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

Chih-Ping Chen[1,2,3,4,5*]

[1]Department of Obstetrics and Gynecology, [2]Department of Medical Research, Mackay Memorial Hospital, Taipei, [3]Department of Biotechnology, Asia University, [4]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, and [5]Institute 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 risk factors. This article provides a comprehensive review of syndromes, disorders, and maternal risk factors associated with NTDs, such as acrocallosal syndrome, autosomal dominant brachydactyly-clinodactyly syndrome, Manouvrier syndrome, short rib–polydactyly syndrome, *Disorganization* (*Ds*)-like human malformations, isolated hemihyperplasia, X-linked NTDs, meroanencephaly, schisis association, diprosopus, fetal valproate syndrome, DiGeorge syndrome/velocardiofacial syndrome, Waardenburg syndrome, folic acid antagonists, diabetes mellitus, and obesity. NTDs associated with syndromes, disorders, and maternal 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 non-syndromic multifactorial NTDs. Perinatal identification of NTDs should alert one to the syndromes, disorders, and maternal risk factors associated with NTDs, and prompt a thorough etiologic investigation and genetic counseling. [*Taiwan J Obstet Gynecol* 2008;47(1):1–9]

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, cloacal exstrophy or 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, thermolabile mutation in the *MTHFR* gene, and others [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 risk factors.

Acrocallosal Syndrome (ACLS)

ACLS (OMIM 200990) is characterized by hallux duplication, postaxial polydactyly of hands and feet, hypoplastic or absent corpus callosum, macrocephaly, and severe mental retardation [2]. ACLS has an autosomal

*Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: cpc_mmh@yahoo.com
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recessive inheritance pattern. However, some cases of ACLS can be caused by mutations in the *GLI3* gene (OMIM 165240) [3]. Pfeiffer et al [4] reported a case of ACLS associated with a *de novo* inverted tandem duplication of 12p11.2–p13.3. The brain defects of ACLS include hypoplastic or absent corpus callosum, intracranial cysts, polymicrogyria, cerebral atrophy, hypothalamic dysfunction, hypoplastic pons, medulla oblongata and cerebellar hemispheres, small cerebellum, agenesis or hypoplasia of cerebellar vermis, and anencephaly [5]. Anencephaly is the severe end of the spectrum of the brain defects in ACLS. Gelman-Kohan et al [6] first reported anencephaly in only one of four cases with ACLS. Cataltepe and Tuncbilek [7] reported a Turkish family with parental consanguinity, one child with ACLS, and one child with anencephaly and polydactyly, and suggested that anencephaly is the extreme of the central nervous system malformations associated with ACLS. Lurie et al [8] reported a family with ACLS in a female proband and anencephaly in her sister, and suggested that anencephaly is an extreme manifestation of ACLS-related brain defects. Kedar et al [9] reported recurrent anencephaly as a primary manifestation of ACLS in a consanguineous Arab family. Christensen et al [10] reported a consanguineous Norwegian family with two pregnancies (male and female) affected with anencephaly, median cleft lip and palate, omphalocele, and preaxial polydactyly, suggesting the diagnosis of ACLS.

Autosomal Dominant Brachydactyly-clinodactyly Syndrome

Stagiannis et al [11] reported exencephaly in a 17-week gestation female fetus with abnormalities of the hands and a family history suggestive of brachydactyly syndrome type C or autosomal dominant brachydactyly-clinodactyly syndrome. Brachydactyly syndrome type C (OMIM 113100) is caused by mutations in the growth/differentiation factor-5 (*GDF5*) gene (OMIM 601146).

Manouvrier Syndrome

Manouvrier et al [12] reported a multiple congenital anomalies syndrome in a family with four affected females with radial ray malformation (preaxial hand anomalies and radioulnar synostosis), and a 14-week gestation male fetus with severe radial ray malformation, anencephaly, unilateral renal agenesis, and a common dorsal mesentery. The report of the affected mother and fetus suggested that this multiple congenital anomalies syndrome could represent a new X-linked dominant multiple congenital anomalies syndrome or an autosomal dominant condition with severe expression limited to males [12].

Short Rib–Polydactyly Syndrome (SRPS)

SRPSs are a heterogeneous group of lethal autosomal recessive skeletal dysplasias. Four types of SRPSs have been recognized [13]. Type I SRPS (Saldino-Noonan; OMIM 263530) is characterized by flipper-like extremities, polydactyly, polycystic kidneys, and pointed metaphyses. Type II SRPS (Majewski; OMIM 263520) is characterized by polydactyly, micromelia, cleft lip/palate, polycystic kidneys, disproportionately short ovoid tibia, and occasionally, hypoplastic epiglottis and larynx. Type III (Verma-Naumoff; OMIM 263510) is characterized by polydactyly, micromelia, metaphyseal spurs, and occasionally, situs inversus totalis. Type IV SRPS (Beemer-Langer; OMIM 269860) clinically resembles type II SRPS other than the polydactyly. Overlapping in the clinical and radiologic manifestations has led to the hypothesis that the different subtypes may be a single genetic disorder with variable expressivity [14–17]. Martínez-Frías et al [18] reported two patients with SRPS from two unrelated Spanish families. One patient had anencephaly, and the other patient had severe brain abnormalities with a family history of an older sister with anencephaly and a brother with SRPS.

