MECKEL SYNDROME: GENETICS, PERINATAL FINDINGS, AND DIFFERENTIAL DIAGNOSIS

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SUMMARY

Meckel syndrome (MKS) is a lethal, autosomal recessive disorder characterized by occipital encephalocele, bilateral renal cystic dysplasia, hepatic ductal proliferation, fibrosis and cysts, and polydactyly. Genetic heterogeneity of MKS 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. The identification of the *MKS3* gene as well as the *MKS1* gene enables molecular genetic testing for at-risk families, and allows accurate genetic counseling, carrier testing, and prenatal diagnosis. Pregnancies with MKS fetuses may be associated with an elevated maternal serum α-fetoprotein level and an abnormal screening result in the second-trimester maternal serum screening test. The classic MKS triad of occipital encephalocele, postaxial polydactyly, and bilateral enlarged multicystic kidneys can be diagnosed before the 14th gestational weeks by ultrasonography. However, later in pregnancy, severe oligohydramnios may make the diagnosis of polydactyly and encephalocele difficult. Differential diagnosis for MKS includes autosomal recessive polycystic kidney disease, trisomy 13, Smith-Lemli-Opitz syndrome, hydrolethalus syndrome, Senior-Loken syndrome, Joubert syndrome, Bardet-Biedl syndrome, and oral-facial-digital syndrome type 1. This article provides an overview of genetics, perinatal findings, and differential diagnosis of MKS. The ciliopathy underlies the pathogenesis of MKS. Prenatal diagnosis of bilateral enlarged multicystic kidneys should alert MKS and prompt a thorough investigation of central nervous system malformations and polydactyly. [*Taiwanese J Obstet Gynecol* 2007;46(1):9–14]

Key Words: differential diagnosis, genetics, Meckel syndrome, prenatal diagnosis

Introduction

Meckel syndrome (MKS), also known as dysencephalia splanchnocystica, Gruber syndrome, or Meckel-Gruber syndrome, is a lethal, autosomal recessive disorder characterized by occipital encephalocele, bilateral renal cystic dysplasia, hepatic ductal proliferation, fibrosis and cysts, and polydactyly. The worldwide incidence of the disease varies from 1/13,250 to 1/140,000 live births, but in Finland, there is a prevalence of 1/9,000 births [1].

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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 [2]. In 1934, George B. Gruber reported several familial cases with encephalocele, polycystic kidneys, and polydactyly using a disease name "dysencephalia splanchnocystica", and suggested a genetic origin of the disease [3]. In 1969, Opitz and Howe [4] delineated the clinical features and proposed a disease name "Meckel syndrome". In 1970, *Journal of American Medical Association* [5] and in 1984, *American Journal of Medical Genetics* [6] separately published biographical information on Meckel. In 2006, Opitz et al [7] gave a detailed review of the role of Meckel in developmental pathology.

Genetics

There are three types of MKS, i.e., MKS, type 1, or *MKS1* (OMIM 249000) [8], MKS, type 2, or *MKS2* (OMIM 603194) [9], and MKS, type 3, or *MKS3* (OMIM 607361) [10].

