callosum at the mildest end of the spectrum.

Neuropathological studies have shown that prosencephalic dysgenesis with absence of the olfactory bulbs and tracts (arhinencephaly) is frequent, as well as defects in midline formation associated with absence of the lateral ventricles. The occipital encephalocele usually comes through an apical defect of the occipital bone or enlarged posterior fontanelle. Often a second, smaller defect of the basal occipital bone is found with or without another meningocele. Anomalies of the rhombic roof with a large supracerebellar cyst including...
dilatation of the ventricles, and changes in the kidneys and liver typical of MKS. They included another similar pair of sibs and considered cerebellar Dandy-Walker malformation as one component of MKS.

Microscopically, polymicrogyria, heterotopias, and neuroepithelial rosettes have been seen. The malformations in MKS represent disturbances in both dorsal and ventral induction as well as proliferation and migration.

THE KIDNEYS
In most cases the kidneys are already grossly enlarged at midtrimester, with a combined weight of up to 1000 g at term. This corresponds to a 5- to 50-fold increase over the body weight adjusted mean of normal. The kidneys are filled with cysts of various sizes (fig 2A). Histological organisation of the renal parenchyma is typical. Beneath the capsule in the peripheral cortex there are very small cysts with a thin zone of normal glomeruli and a few undilated tubules. Under this layer in the cortical area, the cysts become larger, the diameter measuring from 200 to 600 μm. The cysts are thin walled with low cuboidal epithelium and separated by loose connective tissue. The largest cysts, up to several millimetres in size, are in the medullary part of the kidneys. These cysts can have thick, fibromuscular walls separating them from the collagenous stroma.

THE LIVER
Microscopically, intrahepatic bile duct anomalies and fibrotic changes of the liver are a constant finding in typical MKS. This is best seen in the portal areas with proliferation and dilatation of the bile ducts and increase of collagenous connective tissue (fig 2B). Occasionally, macroscopic fibrosis or cysts can be seen. Often the liver is somewhat enlarged.

CYSTIC CHANGES IN OTHER ORGANS
Duct dilatation and periductal fibrosis has also been reported in the pancreas in MKS. Fibrovascular proliferation has been seen also in the lungs, thymus, spleen, lymph nodes, lamina propria of the bowel, and rib metaphysis. Cases with dilated epididymal ducts sometimes lined with cuboidal epithelium and sometimes surrounded by a thick fibromuscular wall, similar to the cysts seen in the kidneys, have been reported. Proliferation of the stromal connective tissue and increase or dilatation of the associated epithelial ducts seems to be a common characteristic of the parenchymal changes in MKS.

GENITALIA
Abnormal development of the male genital organs is common in MKS. The external genitalia may be hypoplastic or ambiguous, leading to initial female gender assignment of fetuses subsequently shown to be 46,XY. Some cases represent male pseudohermaphroditism with variably developed female internal genital organs together with testes. Even true hermaphroditism with both testes and ovaries has been reported.
Meckel syndrome

Figure 3 A male fetus with MKS aborted at 19 weeks of gestation showing the typical lotus-like posture. The legs with club foot deformity are flexed beneath the enlarged abdomen because of oligohydramnios.

LIMBS
Postaxial polydactyly bilaterally in both hands and feet is frequently found in MKS. Probably only 10-20% of cases have no polydactyly. 

Club feet are common, probably because of oligo- or ahydramnios during the pregnancy. Typically, the legs are flexed round the enlarged abdomen in a lotus-like position (fig 3). The long bones may be somewhat short and slightly bowed, but true bone dysplasias have not been observed.

OTHER MALFORMATIONS
Congenital heart defects occur in 20% of cases. Cleft palate is common (45%) but cleft lip is less frequent. Anomalies of the tongue including aplasia and lobulation, and papillomatous or lipomatous tumours on the tongue have been reported. Occasionally, polysplenia or other abnormalities of the spleen and situs inversus have been seen. 

Ocular anomalies are frequent in MKS. Usually microphthalmia is seen. In the few thoroughly investigated cases, Microcornea, microcornea, partial aniridia, cataract, retinal dysplasia, and hypoplasia of the optic nerve were recorded. In two reports, retinal dysplasia with folding of the retina into tubules and rosettes was described. Fibromuscular cores were surrounded by rosettes of pigmented retinal epithelium and polypoid formations of fibromuscular tissue were rimmed with pigmented retinal cells.

FACIAL DYSMORPHOLOGY
The facial dysmorphism has been thought to be Potter-like, that is, caused by lack of amniotic fluid. Sloping forehead, micrognathia, short neck, and low set ears are consistent with this explanation (figs 3 and 4A). Often, however, there are some additional facial characteristics like broad cheeks, hypertelorism, a broad and flattened nose, and a wide mouth with full lips that are typical of MKS (fig 4B) and can be seen in photographs of patients in many of the reports.