A Human Homologue of the Mouse Mutant *Disorganization (Ds)*

Birth defects resembling the mouse mutant gene *Disorganization* (*Ds*) or *Ds*-like human malformations (OMIM 223200) include both common (NTDs, orofacial clefting, gastroschisis and limb defects) and rare (anophthalmia and duplicated rectum) human birth defects [19]. In mice with *Ds* mutations, the defects involve duplications, aplasia or atresia, malformations, malposition, retention of embryonic structures, and hamartomas. Many *Ds*-like human malformations have been reported [19]. ten Donkelaar et al [20] reported a 5-month-old boy with distal transverse defects of both hands, congenital scalp defects, and intestinal mucosa on top of a rudimentary occipital meningocele in amniotic rupture sequence, and suggested a possible *Ds*-like syndrome. Corona-Rivera et al [21] reported a female infant with non-anatomic lumbopedal union

by a skin pedicle, anorectal malformation, meningocele, vertebral segmentation defects, longitudinal limb defects, and vestigial feet and skin papillae, and suggested that *Ds*-like mutations may cause some cases of apparent amniotic band syndrome associated with skin pedicles.

Isolated Hemihyperplasia

Isolated hemihyperplasia (OMIM 235000) or hemi-3 syndrome (hemihypertrophy, hemihypoesthesia, and hemiareflexia) is characterized by asymmetric overgrowth of one or more regions of the body due to an abnormality of cell proliferation. The responsible gene maps to chromosome 11p15. Nudleman et al [22] reported three unrelated girls with hemi-3 syndrome and scoliosis, one of whom had a lumbar myelomeningocele, and all three had a family history of neural tube closure defects.

X-linked NTDs

X-linked NTDs (OMIM 301410) have been previously regarded as an X-linked recessive inheritance by the clinical observations in different families and generations that were genealogically connected through females and had only males affected with NTDs [23–26]. Using linkage analysis, Newton et al [27] and Hol et al [28] excluded the X chromosome and suggested that the susceptibility gene may map elsewhere on one the autosomes. Plaja et al [29] reported an anencephalic fetus with acrania, cervicodorsal rachischisis, a left diaphragmatic hernia, ipsilateral lung hypoplasia, intestinal malrotation, horseshoe kidneys, adrenal gland hypoplasia, del(X)(p22.1 → pter), and the karyotype of 46,X,del(X)(p22.1). Fryns et al [30] reported a spina bifida case with a *de novo* X/autosomal translocation of t(X;22)(q27;q12.1) pointing to a possible causative gene in Xq27. Hol et al [31] reported familial duplication of Xq26–q27 in two brothers, their mother, and their grandmother. The first brother had lower lumbar spina bifida occulta and deep sacral dimples, and the second brother had a large lumbosacral meningomyelocele. Cytogenetic analysis revealed the karyotype of 46,XY, dup(X)(q26q27), and fluorescence *in situ* hybridization analysis revealed that the duplication extended from Xq26.1 to Xq27.3. Hol et al [31] suggested that the two brothers had NTDs that were due to an interruption of a critical gene in the region of the Xq27 breakpoint, and narrowed the interval to Xq27.3 between DXS369 and DXS1200.

Meroanencephaly

Meroanencephaly is characterized by malformed cranial bones and a median cranial defect with a midline frontal mass composed of area cerebrovasculosa, which contains both vascular and glial tissues [32]. Zhao et al [33] found that cartilage homeoprotein (CART1; OMIM 601527) is selectively expressed in chondrocytes. Gordon et al [34] mapped the *CART1* gene to chromosome 12q21.3–q22. Zhao et al [35] found that mice homozygous for deficiency in the *Cart1* gene manifested acrania and meroanencephaly, and prenatal treatment with folic acid will suppress acrania and meroanencephaly in the *Cart1*-deficient mutants.

Schisis Association

Czeizel [36] first proposed the schisis association of a combination of two or more schisis defects such as NTDs (anencephaly, encephalocele, and spina bifida), omphalocele, diaphragmatic defects (diaphragmatic hernia or agenesis of diaphragm), and cleft lip and/or cleft palate. Czeizel [36] observed that 0.29% (130/44,608) of malformed infants had two or more schisis defects without other major congenital malformations, and the most frequent combination of the schisis defects was anencephaly with cleft lip and/or cleft palate (33 cases out of 130 cases). Martínez-Frías et al [37] observed that 0.09% (20/22,264) of live and stillborn malformed infants identified by the Spanish Collaborative Study of Congenital Malformations had two or more schisis defects and were not known to have other major or minor defects, and the most frequent associations were omphalocele with cleft palate and/or cleft lip, and omphalocele with diaphragmatic defects. Martínez-Frías et al [37] suggested that combinations of two schisis defects may represent blastogenetic sequences.

