Syndromes, Disorders and Maternal Risk Factors Associated with Neural Tube Defects (V)

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SUMMARY

Fetuses with neural tube defects (NTDs) may suffer from associated syndromes and disorders. This article provides a comprehensive review of the syndromes and disorders associated with NTDs, including Pallister-Hall syndrome, Walker-Warburg syndrome and Fukuyama congenital muscular dystrophy, MURCS association, Roberts syndrome, cerebro-costo-mandibular syndrome, laterality sequences, hydrolethalus syndrome, Knobloch syndrome, oculoauriculovertebral spectrum (hemifacial microsomia), cervico-oculo-acoustic syndrome, Fanconi anemia, Miller-Dieker lissencephaly syndrome, Fraser syndrome, frontonasal dysplasia, Adams-Oliver syndrome, CHILD syndrome, dyssegmental dysplasia, and monozygotic twinning. NTDs associated with these syndromes and disorders are a rare but important cause of NTDs. The risk of NTDs in subsequent fetuses and the preventive effect of maternal folic acid intake in NTDs associated with syndromes and disorders may be different from those of nonsyndromic multifactorial NTDs. Perinatal diagnosis of NTDs should alert doctors to the syndromes and disorders associated with NTDs, and prompt thorough etiologic investigation and genetic counseling. [*Taiwan J Obstet Gynecol* 2008;47(3):259–266]

Key Words: congenital malformations, disorder, 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 weeks of embryonic development. The three common types of NTDs are anencephaly, spina bifida and encephalocele, while less common types include amniotic band syndrome, limb–body wall complex, cloacal exstrophy or omphalocele-exstrophy-imperforate anus-spinal defects complex and other types of spinal abnormalities. The incidence of NTDs varies with race, geographic location, socioeconomic class, 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 controlling folate metabolism. There is considerable evidence to suggest that both genetic and environmental factors contribute to the etiology of NTDs. Fetuses with NTDs may suffer from associated syndromes and disorders. These are examined below.

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Pallister-Hall Syndrome

Pallister-Hall syndrome (OMIM 146510) is an autosomal dominant disorder with variable expression and is characterized by hypothalamic hamartoblastoma,

hypopituitarism, imperforate anus, and postaxial polydactyly. Occipital encephalocele is an occasional abnormality in Pallister-Hall syndrome [1]. Finnigan et al [2] reported the case of a female infant with Pallister-Hall syndrome who had a large skin-covered occipital encephalocele, bilateral cleft lip and palate, a small tongue and mandible, upper limb postaxial polydactyly, fused digits, and Dandy-Walker malformation. Mutations in the *GLI3* zinc finger transcription factor gene (OMIM 165240) cause Pallister-Hall syndrome and Greig cephalopolysyndactyly syndrome (OMIM 175700) [3]. The zinc finger transcription factor GLI3 is essential for pattern formation in the developing brain, face and limbs [4]. In a mouse model, Aoto et al [4] found that GLI3 regulates *Fgf8* expression and apoptosis in the developing neural tube, face and limb buds.

Walker-Warburg Syndrome and Fukuyama Congenital Muscular Dystrophy

Walker-Warburg syndrome (OMIM 236670) or HARD± E syndrome is an autosomal recessive disorder characterized by hydrocephalus (H), agyria (A), retinal dysplasia (RD) with or without encephalocele (± E), and congenital muscular dystrophy. Associated brain abnormalities include type II lissencephaly (100%), cerebellar malformation (100%), ventriculomegaly (95%), Dandy-Walker malformation (53%), and occipital encephalocele (24%) [5]. Rodgers et al [6] reported three affected siblings whose parents were cousins, and hydrocephalus, a cerebellar cyst and a small occipital encephalocele were detected in the third fetus by prenatal ultrasound at 19 weeks' gestation. Dobyns et al [7] reviewed 21 cases of Walker-Warburg syndrome and found that five cases contained posterior encephaloceles. Walker-Warburg syndrome is caused by mutations in the *POMT1* (OMIM 607423) [8], *FCMD* (OMIM 607440) [9], *FKRP* (OMIM 606596) [10], *POMT2* (OMIM 607439) [11] and *LARGE* (OMIM 603590) [12] genes. *POMT1* and *POMT2* encode proteins O-mannosyltransferase 1 and O-mannosyltransferase 2, respectively. Fukuyama congenital muscular dystrophy (OMIM 253800) has a phenotype that overlaps with mild Walker-Warburg syndrome and is caused by mutations in the *FCMD* gene encoding fukutin [13].

