SYNDROMES, DISORDERS AND MATERNAL RISK FACTORS ASSOCIATED WITH NEURAL TUBE DEFECTS (III)

Chih-Ping Chen1,2,3,4,5

1Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 2Department of Medical Research, Mackay Memorial Hospital, Taipei, 3Department of Biotechnology, Asia University, 4School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, and 5Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan.

SUMMARY

Fetuses with neural tube defects (NTDs) may be associated with syndromes, disorders, and maternal and fetal risk factors. This article provides a comprehensive review of syndromes, disorders, and maternal and fetal risk factors associated with NTDs, such as omphalocele, OEIS (omphalocele-exstrophy-imperforate anus-spinal defects) complex, pentalogy of Cantrell, amniotic band sequence, limb–body wall complex, Meckel syndrome, Joubert syndrome, skeletal dysplasia, diabetic embryopathy, and single nucleotide polymorphisms in genes of glucose metabolism. NTDs associated with syndromes, disorders, and maternal and fetal risk factors are a rare but important cause of NTDs. The recurrence risk and the preventive effect of maternal folic acid intake in NTDs associated with syndromes, disorders and maternal risk factors may be different from those of nonsyndromic multifactorial NTDs. Perinatal identification of NTDs should alert the clinician to the syndromes, disorders, and maternal and fetal risk factors associated with NTDs, and prompt a thorough etiologic investigation and genetic counseling. [Taiwan J Obstet Gynecol 2008;47(2):131–140]

Key Words: congenital malformations, disorder, maternal risk factors, neural tube defects, syndromes

Introduction

Neural tube defects (NTDs) have an incidence of 1–2 per 1,000 births and are considered to be a heterogeneous condition resulting from failure of normal neural tube closure between the third and fourth week of embryonic development. The three common types of NTDs are anencephaly, spina bifida, and encephalocele. The uncommon types of NTDs include amniotic band syndrome, limb–body wall complex (LBWC), cloacal exstrophy or omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex, and other types of spinal abnormalities. The incidence of NTDs varies with race, geographic variation, socioeconomic classes, nutritional status, and multiple predisposing factors such as single gene disorders, chromosomal abnormalities, teratogens, maternal diabetes, family history of NTDs and polymorphisms in the genes of folate metabolism [1]. There is considerable evidence that genetics and environmental factors contribute to the etiology of NTDs. Fetuses with NTDs may be associated with syndromes, disorders, and maternal and fetal risk factors.

Omphalocele

Calzolari et al [2] proposed that omphalocele and NTDs are related congenital anomalies by the findings of a tendency for omphalocele to be associated with
Omphalocele-Exstrophy-Imperforate anus-Spinal defects (OEIS) Complex

OEIS complex (OMIM 258040) arises from a single localized defect in the early development of the mesoderm that will later contribute to infraumbilical mesenchyme, cloacal septum and caudal vertebrae. The incidence of OEIS complex has been reported to range between 1/200,000 and 1/250,000 among live births [4]. OEIS complex, also known as ectopia cloacae, vesi-cointestinal fissure, exstrophy splanchnica or cloacal exstrophy, was named by Carey et al [5] to describe the combination of omphalocele, exstrophy of the bladder, an imperforate anus and spinal defects. This multisystem malformation represents the most severe form of the exstrophy–epispadias sequence, ranging from phallic separation with epispadias, pubic diastasis, bladder exstrophy, cloacal exstrophy to OEIS complex. Most cases of OEIS complex occur spontaneously. There are reports of recurrence in siblings and concurrent occurrence in monozygotic twins, suggesting a genetic contribution to the pathogenesis of OEIS complex [6–8]. Another explanation for the higher reported incidence of OEIS complex in monozygotic twins is that twinning formation with duplication of the organizer center within a single embryonic disc may disrupt the caudal eminence or its derivatives and increase the risk of mesodermal insufficiency resulting in failure of complete development of the cloacal membrane [8–9]. However, there are reports of monozygotic twins discordant for OEIS complex, suggesting a non-genetic etiology for OEIS complex [7,8]. The non-genetic etiology of OEIS complex includes uterine vascular pathogenesis, uteroplacental vascular insufficiency, in vitro fertilization, multiple gestation, trauma to the uterus or uterine vessels, and abnormal placentation [8,10,11]. OEIS complex or cloacal exstrophy has been shown to be associated with prenatal exposure to diazepam, in vitro fertilization and chorionic villus sampling, Opitz BBB syndrome, Goltz syndrome, trisomies 13, 18 and 21, triple X syndrome, oculoauriculo-vertebral syndrome, frontonasal dysplasia, mutations in mitochondrial 12S rRNA, and mutations in homeobox genes such as HLB9, 3q12.2–q13.2 deletion and 9q34.1–qter deletion [5,10,12–20]. Maternal α-fetoprotein is elevated in OEIS complex. Prenatal diagnosis of OEIS complex can be made using ultrasound. The characteristic sonographic findings of OEIS complex include nuchal thickening, omphalocele, lumbosacral myelomenigocele, failure to visualize the bladder and external genitalia, and limb defects such as clubfoot or a missing lower limb [8,10,11,16,21–31].