Diprosopus

Diprosopus is a rare form of conjoined twins consisting of one neck, one body, and a single hand with various forms of duplication of the craniofacial structures. Diprosopus may be associated with anencephaly, craniorachischisis, encephalocele, and spina bifida [38–50]. Changaris and McGavran [38] reported anencephaly, cleft lip and palate, a ventricular septal defect, and an atrial septal defect in a twin with diprosopus. Riccardi and Bergmann [39] reported an anencephalic stillbirth

with craniorachischisis and diprosopus and suggested that the concurrence of NTDs and incomplete twinning is due to a single pathogenetic mechanism common to both NTDs and monozygotic twinning. Barr [40] reported a large frontal encephalocele and a ventricular septal defect associated with diprosopus. Moerman et al [41] reported a case of monocephalus diprosopus with craniorachischisis and duplication of most of the foregut and suggested that certain types of incomplete twinning and NTDs may be caused by a single teratogenic mechanism. Chervenak et al [42] reported the prenatal diagnosis of hydrocephalus in a 37-week gestation fetus with lumbosacral meningomyelocele, cleft lip and palate, and left diaphragmatic hernia associated with diprosopus, and suggested that prenatal diagnosis of fetal hydrocephalus should prompt a careful search for other anomalies, such as diprosopus. Rydnert et al [43] reported a 20-week gestation fetus with diprosopus and craniorachischisis. Pavone et al [44] reported a case of diprosopus with anencephaly and a case of diprosopus with craniorachischisis, ventricular septal defects, and diaphragmatic hernia. Strauss et al [45] reported the prenatal diagnosis of polyhydramnios, hydrocephalus, thoracolumbar spina bifida, and left diaphragmatic hernia in a 20-week gestation fetus with diprosopus. Fontanarosa et al [46] reported the first-trimester sonographic diagnosis of diprosopus twins with craniorachischisis. Sharony et al [47] reported an 18-week gestation fetus with a left diaphragmatic hernia and thoracolumbar spina bifida with meningocele, clubfeet, and ventricular septal defects. al Muti Zaitoun et al [48] reported a 33-week gestation fetus with diprosopus, cleft palate, and craniorachischisis. Bulbul et al [49] reported a 14-week gestation fetus with increased nuchal translucency, facial cleft, and a large lumbosacral spina bifida. Ekinci et al [50] reported a 28-week gestation fetus with anencephaly and diprosopus. Sharony et al [47] reviewed 11 reported cases of diprosopus and found that ten cases had NTDs, six cases had congenital heart defects, and four cases had diaphragmatic hernia.

Fetal Valproate Syndrome (FVS)

Fetuses exposed to sodium valproate, an antiepileptic drug, are at risk of FVS. The NTDs associated with FVS occur in the first trimester of pregnancy, as NTDs are formed by day 28 after conception. FVS or valproate embryopathy (OMIM 609442) is characterized by facial features of trigonocephaly, a tall forehead with bifrontal narrowing, epicanthic folds, an infraorbital groove, medial deficiency of eyebrows, a flat nasal bridge, a broad nasal root, anteverted nares, a shallow philtrum, a long upper lip with thin vermilion border, a thick lower lip, and a small down-turned mouth [51–54]. The most common major congenital malformations associated with FVS include NTDs, congenital heart defects, cleft lip and palate, genitourinary malformations, and radial ray defects, and the other less frequent associated anomalies include abdominal wall defects, tracheomalacia, strabismus, arachnodactyly, and overlapping fingers [54]. The risk factors for the teratogenicity of sodium valproate include the number of drugs that are co-administered, the dosage of drug, the differences in maternal and/or infant metabolism, the fetal gestational age at exposure, and the hereditary susceptibility [55]. Sodium valproate appears to be associated with lower lumbar or sacral spina bifida in humans [54]. The prevalence of spina bifida with FVS is about 1–2%, a 10- to 20-fold increase in NTDs [56]. The spina bifida in FVS is often skin-covered, and the maternal serum α-fetoprotein level is often normal [54]. Omtzigt et al [57] and Guibaud et al [58] suggested that maternal serum α-fetoprotein levels may be unreliable for prenatal screening of fetal NTDs in women on sodium valproate medication, and recommended amniocentesis and prenatal ultrasound for the detection of spina bifida after first-trimester valproate exposure.