MURCS Association

MURCS association (OMIM 601076) is a sporadic disorder of unknown etiology and is characterized by Müllerian duct aplasia (MU), unilateral renal aplasia (R) and cervicothoracic somite dysplasia (CS). Occipital encephalocele is an occasional abnormality seen in MURCS association [14]. Lin et al [15] reported the combination of MURCS association and occipital encephalocele in a 41-week-gestation stillborn girl and suggested that MURCS association is a defect in the organization of the paraxial mesoderm that gives rise to occipital, cervical and thoracic somites, and adjoining intermediate mesoderm. Suri et al [16] reported MURCS association in a 23-week-gestation female fetus with occipital encephalocele, dysraphism of the cervical spine, right renal agenesis, Müllerian agenesis, posterior cleft palate, absent left umbilical artery, and Meckel's diverticulum.

Roberts Syndrome

Roberts syndrome (OMIM 268300), also known as SC phocomelia syndrome, pseudothalidomide syndrome or hypomelia-hypotrichosis-facial hemangioma syndrome, is an autosomal recessive disorder characterized by hypomelia, midface defects, and severe growth deficiency. Frontal encephalocele can be an occasional abnormality [17]. Roberts syndrome is caused by mutations in the *ESCO2* gene (OMIM 609353), and the ESCO2 protein product is required for establishment of sister chromatid cohesion during S phase [18]. Ekong and Rozdilsky [19] reported hydranencephaly and imperforate anus in association with Roberts syndrome.

Cerebro-costo-mandibular Syndrome

Cerebro-costo-mandibular syndrome (CCMS) (OMIM 117650) is characterized by Pierre Robin anomaly, speech difficulties, severe micrognathia with glossoptosis, a small thorax with rib-gap defects, and occasional intellectual impairment. CCMS has an autosomal recessive inheritance pattern, and in some cases, there is parent-to-child transmission, suggesting autosomal dominant inheritance [20]. Corpus callosum agenesis, dilated lateral ventricles, hydranencephaly and meningomyelocele can be occasional brain abnormalities [20]. Hennekam et al [21] reported two brothers affected by CCMS and spina bifida.

Laterality Sequences

Laterality sequences are heterogeneous defects that can be sporadic, autosomal dominant, autosomal recessive

or X-linked recessive [22]. They include bilateral left-sidedness sequence (polysplenia syndrome), bilateral right-sidedness sequence (asplenia syndrome; triad of spleen agenesis, defects of heart and vessels, and situs inversus), and left-right axis malformations such as autosomal recessive Kartagener syndrome (immotile cilia syndrome) (OMIM 244400), autosomal dominant laterality defects (OMIM 601086) and X-linked visceral heterotaxy (OMIM 306955). Kartagener syndrome is characterized by bronchiectasis, sinusitis, dextrocardia and infertility, and can be caused by mutations in the axonemal dynein intermediate chain gene (*DNAI1*) (OMIM 604366) [23] and mutations in the *DNAH5* gene (OMIM 603335) [24]. Vitale et al [25] suggested an autosomal dominant pattern of inheritance of laterality defects with linkage of situs inversus and left-right axis anomalies to chromosome 6p. X-linked visceral heterotaxy is characterized by situs inversus, complex cardiac defects and splenic defects, and can be caused by mutations in the *ZIC3* gene (OMIM 300265) [26–28]. Meningomyelocele, cerebellar hypoplasia and arrhinencephaly are occasional brain abnormalities associated with laterality sequences [22]. Abu Musa et al [29] reported a case of exencephaly with rachischisis, situs ambiguous and club feet diagnosed prenatally by ultrasound at 20 weeks' gestation. Sohail et al [30] reported a female child with situs ambiguous, bronchiectasis, duodenal malrotation, umbilical hernia, and spina bifida.