MKS, type 1

In 1995, Paavola et al [11] mapped the locus for MKS to chromosome 17q21-q24. In 1999, Paavola et al [12] further narrowed down the critical region for MKS on chromosome 17q22-q23. In 2006, Kyttala et al [8] identified a gene *MKS1* (*FLJ20345*) (OMIM 609883) on 17q23 using positional cloning. *MKS1* encodes a component of flagellar apparatus basal body proteome. *MKS1* has 14-kb and consists of 18 exons. *MKS1* contains an open reading frame (bp 76-1755) coding for a 559-amino acid polypeptide containing a conserved B9 domain. Genes encoding polypeptides with B9 domains such as *MKS1*, *LOC80776*, and *EPPB9* are responsible for flagellar apparatus basal body proteome and are associated with ciliary function. Cilia and flagella are ancient, evolutionarily conserved organelles that project from cell surface and serve the roles of whole-cell locomotion, movement of fluid, chemo-, mechano-, and photosensation, and sexual reproduction [13]. *In situ* hybridization analysis of *MKS1*, the mouse homologue of *MKS1* mapping to mouse chromosome 11, in the mouse embryo at day 15.5 showed a prominent expression in the tissues of bronchiolar epithelium, brain, liver, kidneys, and digits of the upper limbs [8]. The identification of the gene *MKS1* implicates a link of MKS to ciliary dysfunction. Ciliary dysfunction is associated with pronephric cyst formation and hydrocephalus in zebrafish embryos [14]; polycystic kidney disease (PKD) and Bardet-Biedl syndrome (BBS) [15,16]; PKD in the mouse model [17]; primary ciliary dyskinesia, polycystic liver disease, retinal degeneration, Astrom syndrome, MKS, Joubert syndrome (JBTS), and Senior-Loken syndrome (SLSN) [13]; hypogonadism, deafness, obesity, mental retardation, neural tube defects, laterality defects, and palatal clefts [18]; and oral-facial-digital syndrome type 1 (OFD1) [19]. The identification of the *MKS1* gene highlights the molecular diagnosis of MKS, and provides new insights into the role of cilia in early embryonic development and organo- and histogenesis.

MKS, type 2

The *MKS2* gene is to be found at the time of this writing. In 1998, Roume et al [9] mapped the locus for MKS to chromosome 11q13. Roume et al [9] pointed out that the D11S911-D11S906 interval encompassing the gene also encompasses a gene *Phox2a*, which is strongly expressed in the mouse hindbrain.

MKS, type 3

In 2002, Morgan et al [20] mapped the locus for MKS to chromosome 8q24. In 2006, Smith et al [10] identified a gene *MKS3* (*TMEM67*) (OMIM 609884) on 8q21.13-q22.1 by positional cloning of the *Wpk* gene from a rodent model, the Wistar wpk rat. *MKS3* encodes a transmembrane protein, meckelin. *MKS3* spans 62018 bp, and consists of 28 exons. *MKS3* codes for a 995-amino acid, seven-transmembrane receptor protein, or meckelin. The human locus of *MKS3* is syntenic to the *Wpk* locus in rat, which has birth defects similar to MKS such as PKD, agenesis of the corpus callosum, and hydrocephalus [21,22]. Human and rat meckelin are 84% identical and 91% similar [10]. Meckelin contains a signal peptide, at least two cysteine-rich repeats, a 490-residue extracellular region with 4N-linked glycosylated sites, seven transmembrane domains, and a 30-residue cytoplasmic tail. The identification of the *MKS3* gene as well as the *MKS1* gene enables molecular genetic testing for at-risk families, and allows accurate genetic counseling, carrier testing, and prenatal diagnosis.

Perinatal Findings

Figures 1–7 demonstrate the typical gross and histologic findings of MKS. Pregnancies with MKS fetuses may be associated with an elevated maternal serum α-fetoprotein level and an abnormal screening result in the second-trimester maternal serum screening test. The classic MKS triad of occipital encephalocele, postaxial polydactyly, and bilateral enlarged multicystic

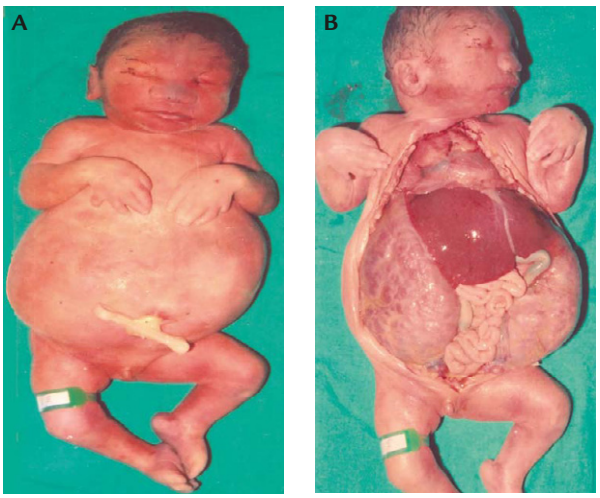

Figure 1. (A,B) Gross appearance of bilateral enlarged multicystic kidneys.