DiGeorge Syndrome (DGS)/ Velocardiofacial Syndrome (VCFS)

DGS (OMIM 188400)/VCFS (OMIM 192430) or 22q11.2 deletion syndrome is characterized by hypocalcemia, parathyroid hypoplasia, thymic hypoplasia, conotruncal cardiac defects, and facial features of a prominent tubular nose, narrow palpebral fissures and a slightly retruded mandible. DGS/VCFS is caused by a hemizygous deletion of chromosome 22q11.2 or point mutations in the *TBX1* gene. Haploinsufficiency of the *TBX1* gene (OMIM 602054) is responsible for the physical malformations. Nickel et al [59] reported three unrelated children with meningocele, of whom one had DGS and two had with VCFS, and all were with a 22q11.2 deletion. Seller et al [60] reported a 22-week gestation fetus with sacral spina bifida, conotruncal cardiac defects, cleft palate, facial dysmorphism, Kousseff syndrome, and del(22)(q11.2q11.2). Forrester et al [61] studied the family described by Kousseff [62] and found a deletion of chromosome 22q11–q13 in the proband, his diseased brother, and his father. The proband, his brother, and his sister had myelomeningocele and clinical findings consistent with DGS/VCFS. Maclean et al [63] reported two cases

of sacral meningomyelocele, conotruncal cardiac anomalies, Kousseff syndrome, and a 22q11.2 microdeletion, and suggested that Kousseff syndrome is a distinct clinical entity that is genetically heterogeneous.

Waardenburg Syndrome

Waardenburg syndrome type I (OMIM 193500), an autosomal dominant disorder, is characterized by a wide bridge of the nose, lateral displacement of the inner canthus of each eye, pigmentary disturbance of frontal white blaze of hair, heterochromia iridis, white eye lashes, leukoderma, and cochlear deafness, and is caused by mutations in the *PAX3* gene at chromosome 2q35. Waardenburg syndrome type III (OMIM 148820) is characterized by a more severe phenotype of partial albinism, blue eyes, deaf-mutism, undeveloped muscles and fused joints in the arms, and skeletal dysplasia, and is caused by an allelic mutation in the *PAX3* gene or a contiguous gene syndrome because of a deletion of the *PAX3* gene and adjacent genes. Waardenburg syndrome may be associated with NTDs. Chatkupt et al [64] reported Waardenburg syndrome type I and myelomeningocele in a family. The mother had Waardenburg syndrome, and her two sons had both Waardenburg syndrome and lumbosacral myelomeningocele. Nye et al [65] reported lumbosacral myelomeningocele and Waardenburg syndrome type III in patients with an interstitial deletion of 2q35 and the *PAX3* gene. The *PAX3* gene was mapped to chromosome 2q35. Hol et al [66] reported a girl with spina bifida, mild signs of Waardenburg syndrome, and a frameshift mutation in the gene for *PAX3*. Shim et al [67] reported a 6-year-old boy with bilateral sensorineural deafness, lateral displacement of inner canthi, a bulbous nasal tip, synophrys, cryptorchidism, Waardenburg syndrome type I, a lumbar spina bifida, and the karyotype of 46,XY,der(2)inv(2)(q13q21) inv(2)(q21q24.2)ins(2)(q24.2q33q35). Fluorescence *in situ* hybridization study showed a breakpoint at 2q35 being proximal to and without involvement of the *PAX3* gene. Kujat et al [68] reported the prenatal diagnosis of spina bifida in a fetus, leading to the initial diagnosis of Waardenburg syndrome type I in the members of a four-generation family and a novel splice site mutation within the *PAX3* gene in intron 5 in all affected family members but in none of the unaffected relatives. Zlotogora et al [69] reported homozygosity of Waardenburg syndrome with a severe phenotype of Waardenburg syndrome type III, including dystopia canthorum, partial albinism and severe upper-limb defects. The proband's parents were first cousins who manifested only a mild form of Waardenburg syndrome type I. Aymé and Philip [70] reported anencephaly, arthrogryposis, a small ventricular septal defect, imperforate anus, and skeletal dysplasia in a fetus with possible homozygous Waardenburg syndrome. The parents were a brother and a sister, both of whom had Waardenburg syndrome.

Folic Acid Antagonists

Folic acid antagonists include valproic acid, aminopterin, methotrexate, carbamazepine, phenobarbital, phenytoin, primidone, sulfasalazine, triamterene, and trimethoprim. Most members of the folic acid antagonists seem to induce NTDs, except phenobarbital and phenytoin [71]. NTDs occur in 1–2% of infants exposed to valproic acid during early pregnancy [72]. *In utero* exposure to carbamazepine without concurrent exposure to valproic acid carries a 1% risk of spina bifida [73,74]. Hernández-Díaz et al [71] observed a more than sixfold increased risk in NTDs after carbamazepine exposure and a more than fourfold increased risk in NTDs after trimethoprim exposure. In a meta-analysis of 1,255 exposures of carbamazepine, Matalon et al [75] concluded that among infants with carbamazepine exposure, there is a two- or threefold increase in the rate of major congenital anomalies including NTDs, cardiovascular anomalies, urinary tract anomalies and cleft palate, and that polytherapy with a combination of carbamazepine with other antiepileptic drugs is more teratogenic than carbamazepine monotherapy.