Hydrolethalus Syndrome

Hydrolethalus syndrome (OMIM 236680) is an autosomal recessive disorder characterized by hydrocephalus, micrognathia and polydactyly [31]. Mee et al [32] identified mutations in the *HYLS1* gene (OMIM 610693) in the hydrolethalus syndrome belonging to the Finnish disease heritage. Anencephaly can be an occasional abnormality associated with hydrolethalus syndrome [31]. Although the main central nervous system (CNS) derangement in hydrolethalus syndrome is hydrocephalus, NTDs have also been described in hydrolethalus syndrome [33–36]. Salonen et al [33] reported one case of anencephaly rather than hydrocephalus among 28 cases of hydrolethalus syndrome. Christensen et al [34] reported two siblings (a male fetus and a female fetus) with anencephaly, median cleft lip, omphalocele and polydactyly, suggesting the diagnosis of acrocallosal syndrome or hydrolethalus syndrome. Camera et al [35] reported prenatal diagnosis of hydrolethalus syndrome at 26 weeks' gestation in a pregnancy complicated by polyhydramnios, and the female newborn showed hydrocephalus, occipital encephalocele, micrognathia, interventricular defects, and hallucal duplication. Chan et al [36] reported prenatal diagnosis of hydrolethalus syndrome at 12 weeks' gestation in a female fetus with increased nuchal translucency, polydactyly, syndactyly, occipital encephalocele, and a univentricular heart.

Knobloch Syndrome

Knobloch and Layer [37] were the first to describe a family in which five of ten siblings from unrelated parents had high myopia, vitreoretinal degeneration with occipital encephalocele, and normal intelligence. Knobloch syndrome (OMIM 267750), also known as retinal detachment and occipital encephalocele, is an autosomal recessive disorder characterized by high myopia, vitreoretinal degeneration, retinal detachment, macular abnormalities, and midline encephalocele, mainly in the occipital region. There is intra- and interfamilial variability in Knobloch syndrome, particularly for encephalocele, and allelic variants of the affected gene may play a role in the variability of encephalocele [38–39]. Knobloch syndrome is caused by mutations in the collagen XVIII gene (*COL18A1*) at 21q22.3 [40]. Sniderman et al [41] reported a patient with Knobloch syndrome and a midline scalp defect of the frontal region. Seaver et al [42] found heterotopic neuronal tissue in the occipital scalp defect associated with Knobloch syndrome. Wilson et al [43], in histologic examinations of the wall of the scalp defect associated with Knobloch syndrome, found a cystic-like space lined by multilayered meningothelium containing a small amount of neuroglial tissue, and supported the use of the term "encephalocele" in Knobloch syndrome. Kliemann et al [39] reviewed 24 reported cases of Knobloch syndrome and found that neural tube closure defects occurred in 22 cases of these. Kliemann et al [39] hypothesized that Knobloch syndrome was a neuronal migratory defect and suggested that collagen XVIII plays a role in neuronal migration.