Pentalogy of Cantrell

The incidence of pentalogy of Cantrell has been estimated to be 1/65,000 among live births [32]. Cantrell et al [33] first described a specific combination of congenital defects with the following full pentalogy: (1) a midline supraumbilical abdominal wall defect, (2) a defect of the lower sternum, (3) a defect of the diaphragmatic pericardium, (4) a deficiency of the anterior diaphragm, and (5) congenital cardiac anomalies. Although incomplete expression of the syndrome is well recognized, the full pentalogy is a rare occurrence. Pentalogy of Cantrell is the most severe expression of anomalies in the ventral midline developmental field and is thought to be the result of mechanical teratogenesis [34], major gene mutation [35,36], chromosomal abnormalities, particularly trisomy 18 [37,38], and disruptive vascular defects [39]. Carmi and Boughman [40] reported that a cleft lip with or without a cleft palate, together with encephalocele, tended to be especially associated with ventral midline anomalies within the spectrum of pentalogy of Cantrell. Toyama [41], Spitz et al [42] and Ghidini et al [43] reviewed the literature and found that craniofacial malformations such as anencephaly, meningocele, encephalocele and hydrocephalus were associated with pentalogy of Cantrell. Other midline anomalies such as sirenomelia [39], frontonasal dysplasia [44], encephalophy [45–48], craniorachischisis [49], spina bifida [50] and a small posterior encephalocele with myelomenigocele [51] have also been reported to be associated with pentalogy of Cantrell. These findings support the proposal by Carmi and Boughman [40] that pentalogy of Cantrell is included among the defects of the midline developmental field.

Amniotic Band Sequence (ABS)

ABS consists of a group of sporadic abnormalities characterized by congenital ring constrictions or
amputation of digits and limbs, terminal digital fusion (pseudosyndactyly), talipes, and multiple craniofacial, visceral and body wall defects. Cranial defects associated with ABS include hydrocephalus, microcephaly, asymmetric encephalocele, meningocoele, exencephaly, acrania, acalvaria, and anencephaly. Facial anomalies include cleft lip (usually bilateral), bizarre midfacial clefts, nasal deformity, bony orbital clefts, hypertelorism, eye-lid colobomas, prosis, ectropion, lacrimal outflow obstruction, and corneal opacities. ABS is usually a sporadic event, although a few reported cases have been associated with teratogens such as methadone and lysergic acid diethylamide [32]. Familial ABS is due to hereditary connective tissue abnormalities such as Ehlers-Danlos syndrome type IV and osteogenesis imperfecta [32].

Limb–Body Wall Complex (LBWC)

LBWC describes a heterogeneous group of fetal malformations, including lateral body–wall defects and limb reduction anomalies [32,33–59]. Cases of LBWC with craniofacial defects frequently show severe anomalies of the upper limbs, craniofacial defects, constrictive amniotic bands, and cranioplacental attachment, whereas cases of LBWC without craniofacial defects usually present with major anomalies of the lower limbs, abnormal genitalia, anal atresia, renal defects, abdominoplacental attachment, and umbilical cord abnormalities [57,60]. The difference in the birth incidence between these two groups may be due in part to different pathogenesis or the lethality in cases of LBWC with craniofacial defects causing early pregnancy loss [57]. The pathogenetic theories concerning LBWC include early amnion rupture [61], vascular disruption [32,53], and early embryonic maldevelopment [62,63]. Russo et al [60] suggested that LBWC with craniofacial defects is caused by an early vascular disruption. LBWC without craniofacial defects is related to a defective lateral and caudal folding process of the embryonic disk [60].