Differential diagnosis
Trisomy 13 has been presented as a differential diagnosis for MKS, but karyotype analysis differentiates these cases easily. Even if the chromosomes have not been studied, distinguishing trisomy 13 from MKS does not cause problems. In trisomy 13 microcephaly, often with alobar holoprosencephaly, is seen instead of posterior encephalocoele. Typically, the holoprosencephaly is combined with hypertelorism and bilateral cleft lip and palate, which are not so common in MKS. Polydactyly is common in the hands but rare in the feet in trisomy 13, whereas in MKS it usually occurs in
MKS shows Figure Hospital.) been with or various ble before the malformation and tyly, which do been well Autosomal recessive inheritance of MKS has to CNS anomalies, with the liver problems, be defined with Bangladeshi, African, and other national groups.22 Prenatal diagnosis Prenatal diagnosis of MKS by vaginal ultrasound scan is possible from 11-12 weeks of pregnancy, especially in families known to be at risk. By this stage, the abnormalities of the skull and CNS can be seen together with the enlarged kidneys (fig 5). Ultrasound screening

Figure 5  A vaginal ultrasound investigation at 11-12 weeks of pregnancy of a family with a previous pregnancy with MKS shows an affected fetus. The arrows point to the occipital encephalocele (A) and enlarged cystic kidneys (B). (Photographs by courtesy of P Ammalä, Department of Obstetrics and Gynaecology, Helsinki University Central Hospital.)

both the hands and feet. Cystic kidneys can occur in trisomy 13, but cystic and fibrotic changes of the liver are not seen.

There are known and unknown syndromes with various CNS anomalies, cystic kidneys with or without the liver changes, and polydactyly, which do not represent MKS.29 The differentiation of cases with Dandy-Walker malformation and cystic kidneys from MKS may still cause problems, and may be impossible before the genes involved in MKS have been characterised. The same applies for patients with longer survival and similar malformations.30-32 Identification of the MKS gene(s) will enable minimum diagnostic criteria to be defined with greater precision than is currently possible.9 12 36

Genetics and pathogenesis
Autosomal recessive inheritance of MKS has been well established.8 12 In 17 Finnish MKS families, the gene locus was mapped to chromosome 17q21-q24 by genome wide linkage study.33 This locus was later confirmed in additional Finnish MKS families, and now we have refined the locus to within a region of less than 1 cM on 17q22. In this very narrow region most of the Finnish MKS patients share a common chromosomal haplotype, suggesting one major and relatively old mutation. However, in most of the non-Finnish MKS families studied (British, Turkish, Pakistani, Bangladeshi, North African, Middle Eastern), the linkage could not be confirmed.33 39 Some of the cases seemed typical enough, but some were atypical on clinical grounds. The linkage studies provide further evidence that more than one locus is involved in causing the combination of CNS malformations, cystic kidneys, and polydactyly, perhaps even in typical cases of MKS.

In MKS, the pathological findings in the multiple affected tissues share considerable similarity, suggesting that inductive interactions fail at some stage of development resulting in abundant fibrosis and cysts as well as structural abnormalities observed in the kidneys, liver, CNS, eye, pancreas, lungs, and male genitalia.

Population genetics
Although Meckel syndrome has been reported world wide, more extended reports on the true birth prevalence of MKS in different populations are scarce. Among Jews in Israel, it was calculated in 1973 by Fried44 to be 1:50 000. In Finland, MKS is effectively screened and occurs relatively frequently with a birth prevalence of 1:9000.44 Even higher incidences have been reported in some other populations, such as Belgians (1:3400), Gujarati Indians (1:1300), and Bedouins in Kuwait (1:3530).14 15 In Belorussia it has been reported to be more common in Tartars than other national groups.42

Heterozygote manifestations
There are a few reports that suggest that malformations like cleft lip/palate, polydactyly, syndactyly, and congenital heart defect occur in relatives of cases with MKS more frequently than expected.13 45-47 The possibility that these are heterozygote manifestations cannot be tested properly before the gene defect(s) can be traced in the family and compared with the occurrence of the other malformations.

Figure 6  At 19 weeks of pregnancy ultrasound investigation shows oligohydramnios. A transverse section of the abdomen filled by large cystic kidneys is seen (left). The diameter of the abdomen is much larger than the bipartietal diameter of the head (right). A defect in the bones of the skull is seen posteriorly. (The same fetus after termination of the pregnancy is shown in fig 4.)
studies are often performed later in pregnancy, when oligo- or anhydramnios, invisible bladder, and discrepancy in the biparietal and abdominal diameter can lead to the diagnosis. When lack of amniotic fluid impairs visibility and normal kidneys are not found, it may be difficult to see that the cystic kidneys in fact fill the whole abdomen (fig 6). In those families where linkage to 17q22 is established, prenatal diagnosis by DNA analysis is possible.

1 Meckel JF. Beschreibung zweier, durch sehr ähnliche bildungsabweichungen entstehende geschwister. Dtsch Arch Physiol 1822;7:99-172.
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