Diabetes Mellitus

Chen [76] reported the prenatal diagnosis of lumbosacral myelomeningocele, ventriculomegaly, and Arnold-Chiari malformation type II with a lemon-shaped calvaria, dislocation of the hip and bilateral club feet in a 21-week gestation fetus, owing to poor maternal metabolic control. Mills et al [77] found a twofold ratio of incidence for spina bifida, hydrocephalus and other central nervous system defect and a threefold ratio of incidence for anencephaly in infants of diabetic mothers, as compared with those of the control group. Ray et al [78] found an increased risk of having a fetus with an open NTD among pregestational diabetic women undergoing second-trimester maternal serum screening. Recently, in the mouse model of diabetic embryopathy and genotoxicity, impaired expression of developmental control genes

has been shown to be a cause of defective morphogenesis. For instance, impaired expression of *Pax-3*, a gene that regulates neural tube closure, is sufficient to prevent normal formation of the neural tube [79]. Phelan et al [80] noted that expression of *Pax-3* is significantly reduced in embryos of diabetic mice before the manifestation of morphologic defects. Fine et al [81] showed that hyperglycemia inhibits *Pax-3* gene expression and increases neuroepithelial apoptosis in the embryo leading to NTDs. Chang et al [82] demonstrated that oxidative stress in the embryo caused by maternal hyperglycemia inhibits expression of *Pax-3* and contributes to the occurrence of NTDs in diabetic pregnancy. Pani et al [83] provided evidence for polymorphic susceptibility to the molecular causes of NTDs during diabetic embryopathy. Pani et al [84] additionally found that *Pax-3* regulates neural tube closure by inhibiting p53-dependent apoptosis. Loeken [85] concluded that maternal diabetes causes birth defects such as NTDs by disturbing expression of genes that control essential developmental process, and that oxidative stress is involved. Loeken [85] further hypothesized that antioxidants, vitamin E, vitamin C, a combination of antioxidants and lipids, or N-acetylcystein, might have a positive impact on the outcome of human pregnancy. Loeken [86] summarized the causes of NTDs resulting from diabetic pregnancy: (1) maternal diabetes increases glucose concentrations in maternal circulation, glucose transportation to embryo cells, and oxidative metabolism in embryo, causing embryonic oxidative stress; and (2) oxidative stress leads to decreased expression of *Pax3*, causing synthesis or stability of p53 protein, activation of cell death, and abortion of the neural tube closure process.

Obesity

Obesity is defined as body mass index (BMI) of ≥ 30 kg/m^2. Overweight is defined as a BMI of 25.0–29.9 kg/m^2. Compared with normal-weight women, obese women have an increased risk of infertility, miscarriage, chronic hypertension, preeclampsia, thromboembolic diseases, sleep apnea, gestational diabetes/glucose intolerance, urinary tract infection, increased incidence of labor induction and cesarean section, postsurgical wound infection, postpartum endometritis, and poor lactational outcomes [87]. The possible offspring risks associated with maternal obesity include NTDs, heart defects, other birth defects, stillbirth, multiple congenital anomalies, neonatal death, macrosomia, shoulder dystocia, birth trauma, meconium aspiration, and juvenile obesity [87]. Various reports have shown that obese women have a 1.5- to 3.5-fold risk of having a child with NTDs than normal-weight women [88–96]. Waller et al [88] first suggested that obese women are at a higher risk for producing NTDs (odds ratio, OR, 1.8; 95% confidence interval, CI, 1.1–3.0), especially spina bifida (OR, 2.6; 95% CI, 1.5–4.5). Watkins et al [93] found that obese women had almost twice the risk of having an infant with spina bifida or anencephaly compared with average-weight women (OR, 1.9; 95% CI, 1.1–3.4). Werler et al [92] suggested that the risk of NTDs increases with increasing prepregnant weight, independent of the effects of folate intake. They found that the relative risk of NTDs in the offspring of women weighing 80–89 kg was 1.9 (95% CI, 1.2–2.9) and the risk in the offspring of women weighing ≥ 110 kg was 4.0 (95% CI, 1.6–9.9) compared with women who weighed 50–59 kg. Shaw et al [89] reported an increase risk for NTD-affected pregnancy among obese women (OR, 1.9; 95% CI, 1.3–2.9), and the risk associated with maternal obesity was greater for spina bifida than for anencephaly. Shaw et al [90] revealed a positive association between NTD risk and maternal prepregnant BMI and a negative association between NTD risk and maternal height. Hendricks et al [95] observed that both hyperinsulinemia and obesity were related to increased NTD risk (OR, 1.91; 95% CI, 1.21–3.01; and OR, 1.73; 95% CI, 1.03–2.92, respectively) and suggested that hyperinsulinemia is a strong risk factor for NTDs in obese women. Watkins et al [94] found that obese women were more likely than average-weight women to have infants with spina bifida (OR, 3.5; 95% CI, 1.2–10.3), omphalocele (OR, 3.3; 95% CI, 1.0–10.3), congenital heart defects (OR, 2.0; 95% CI, 1.2–3.4), and multiple anomalies (OR, 2.0; 95% CI, 1.0–3.2), and overweight women were more likely than average-weight women to have infants with congenital heart defects (OR, 2.0; 95% CI, 1.2–3.1) and multiple anomalies (OR, 1.9; 95% CI, 1.1–3.4). Watkins et al [94] recommended obesity prevention efforts in reproductive-aged women before they become pregnant. Shaw et al [91] found that elevated NTD risks were associated with maternal intakes of periconceptional diets having higher glycemic index values and higher sucrose content, and that no increased NTD risks were associated with higher intakes of glucose and fructose. Anderson et al [96] found that obese women had increased risks of delivering offspring with anencephaly (OR, 2.3; 95% CI, 1.2–4.3), spina bifida (OR, 2.8; 95% CI, 1.7–4.5) or isolated hydrocephalus (OR, 2.7; 95% CI, 1.5–5.0) but not holoprosencephaly (OR, 1.4; 95% CI, 0.5–3.8), and suggested that maternal obesity and gestational diabetes

may increase the risk of central nervous system birth defects through the joint of causal mechanisms.