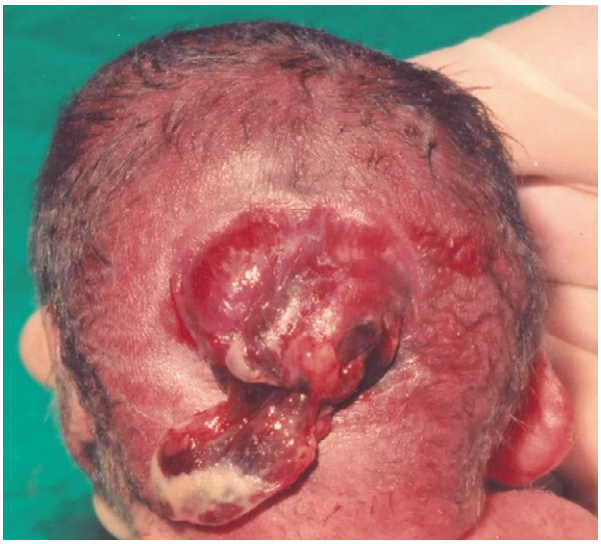

Figure 2. Occipital encephalocele.

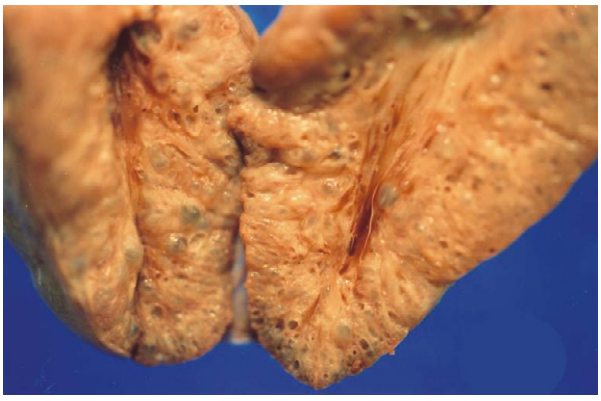

Figure 3. Gross appearance of cystic renal dysplasia.

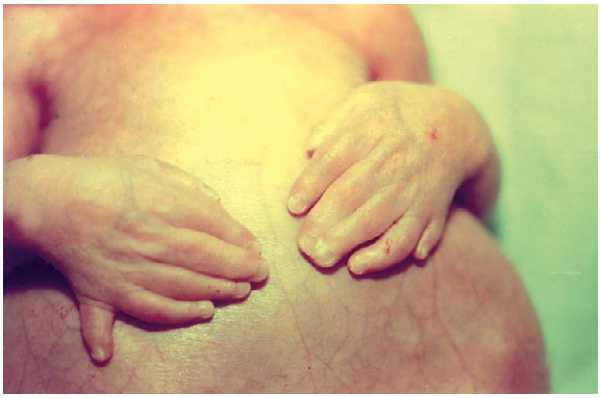

Figure 4. Postaxial polydactyly of the hands.

Figure 5. Postaxial polydactyly of the feet.

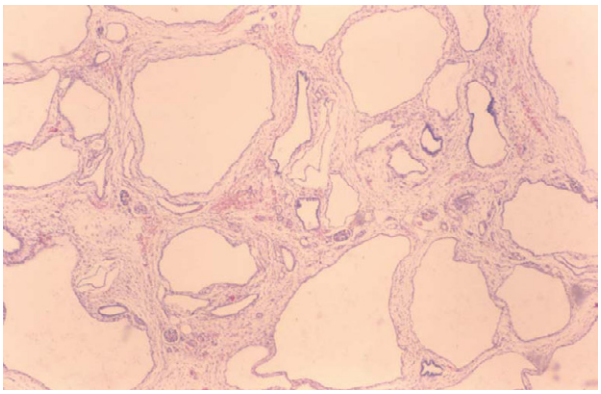

Figure 6. Histologic appearance of diffuse multicystic renal dysplasia (hematoxylin and eosin, 40×).