Oculoauriculovertebral Spectrum or Hemifacial Microsomia

Oculoauriculovertebral spectrum (OAVS), hemifacial microsomia (OMIM 164210) or Goldenhar syndrome is characterized by birth defects involving the first and second brachial arches, such as unilateral deformity of the external ears and small ipsilateral half of the face with epibulbar dermoid, vertebral anomalies, coloboma of the upper eyelid, and microphthalmia. Most cases

of OAVS occur sporadically. However, there are familial cases consistent with autosomal dominant and autosomal recessive inheritance. Wang et al [44] found that infants of diabetic mothers were at increased risk for OAVS. Wieczorek et al [45] suggested that assisted reproductive technologies were associated with increased risk of OAVS. In a review of 21 cases with OAVS, Castori et al [46] found that CNS anomalies occurred in 10 cases (47.6%), including hydrocephalus (seven cases), occipital encephalocele (one case), cerebral hemisphere/vermis hypoplasia (one case) and hydrocephalus with lipoma of the corpus callosum (one case). Aleksic et al [47] reported encephalocele in a case with Goldenhar-Gorlin syndrome. Gustavon and Chen [48] reported Goldenhar syndrome, hemifacial microsomia, tetralogy of Fallot, anterior encephalocele and aqueductal stenosis in a male infant following fetal primidone exposure. Kita et al [49] reported a male neonate with Goldenhar syndrome, facial microsomia, auricular malformation, and occipital meningoencephalocele. Strömland et al [50], in a review of Swedish patients, found one occipital encephalocele among 18 OAVS cases.

Cervico-oculo-acoustic Syndrome

Cervico-oculo-acoustic syndrome (COAS) (OMIM 314600) or Wildervanck syndrome is characterized by Klippel-Feil anomaly (congenitally fused cervical vertebrae), abducens paralysis with retraction of the eyeball (Duane syndrome), and sensorineural deafness. COAS has polygenic inheritance limited to females [51]. There is possible lethality in the hemizygous males. Occipital meningocele, cerebellar and brainstem hypoplasia, primarily involving the pons and medulla, cervical diastematomyelia, and hydrocephalus can be occasional CNS anomalies associated with COAS [52]. Wildervanck et al [53] originally described rachischisis as a salient feature of COAS. Fraser and MacGillivray [54] reported two adult females with COAS and occipital meningocele. Primrose [55] reported an adult female with COAS and occipital meningocele.

Fanconi Anemia

Fanconi anemia (FA) (OMIM 227650) is an autosomal recessive disorder characterized by radial hypoplasia, hyperpigmentation, pancytopenia, a unique cellular hypersensitivity to DNA cross-linking agents, and high risk of malignancies. FA can be caused by mutations in the Fanconi anemia complementation group genes such as *FANCA* (OMIM 607139), *FANCB* (OMIM 300515), *FANCC* (OMIM 227645), *FANCD1* (OMIM 605724), *FANCD2* (OMIM 227646), *FANCE* (OMIM 600901), *FANCF* (OMIM 603467), *FANCG* (OMIM 602956), *FANCI* (OMIM 611360), *FANCJ* (OMIM 605882), *FANCL* (OMIM 608111), *FANCM* (OMIM 609644) or *FANCN* (OMIM 610832). FA has the feature of genetic instability and a strong predisposition to cancer [56], because the FA/BRCA pathway is involved in the repair of DNA damage [57]. CNS abnormalities occur in 8% of FA patients and include hydrocephalus, absent septum pellucidum, absent corpus callosum, NTDs, migration defects, Arnold-Chiari malformation, and single ventricle [58]. Giampietro et al [59] reviewed 370 reported cases of FA and found that NTDs occurred in three cases (0.8%).

Miller-Dieker Lissencephaly Syndrome

Miller-Dieker lissencephaly syndrome (MDLS) (OMIM 247200) is characterized by microcephaly, lissencephaly (smooth brain), and a distinctive facial appearance consisting of prominent forehead, bitemporal hollowing, a short nose with upturned nares, a protuberant upper lip and a small jaw. MDLS is a chromosomal disorder caused by deletion of chromosome 17p13.3. Deletion or mutation in the *LIS1* gene (*PAFAH1B1*) (OMIM 601545) on 17p13.3 causes lissencephaly [60], and deletion of the additional genes such as *14-3-3ε* and *CRK* in combination with deletion of *LIS1* may contribute to the more severe form of lissencephaly seen only in patients with MDLS [61]. MDLS can be associated with lipomeningocele with tethered cord [62]. Dobyns et al [63] reported a patient with tethered cord resulting from lipomyelomeningocele.