Meckel Syndrome (MKS)

MKS, also known as dysencephalia splanchnocystica, Gruber syndrome or Meckel-Gruber syndrome, is a lethal, autosomal recessive ciliary dysfunction 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, its prevalence is 1/9,000 births [64]. MKS is genetically heterogeneous. Reported MKS loci include MKS1 (FLJ20345; OMIM 609883) in Meckel syndrome type 1 (MKS1; OMIM 249000) [65], MKS2 at 11q13 in MKS type 2 (MKS2; OMIM 603194) [66], MKS3 (TMEM67; OMIM 609884) in MKS type 3 (MKS3; OMIM 607361) [67], MKS4 (CEP290; OMIM 610142) in MKS type 4 (MKS4; OMIM 611134) [68], and MKS5 (RPGRIP1L; OMIM 610937) in MKS type 5 (MKS5; OMIM 611561) [69]. 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 [70]. Occasional abnormalities include craniostenosis, 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 [70].

MKS1

Paavola et al mapped the locus for MKS to chromosome 17q21–q24 [71] and further narrowed down the critical region for MKS on chromosome 17q22–q23 [72]. Kyttala et al [65] identified a gene MKS1 (FLJ20345; OMIM 609883) on 17q23 using positional cloning. MKS1 encodes a component of flagellar apparatus basal body proteome. MKS1 is 14 kb and consists of 18 exons. MKS1 contains an open reading frame (76–1755 base pairs) 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 the 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 a role in whole-cell locomotion, movement of fluid, chemo-, mechano- and photosensation,
and sexual reproduction [73]. 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 [65]. The identification of the gene MKS1 has provided a link between MKS and ciliary dysfunction. Ciliary dysfunction is associated with: (1) pronephric cyst formation and hydrocephalus in zebrafish embryos [74]; (2) polycystic kidney disease and Bardet-Biedl syndrome [75,76]; (3) polycystic kidney disease in the mouse model [77]; (4) primary ciliary dyskinesia, polycystic liver disease, retinal degeneration, and sexual reproduction [73]; (5) hypogonadism, deafness, obesity, mental retardation, NTDs, lateral defects and palatal clefts [78]; and (6) oral-facial-digital syndrome type 1 [79]. 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.

**MKS2**

The MKS2 gene has yet to be identified at the time of this writing. However, Roume et al [66] mapped the locus for MKS to chromosome 11q13. The authors pointed out that the D11S911–D11S906 interval encompassing the gene also encompasses a gene Phox2a, which is strongly expressed in the mouse hindbrain.

**MKS3**

Morgan et al [80] mapped the locus for MKS to chromosome 8q24. Smith et al [67] 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 the transmembrane protein meckelin. MKS3 spans 62,018 base pairs and consists of 28 exons. MKS3 code for a 995-amino acid, seven-transmembrane receptor protein known as meckelin. The human locus of MKS3 is syntenic to the Wpk locus in rat, which has birth defects similar to MKS such as polycystic kidney disease, agenesis of the corpus callosum and hydrocephalus [81,82]. Human and rat meckelin are 84% identical and 91% similar [67]. Meckelin contains a signal peptide, at least two cysteine-rich repeats, a 490-residue extracellular region with four N-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 for accurate genetic counseling, carrier testing and prenatal diagnosis.

**MKS4**

Baala et al [68] performed a genome-wide linkage scan in eight families unlinked to MKS1, MKS2, or MKS3 and identified truncating mutations in CEP290 or NPHP6 (OMIM 610142) on 12q21.3 in two families with MKS and in four families with a cerebro-reno-digital syndrome having a phenotype overlapping with MKS and JBTS. Frank et al [83] identified a frameshift mutation in CEP290 in a consanguineous family with two MKS fetuses and suggested the pleiotropic effects of CEP290 mutations ranging from single-organ involvement with isolated Leber congenital amaurosis to JBTS and lethal early embryonic multisystemic malformations in MKS. CEP290 gene or NPHP6 encodes nephrocystin-6 (NPHP6) or 3H11Ag, which is a peripheral membrane protein associated with the nuclear membrane [84]. Valente et al [85] detected CEP290 expression in proliferating cerebellar granule populations and showed centrosome and ciliary localization. Mutations in CEP290 cause pleiotropic forms of JBTS [85] and oculo-renal form of JBTS-related disorders [86].