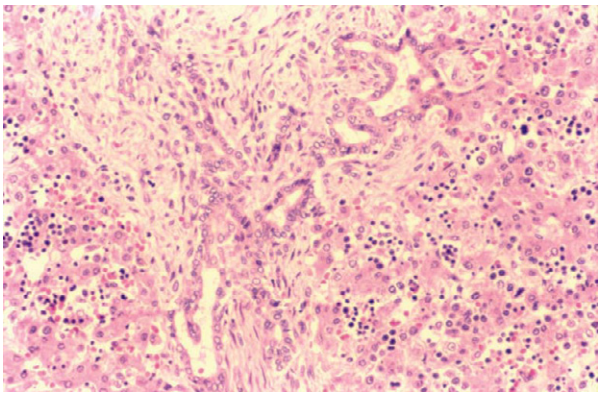

Figure 7. Histologic appearance of hepatic ductal proliferation (hematoxylin and eosin, 200×).

kidneys can be diagnosed before the 14th gestational weeks by ultrasonography [23,24]. Ickowicz et al [25] suggested that the kidneys of fetuses with MKS are enlarged and cystic, and have unusual corticomedullary differentiation, which can be observed as early as the first and early second trimesters. However, later in pregnancy, severe oligohydramnios may make the diagnosis of polydactyly and encephalocele difficult. MKS has variability in clinical features. Salonen [26] in a study of clinicopathologic findings in 67 patients with MKS found that all had cystic dysplasia of the kidneys, 85% had an occipital encephalocele, and 96% had polydactyly. For the uncharacteristic cases, an accurate diagnosis may rely on molecular genetic testing and pathologic examination. The common abnormalities of MKS include occipital encephalocele, microcephaly with sloping forehead, cerebral and cerebellar hypoplasia, anencephaly,

hydrocephaly with or without an Arnold-Chiari malformation, absence of olfactory lobes, olfactory tract, corpus callosum, and septum pellucidum, microphthalmia, cleft palate, micrognathia, ear anomalies, a short neck, postaxial polydactyly, talipes, renal dysplasia with varying degrees of cystic formation, bile duct proliferation, hepatic fibrosis and cysts, cryptorchidism, and incomplete development of external and/or internal genitalia [27]. Occasional abnormalities include craniosynostosis, coloboma of iris, hypoplastic optic nerve, hypoplastic philtrum and/or nasal septum, hypertelorism, midline cleft lip, a lobulated tongue, cleft epiglottis, neonatal teeth, a webbed neck, relatively short boned limbs, syndactyly, simian creases, clinodactyly, cardiac septal defects, patent ductus arteriosus, coarctation of aorta, pulmonary stenosis, pulmonary hypoplasia, Dandy-Walker malformation, single umbilical artery, patent urachus, omphalocele, intestinal malrotation, spleen abnormalities, laterality defects, adrenal hypoplasia, imperforate anus, missing or duplicated ureters, absent or hypoplastic urinary bladder, and enlarged placenta [27].

Differential Diagnosis

Differential diagnosis for MKS includes autosomal recessive PKD, trisomy 13, Smith-Lemli-Opitz syndrome (SLOS), hydrolethalus syndrome, SLSN, JBTS, BBS, and OFD1 [13,18,28].

Autosomal recessive PKD

Autosomal recessive PKD (ARPKD) (OMIM 263200) is caused by mutations in the *PKHD1* gene, which encodes fibrocystin, a receptor protein that acts in collecting-duct and biliary differentiation [29]. ARPKD is characterized by cystic, enlarged kidneys and hepatic fibrosis with severe early-onset symptoms.

Trisomy 13

Trisomy 13 is associated central nervous system abnormalities such as holoprosencephaly, agenesis of corpus callosum, hydrocephalus, fusion of basal ganglia, cerebellar hypoplasia and meningomyelocele, polycystic kidneys (31%), hydronephrosis, horseshoe kidneys and duplicated ureters, postaxial polydactyly of hands and sometimes feet, heterotopic pancreatic or splenic tissues, cardiovascular malformations, and ocular anomalies, but does not have hepatic fibrosis [27].