Fraser Syndrome

Fraser syndrome (OMIM 219000) or cryptophthalmos syndrome is an autosomal recessive disorder characterized by: the major criteria of cryptophthalmos, syndactyly, abnormal genitalia and sib with Fraser syndrome; and minor criteria of congenital malformation of nose, congenital malformation of ears, congenital malformation of larynx, cleft lip with or without cleft palate, skeletal defects, umbilical hernia, renal agenesis, and mental retardation [64]. Fraser syndrome can be caused by mutations in the *FRAS1* gene (OMIM 607830) [65] and the *FREM2* gene (OMIM 608945) [66], both of which encode extracellular matrix proteins. In a review of 117 cases diagnosed

as Fraser syndrome or cryptophthalmos, Slavotinek and Tifft [64] found that four had hydrocephalus, three polymicrogyria or abnormal brain gyri and two encephaloceles. Other single findings included mild cerebellar hypoplasia, holoprosencephaly, periventricular leucomalacia, and diffuse gliosis of the brain. Kulkarni et al [67] reported an infant with cryptophthalmos, occipital encephalocele, and bilateral cutaneous syndactyly. Gündüz and Günalp [68] reported an 18-year-old male patient with right congenital symblepharon (abortive cryptophthalmos) and right frontal meningoencephalocele.

Frontonasal Dysplasia

Frontonasal dysplasia (OMIM 136760) or median cleft face syndrome is characterized by hypertelorism, a broad nasal root, lack of a nasal tip, a widow's peak, and anterior cranium bifidum. Basal encephalocele is sometimes part of the syndrome and may cause serious or even life-threatening symptoms. Most cases are thought to be sporadic, although autosomal dominant inheritance, multifactorial inheritance, autosomal recessive inheritance and X-linked dominant inheritance have been proposed. Guion-Almeida et al [69], in an analysis of 21 Brazilian patients with frontonasal dysplasia, found a high frequency of associated brain abnormalities, such as basal encephalocele (10 cases; 47.6%), macrocephaly (six cases; 28.6%), agenesis of the corpus callosum (12 cases; 57.1%), lipoma of the corpus callosum (four cases; 19%) and mental deficiency (11 cases; 52.4%). Grubben et al [70] reported two cases of frontonasal dysplasia associated with anterior basal encephalocele. Moore et al [71] reported imaging identification of previously unsuspected basal encephalocele in patients with frontonasal dysplasia. Mohammed et al [72] reported five cases of monozygotic (MZ) twins discordant for frontonasal dysplasia, of which two cases had frontal encephalocele.

Adams-Oliver Syndrome

Adams-Oliver syndrome (AOS) (OMIM 100300) is characterized by congenital scalp defects with distal limb reduction defects and underlying osseous skull defects. If there is an underlying osseous skull defect, the meninges can be involved [73]. In most cases, AOS has an autosomal dominant inheritance pattern, although autosomal recessive inheritance has also been reported. Occasional CNS abnormalities associated with AOS include encephalocele, acrania, microcephaly, arrhinencephaly, defects of neuronal migration with combined focal pachygyria and dysplastic cerebral cortex [74]. Farrell et al [75], in a review of 102 cases of AOS, found that 78% of the cases had defects of lower limbs, 59% had defects of the upper limbs, 56% had scalp defects, and 21% had skull defects. Chitayat et al [76] reported a 10-year-old male with AOS and acrania. ten Donkelaar et al [77] reported a case of possible AOS with rudimentary occipital encephalocele.