**MKS5**

Delous et al [69] identified homozygous or compound heterozygous truncating mutations in RPGRIP1L gene (OMIM 610937) on 16q12.2 of three patients with MKS and missense mutations in RPGRIP1L of five patients with JBTS. Their findings suggested that mutations in RPGRIP1L can cause the multiorgan phenotypic abnormalities in MKS or JBTS. Arts et al [87] identified homozygous or compound heterozygous mutations in RPGRIP1L of patients with JBTS. RPGRIP1L gene or KIAA1005 encodes RPGRIP1L protein which is localized to basal bodies and ciliary axonemes at the base of primary cilia and is a nephrocystin-4 interactor [69,87].

**Joubert Syndrome (JBTS)**

JBTS (OMIM 213300) is an autosomal recessive ciliary dysfunction disorder characterized by hypoplasia of the cerebellar vermis with the characteristic brain stem malformation and neuroradiologic “molar tooth sign”, and variable features including retinal dystrophy and renal anomalies. About a quarter of patients with JBTS have nephronophthisis (NPHP) and retinal dystrophy, which is termed as cerebello-ocular-renal syndrome or JBTS type B. NPHP consists of tubulointerstitial fibrosis and cysts at the corticomedullary junction. JBTS has an incidence of 1 in 100,000 births [88]. Reported JBTS loci include AHI1 [89], NPHP1 [90], MKS3/TMEM67 [91], MKS4/CEP290 [92], and MKS5/RPGRIP1L [69,87]. JBTS4 is caused by mutations in
the NPHP1 gene [90], JBTS5 is caused by mutations in the MKS4/CEP290 gene [85], JBTSS6 is caused by mutations in the MKS3/TMEM67 gene [91], and JBTSS7 is caused by mutations in the MKS5/RPGRIP1L gene [69,87]. Mutations in four genes, MKS1/FLJ20345 [65], MKS3/TMEM67 [67], MKS4/CEP290 [68] and MKS5/RPGRIP1L [69,87], have been identified in MKS, and mutations in MKS3/TMEM67 [91], MKS4/CEP290 [85,86,91] and MKS5/RPGRIP1L [69,87] have been identified in JBTS, indicating that MKS and JBTS constitute a continuum of the same disorder. 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 [73]. Senior-Loken syndrome (SLSN; OMIM 266900) is an autosomal recessive ciliary dysfunction disorder caused by mutations in the NPHP1 gene [93] and MKS4/CEP290 [94]. NPHP is a cystic renal disease characterized by progressive wasting of the filtering unit of the kidney with or without medullary involvement. NPHP is associated with mutations in the genes of NPHP1 and MKS4/CEP290 [94]. 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 [73]. NPHP, MKS and SLSN share JBTS phenotypes. Among the five JBTS genes (AH11, NPHP1, MKS3/TMEM67, MKS4/CEP290 and MKS5/RPGRIP1L), three genes (MKS3/TMEM67, MKS4/CEP290 and MKS5/RPGRIP1L) are also associated with MKS, and two genes (NPHP1 and MKS4/CEP290) are also associated with SLSN and NPHP, indicating genetic complexity in JBTS and related disorders [88].