Smith-Lemli-Opitz syndrome

SLOS (OMIM 270400) is an autosomal recessive disorder caused by mutations in the *DHCR7* gene and deficiency of 7-dehydrocholesterol δ^7-reductase (DHCR7) in the cholesterol biosynthesis pathway [30]. SLOS is characterized by central nervous system malformations such as microcephaly, ventriculomegaly, agenesis of corpus callosum, cerebellar hypoplasia and less often holoprosencephaly (5%), genital abnormalities such as ambiguous genitalia and sex reversal, upper urinary tract malformations such as ureteropelvic junction obstruction, hydronephrosis, renal cystic dysplasia, renal duplication, renal agenesis, and reflux, postaxial polydactyly of hands but less often of feet, hepatic dysfunction, and cholestatic liver disease [27].

Hydrolethalus syndrome

Hydrolethalus syndrome (OMIM 236680) is an autosomal recessive disorder caused by mutations in the *HYLS1* gene [31]. Hydrolethalus syndrome is characterized by polyhydramnios, lethality, postaxial polydactyly of hands, preaxial polydactyly of feet, micrognathia, cleft lip and palate, cardiac septal defects, and hydrocephaly with absent midline structure of the brain but does not have cystic kidneys, hepatic ductal plate malformations, or encephalocele [27,31].

Senior-Loken syndrome

SLSN (OMIM 266900) is an autosomal recessive ciliary dysfunction disorder caused by mutations in the *NPHP* genes responsible for nephronophthisis (NPHP) [32]. NPHP is a cystic renal disease characterized by progressive wasting of the filtering unit of the kidney with or without medullary involvement. SLSN can be associated with retinitis pigmentosa, renal cystic disease, *situs inversus*/isomerism, Dandy-Walker malformation, and hepatic disease but does not have polydactyly and posterior encephalocele [13].

Joubert syndrome

JBTS (OMIM 213300) is a genetically heterogeneous ciliary dysfunction disorder characterized by hypoplasia of the cerebellar vermis with the characteristic neuroradiologic "molar tooth sign" and neurologic syndrome. Other variable features include retinal dystrophy and renal anomalies. JBTS4 is caused by mutations in the *NPHP1* gene [33], and JBTS5 is caused by mutations in the *CEP290* or *NPHP6* gene [34]. JBTS can be associated with retinitis pigmentosa, renal polycystic disease, polydactyly, *situs inversus*/isomerism, mental retardation/developmental delay, hypoplasia of corpus callosum, Dandy-Walker malformation, posterior encephalocele, and hepatic disease [23].

Bardet-Biedl syndrome

BBS (OMIM 209900) is a genetically heterogeneous ciliary dysfunction disorder, and 11 genes (*BBS1-BBS11*)

were identified. BBS is characterized by postaxial polydactyly, progressive retinal dystrophy, obesity, hypogonadism, learning difficulty, and renal dysfunction [35]. Other features include diabetes mellitus, ataxia, congenital heart defects, dental malformations, hepatic fibrosis, anosmia, and asthma. Karmous-Benailly et al [35] identified a recessive mutation in a BBS gene in six cases (three in the *BBS2* gene, two in the *BBS4* gene, and one in the *BBS6* gene), and observed a heterozygous mutation in the *BBS6* gene in three additional cases in a series of 13 antenatal cases presenting with cystic kidneys, polydactyly, and/or hepatic fibrosis but no encephalocele. Karmous-Benailly et al [35] demonstrated a clinical overlap between BBS and MKS and suggested that prenatal presentation of BBS may mimic MKS.

Oral-facial-digital syndrome type 1

OFD1 (OMIM 311200) is an X-linked dominant male-lethal ciliary dysfunction disorder caused by mutations in the *OFD1* or *CXORF5* gene [19,36]. OFD1 is characterized by oral frenula and clefts, hypoplasia of alae nasi, digital asymmetry with clinodactyly, syndactyly or brachydactyly of hands and unilateral polydactyly of feet, variable mental deficiency, occasional brain malformations (20%) including absent of corpus callosum, porencephaly, hydrocephalus, vermis hypoplasia and Dandy-Walker malformation, and adult PKD but does not have occipital encephalocele [27].

Conclusion

This article provides an overview of genetics, perinatal findings, and differential diagnosis of MKS. The ciliopathy underlies the pathogenesis of MKS. Prenatal diagnosis of bilateral enlarged multicystic kidneys should alert MKS and prompt a thorough investigation of central nervous system malformations and polydactyly.

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