Conclusion

This article provides a comprehensive review of syndromes, disorders, and maternal risk factors associated with NTDs, such as ACLS, autosomal dominant brachydactyly-clinodactyly syndrome, Manouvrier syndrome, SRPS, *Disorganization* (*Ds*)-like human malformations, isolated hemihyperplasia, X-linked NTDs, meroanencephaly, schisis association, diprosopus, FVS, DGS/VCFS, Waardenburg syndrome, folic acid antagonists, diabetes mellitus, and obesity. NTDs associated with syndromes, disorders, and maternal 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 non-syndromic multifactorial NTDs. Perinatal identification of NTDs should alert one to the syndromes, disorders, and maternal risk factors associated with NTDs, and prompt a thorough etiologic investigation and genetic counseling.

References

1. McGahan JP, Pilu G, Nyberg DA. Neural tube defects and the spine. In: Nyberg DA, McGahan JP, Pretorius DH, Pilu G, eds. *Diagnostic Imaging of Fetal Anomalies*. Philadelphia: Lippincott Williams & Wilkins, 2003:291–334.
2. Schinzel A. Postaxial polydactyly, hallux duplication, absence of the corpus callosum, macrencephaly and severe mental retardation: a new syndrome? *Helv Paediatr Acta* 1979;34:141–6.
3. Elson E, Perveen R, Donnai D, Wall S, Black GCM. *De novo GLI3* mutation in acrocallosal syndrome: broadening the phenotypic spectrum of *GLI3* defects and overlap with murine models. *J Med Genet* 2002;39:804–6.
4. Pfeiffer RA, Legat G, Trautmann U. Acrocallosal syndrome in a child with *de novo* inverted tandem duplication of 12p11.2–p13.3. *Ann Genet* 1992;35:41–6.
5. Jones KL. Acrocallosal syndrome. In: Jones KL, ed. *Smith's Recognizable Patterns of Human Malformation*. Philadelphia: Elsevier Saunders, 2006:252–3.
6. Gelman-Kohan Z, Antonelli J, Ankori-Cohen H, Adar H, Chemke J. Further delineation of the acrocallosal syndrome. *Eur J Pediatr* 1991;150:797–9.
7. Cataltepe S, Tuncbilek E. A family with one child with acrocallosal syndrome, one child with anencephaly-polydactyly, and parental consanguinity. *Eur J Pediatr* 1992;151:288–90.
8. Lurie IW, Naumchik IV, Wulfsberg EA. The acrocallosal syndrome: expansion of the phenotypic spectrum. *Clin Dysmorphol* 1994;3:31–4.
9. Kedar I, Amiel A, Fejgin M, Drugan A. Recurrent anencephaly as a primary manifestation of the acrocallosal syndrome. *Am J Med Genet* 1996;62:415–6.
10. Christensen B, Blaas HG, Isaksen CV, Roald B, Ørstavik KH. Sibs with anencephaly, anophthalmia, clefts, omphalocele, and polydactyly: hydrolethalus or acrocallosal syndrome? *Am J Med Genet* 2000;91:231–4.
11. Stagiannis KD, Sepulveda W, Fusi L, Garrett C, Fisk NM. Exencephaly in autosomal dominant brachydactyly syndrome. *Prenat Diagn* 1995;15:70–3.
12. Manouvrier S, Moerman A, Coeslier A, Devisme L, Boute O, Le Merrer M. Radioulnar synostosis, radial ray abnormalities, and severe malformations in the male: a new X-linked dominant multiple congenital anomalies syndrome? *Am J Med Genet* 2000;90:351–5.
13. Lachman RS. Skeletal dysplasia. In: Taybi H, Lachman RS, eds. *Radiology of Syndromes, Metabolic Disorders, and Skeletal Dysplasias*, 4th edition. St Louis: Mosby, 1996:745–951.
14. Martínez-Frías M-L, Bermejo E, Urioste M, Huertas H, Arroyo I. Lethal short rib-polydactyly syndromes: further evidence for their overlapping in a continuous spectrum. *J Med Genet* 1993;30:937–41.
15. Sarafoglou K, Funai EF, Fefferman N, et al. Short rib-polydactyly syndrome: more evidence of a continuous spectrum. *Clin Genet* 1999;56:145–8.
16. Ho NC, Francomano CA, van Allen M. Jeune asphyxiating thoracic dystrophy and short-rib polydactyly type III (Verma-Naumoff) are variants of the same disorder. *Am J Med Genet* 2000;90:310–4.
17. Elçioglu NH, Hall CM. Diagnostic dilemmas in the short rib-polydactyly syndrome group. *Am J Med Genet* 2002;111: 392–400.
18. Martínez-Frías ML, Bermejo E, Urioste M, Egüés J, López Soler JA. Short rib-polydactyly syndrome (SRPS) with anencephaly and other central nervous system anomalies: a new type of SRPS or a more severe expression of a known SRPS entity? *Am J Med Genet* 1993;47:782–7.
19. Robin NH, Abbadi N, McCandless SE, Nadeau JH. *Disorganization* in mice and humans and its relation to sporadic birth defects. *Am J Med Genet* 1997;73:425–36.
20. ten Donkelaar HJ, Hamel BC, Hartman E, van Lier JA, Wesseling P. Intestinal mucosa on top of a rudimentary occipital meningocele in amniotic rupture sequence: disorganization-like syndrome, homeotic transformation, abnormal surface encounter or endoectodermal adhesion? *Clin Dysmorphol* 2002;11:9–13.
21. Corona-Rivera JR, Corona-Rivera E, Navarro-Ramírez P, Castro-Hernández JF, Acosta-León J, Corona-Rivera A. Lumbopedal skin pedicle in an infant with the amniotic band syndrome: a disorganization-like defect? *Clin Dysmorphol* 2003;12:51–4.
22. Nudleman K, Andermann E, Andermann F, Bertrand G, Rogala E. The hemi 3 syndrome. Hemihypertrophy, hemihypaesthesia, hemiareflexia and scoliosis. *Brain* 1984; 107:533–46.
23. Toriello HV, Warren ST, Lindstrom JA. Possible X-linked anencephaly and spina bifida: report of a kindred. *Am J Med Genet* 1980;6:119–21.
24. Baraitser M, Burn J. Neural tube defects as an X-linked condition. *Am J Med Genet* 1984;17:383–5.