Diabetic Embryopathy

Reece [101,102] has summarized the oxidative stress model of diabetic embryopathy as follows: (1) hyperglycemia increases the levels of free radicals and the production of reactive species, causing oxidative stress; and (2) oxidative stress increases the levels of apoptosis-inducing signaling molecules and simultaneously decreases the levels of molecules that are protective of the cell, leading to cell suicide or apoptosis. Pampfer et al [103] reported increase in the activity of apoptotic pathways and increased cell death in the mouse blastocysts exposed to high glucose in utero or tumor necrosis factor-α in vitro. Reece [104] hypothesized that hyperglycemia results in the excess production of reactive oxygen species which lead to oxidative stress. Dhanasekaran et al [105] hypothesized that signaling pathways play a critical role in diabetic embryopathy. Reece et al [106] noted that hyperglycemia in maternal diabetes triggered oxidative stress, which enhanced apoptotic signaling pathways and inhibited cell survival pathways, leading to diabetes-induced embryopathy. In that study by Reece et al, hyperglycemia induced disruption of cellular apoptotic signaling pathways with findings of a significantly decreased level of the cell survival factor, phosphorylated Akt, and an increased level of the proapoptotic protein Bax. Gäreskog et al [107] found that supplementation of N-acetylcysteine, an apoptosis inhibitor, ameliorated diabetes-induced birth defects. Reece et al [108] reported that dietary vitamin and lipid therapy rescued aberrant signaling and apoptosis, and prevented hyperglycemia-induced diabetic embryopathy in mice. Using DNA microarray analysis, Reece et al [109] determined the developmental genes and molecular pathways involved in diabetic embryopathy, such as those in insulin signaling stress response (insulin 2, insulin-binding protein 1, GSTπ1), cell growth (GAP43, CSF1R, HGF), and calcium signaling (calbindin-3, CBPA6) and PKC signaling (PKCBP15, FABP5). Yang et al [110,111] found that activation of the kinase c-Jun N-terminal kinases (JNKs), the most prominent mediator of oxidative stress-induced apoptosis, mediated the deleterious effect of hyperglycemia on yolk sac vasculature and embryonic development. In the mouse model of diabetic embryopathy, Yang et al [112] found that there

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were activation of mediators of oxidative stress-induced apoptosis, such as JNKs and P66Shc, and increase of apoptotic markers.

Single Nucleotide Polymorphisms (SNPs) in Genes of Glucose Metabolism

Genes of glucose metabolism have been suggested to be associated with impaired development and deformities that are similar to diabetic embryopathy in mice [113] and in humans [114]. Heilig et al [113] reported that isolated glucose transporter 1 (GLUT1) suppression in mice impaired embryonic development, leading to developmental malformations that were similar to diabetic embryopathy. In the study of Heilig et al [113], the appearance of apoptosis in the GLUT1-deficient mouse embryos suggested that GLUT1 deficiency may play a role in producing embryonic malformations resulting from the hyperglycemia of maternal diabetes mellitus. Davidson et al [114] found three SNPs in the three glucose metabolism genes, GLUT1, HK1 and LEPR, to be associated with spina bifida in humans. GLUT1, HK1 and LEPR are responsible for the respective proteins, glucose transporter 1 (GLUT1), hexokinase 1 (HK1) and leptin receptor (LEPR), which are key signaling intermediates in the glucose transporter pathway, the hexokinase pathway and the leptin pathway, respectively. GLUT1 is essential for human brain development and function. GLUT1 deficiency results in aberrant brain organogenesis and apoptosis during embryonic development in zebrafish embryos [115]. The glycolytic enzyme HK1 binds mitochondria with high affinity at outer mitochondrial membrane and changes in outer mitochondrial membrane permeability leads to apoptosis. Majewski et al [116] found that Akt inhibited apoptosis by maintenance of hexokinase–mitochondria interaction. Leptin actions are delivered through the Ob (leptin) receptor, and leptin inhibits apoptosis through several intracellular signaling pathways [117]. SNPs on GLUT1, HK1 and LEPR may result in functionally inactive or dominant negative proteins that blunt the prosurvival functions, leading to apoptosis and increased susceptibility to spina bifida [101,114].

Conclusion

This article provides a comprehensive review of syndromes, disorders, and maternal and fetal risk factors associated with NTDs, such as omphalocoele, OEIS complex, pentalogy of Cantrell, ABS, LBWC, Meckel syndrome, JBTS, skeletal dysplasia, diabetic embryopathy, and SNPs in genes of glucose metabolism. NTDs associated with syndromes, disorders, and maternal and fetal risk factors are a rare but important cause of NTDs. The recurrence risk and the preventive effect of maternal folic acid intake in NTDs associated with syndromes, disorders, and maternal and fetal risk factors may be different from those of nonsyndromic multifactorial NTDs. Perinatal identification of NTDs should alert the clinician to the syndromes, disorders, and maternal and fetal risk factors associated with NTDs, and prompt a thorough etiologic investigation and genetic counseling.

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