CHILD Syndrome

CHILD syndrome (OMIM 308050) is an acronym for unilateral congenital hemidysplasia (CH) with ichthyosiform erythroderma (I) and limb defects (LD). The CHILD syndrome is an X-linked dominant disorder with lethality in males. The right-sided involvement is more common than the left-sided involvement, and the face is spared. The CHILD syndrome has been found to be caused by mutations in the *NSDHL* gene (OMIM 300275) at Xq28 encoding a 3β-hydroxysteroid dehydrogenase, which functions in the cholesterol biosynthetic pathway [78]. Neurologic abnormalities such as ipsilateral hypoplasia of the brain, cranial nerves and spinal cord, and meningomyelocele may occasionally be associated with the CHILD syndrome [79]. Hebert et al [80] reported a case of CHILD syndrome with Shone's syndrome (parachute mitral valve, supravalvular ring of the left atrium, subaortic stenosis, and coarctation of the aorta), hydrocephalus, dextrocardia, left hemiatrophy, absence of the fourth left toe, contracture of the left hand and elbow, and lumbar meningomyelocele.

Dyssegmental Dysplasia

Dyssegmental dysplasia is an autosomal recessive disorder characterized by camptomicromelic dysplasia, and anisospondyly or marked differences in size and shape of the vertebral bodies due to errors in segmentation. Dyssegmental dysplasia, Silverman-Handmaker type (DDSH) (OMIM 224410), is lethal with severe dwarfism and micromelia, and frequent encephalocele, cleft palate and a variety of other congenital anomalies [81]. Dyssegmental dysplasia, Rolland-Desbuquois type (DDRD) (OMIM 224400), is less severe with frequent survival past infancy and less severe dwarfism and micromelia [81]. DDSH is caused by mutations in the *HSPG2* gene encoding perlecan (OMIM 142461) [82].

Stoll et al [83], in a review of 19 cases of DDSH and 13 cases of DDRD, showed encephalocele in 5/16 (31.3%) cases of DDSH and in 1/11 (9.1%) case of DDRD. Hsieh et al [84] reported prenatal diagnosis of dyssegmental dysplasia in a 27-week-gestation fetus associated with cystic hygroma, massive ascites, micromelia, spinal disorganization, polyhydramnios, and occipital encephalocele.

Monozygotic Twinning

It has been noted that malformations in MZ twins are predominantly early malformations engendered at the same time as the MZ twinning, such as sacrococcygeal teratoma, sirenomelia, the VATER association, extrophy of the cloaca malformation sequence, holoprosencephaly malformation sequence and anencephaly [85–86]. James [87] found an excess of anencephaly in MZ but not in dizygotic (DZ) twins. As with MZ twins, there is also a high incidence of anencephaly in conjoined twins, especially in diprosopus, a rare form of conjoined twins consisting of one neck, one body and a single head with various forms of duplication of the craniofacial structures [88]. James [88] observed that anencephaly was least common in dichorionic MZ twins and most common in conjoined twins and other monoamniotic twins, and that anencephaly was more closely related to MZ twinning than was spina bifida. James [89] also observed a raised concordance rate for anencephaly in MZ twins but not in DZ twins.

Conclusion

This article provides a comprehensive review of the syndromes and disorders associated with NTDs, including Pallister-Hall syndrome, Walker-Warburg syndrome and Fukuyama congenital muscular dystrophy, MURCS association, Roberts syndrome, CCMS, laterality sequences, hydrolethalus syndrome, Knobloch syndrome, OAVS (hemifacial microsomia), COAS, FA, MDLS, Fraser syndrome, frontonasal dysplasia, AOS, CHILD syndrome, dyssegmental dysplasia and MZ twinning. NTDs associated with syndromes and disorders 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 and disorders may be different from those of nonsyndromic multifactorial NTDs. Perinatal identification of NTDs should alert doctors to the syndromes and disorders associated with NTDs, and prompt thorough etiologic investigation and genetic counseling.

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