25. Toriello HV. Report of a third kindred with X-linked anencephaly/spina bifida. *Am J Med Genet* 1984;19:411–2.
26. Jensson O, Arnason A, Gunnarsdottir H, Petursdottir I, Fossdal R, Hreidarsson S. A family showing apparent X linked inheritance of both anencephaly and spina bifida. *J Med Genet* 1988;25:227–9.
27. Newton R, Stanier P, Loughna S, et al. Linkage analysis of 62 X-chromosomal loci excludes the X chromosome in an Icelandic family showing apparent X-linked recessive inheritance of neural tube defects. *Clin Genet* 1994;45:241–9.
28. Hol FA, Geurds MP, Jensson O, Hamel BC, Moore GE, Newton R, Mariman EC. Exclusion mapping of the gene for X-linked neural tube defects in an Icelandic family. *Hum Genet* 1994;93:452–6.
29. Plaja A, Vendrell T, Sarret E, Toran N, Mediano C. Terminal deletion of Xp in a dysmorphic anencephalic fetus. *Prenat Diagn* 1994;14:410–2.
30. Fryns JP, Devriendt K, Moerman P. Lumbosacral spina bifida and myeloschizis in a female foetus with *de novo* X/autosomal translocation (t(X;22)(q27;q121)). *Genet Couns* 1996;7:159–60.
31. Hol FA, Schepens MT, van Beersum SE, et al. Identification and characterization of an Xq26–q27 duplication in a family with spina bifida and panhypopituitarism suggests the involvement of two distinct genes. *Genomics* 2000;69:174–81.
32. Isada NB, Qureshi F, Jacques SM, Holzgreve W, Tout MJ, Johnson MP, Evans MI. Meroanencephaly: pathology and prenatal diagnosis. *Fetal Diagn Ther* 1993;8:423–8.
33. Zhao GQ, Zhou X, Eberspaecher H, Solursh M, de Crombrugghe B. Cartilage homeoprotein 1, a homeoprotein selectively expressed in chondrocytes. *Proc Natl Acad Sci USA* 1993;90:8633–7.
34. Gordon DF, Wagner J, Atkinson BL, Chiono M, Berry R, Sikela J, Gutierrez-Hartmann A. Human Cart-1: structural organization, chromosomal localization, and functional analysis of a cartilage-specific homeodomain cDNA. *DNA Cell Biol* 1996;15:531–41.
35. Zhao Q, Behringer RR, de Crombrugghe B. Prenatal folic acid treatment suppresses acrania and meroanencephaly in mice mutant for the Cart1 homeobox gene. *Nat Genet* 1996;13:275–83.
36. Czeizel A. Schisis-association. *Am J Med Genet* 1981;10:25–35.
37. Martínez-Frías ML, Frías JL, Bermejo E, Rodríguez-Pinilla E, Urioste M. Epidemiological analysis of the schisis association in the Spanish registry of congenital malformations. *Am J Med Genet* 1997;70:16–23.
38. Changaris DG, McGavran MH. Craniofacial duplication (diprosopus) in a twin. *Arch Pathol Lab Med* 1976;100:392–4.
39. Riccardi VM, Bergmann CA. Anencephaly with incomplete twinning (diprosopus). *Teratology* 1977;16:137–40.
40. Barr M Jr. Facial duplication: case, review, and embryogenesis. *Teratology* 1982;25:153–9.
41. Moerman P, Fryns JP, Goddeeris P, Lauweryns JM, Van Assche A. Aberrant twinning (diprosopus) associated with anencephaly. *Clin Genet* 1983;24:252–6.
42. Chervenak FA, Pinto MM, Heller CI, Norooz H. Obstetric significance of fetal craniofacial duplication. A case report. *J Reprod Med* 1985;30:74–6.
43. Rydnert J, Holmgren G, Nielsen K, Bergman F, Joelsson I. Prenatal diagnosis of conjoined twins (diprosopus) with myelomeningocele. *Acta Obstet Gynecol Scand* 1985;64:687–8.
44. Pavone L, Camera G, Grasso S, Gambini C, Barberis M, Garaffo S, Russo S. Diprosopus with associated malformations: report of two cases. *Am J Med Genet* 1987;28:85–8.
45. Strauss S, Tamarkin M, Engelberg S, Ben Ami T, Goodman RM. Prenatal sonographic appearance of diprosopus. *J Ultrasound Med* 1987;6:93–5.
46. Fontanarosa M, Bagnoli G, Ciolini P, Spinelli G, Curiel P. First trimester sonographic diagnosis of diprosopus twins with craniorachischisis. *J Clin Ultrasound* 1992;20:69–71.
47. Sharony R, Pepkowitz SH, Hixon H, Machin GA, Graham JM Jr. Diprosopus: a pregastrulation defect involving the head, neural tube, heart, and diaphragm. *Birth Defects Orig Artic Ser* 1993;29:201–9.
48. al Muti Zaitoun A, Chang J, Booker M. Diprosopus (partially duplicated head) associated with anencephaly: a case report. *Pathol Res Pract* 1999;195:45–50.
49. Bulbul Y, Drummond CL, Hillion Y, Bidat L, Ville Y. Diprosopus associated with neural tube defect and facial cleft in the first trimester. *Fetal Diagn Ther* 2004;19:246–50.
50. Ekinci G, Balci S, Erzen C. An anencephalic monocephalus diprosopus "headed twin": postmortem and CT findings with emphasis on the cranial bones. *Turk J Pediatr* 2005;47:195–8.
51. DiLiberti JH, Farndon PA, Dennis NR, Curry CJ. The fetal valproate syndrome. *Am J Med Genet* 1984;19:473–81.
52. Winter RM, Donnai D, Burn J, Tucker SM. Fetal valproate syndrome: is there a recognisable phenotype? *J Med Genet* 1987;24:692–5.
53. Ardinger HH, Atkin JF, Blackston RD, et al. Verification of the fetal valproate syndrome phenotype. *Am J Med Genet* 1988;29:171–85.
54. Clayton-Smith J, Donnai D. Fetal valproate syndrome. *J Med Genet* 1995;32:724–7.
55. Alsdorf R, Wyszynski DF. Teratogenicity of sodium valproate. *Expert Opin Drug Saf* 2005;4:345–53.
56. Lindhout D, Schmidt D. *In-utero* exposure to valproate and neural tube defects. *Lancet* 1986;1:1392–3.
57. Omtzigt JG, Los FJ, Hagenaars AM, Stewart PA, Sachs ES, Lindhout D. Prenatal diagnosis of spina bifida aperta after first-trimester valproate exposure. *Prenat Diagn* 1992; 12:893–7.
58. Guibaud S, Robert E, Simplot A, Boisson C, Francannet C, Patouraux MH. Prenatal diagnosis of spina bifida aperta after first-trimester valproate exposure. *Prenat Diagn* 1993; 13:772–3.
59. Nickel RE, Pillers DA, Merkens M, Magenis RE, Driscoll DA, Emanuel BS, Zonana J. Velo-cardio-facial syndrome and DiGeorge sequence with meningomyelocele and deletions of the 22q11 region. *Am J Med Genet* 1994;52:445–59.
60. Seller MJ, Mohammed S, Russell J, Ogilvie C. Microdeletion 22q11.2, Kousseff syndrome and spina bifida. *Clin Dysmorphol* 2002;11:113–5.
61. Forrester S, Kovach MJ, Smith RE, Rimer L, Wesson M, Kimonis VE. Kousseff syndrome caused by deletion of chromosome 22q11–13. *Am J Med Genet* 2002;112:338–42.
62. Kousseff BG. Sacral meningocele with conotruncal heart defects: a possible autosomal recessive trait. *Pediatrics* 1984;74:395–8.
63. Maclean K, Field MJ, Colley AS, Mowat DR, Sparrow DB, Dunwoodie SL, Kirk EP. Kousseff syndrome: a causally heterogeneous disorder. *Am J Med Genet A* 2004;124:307–12.

64. Chatkupt S, Chatkupt S, Johnson WG. Waardenburg syndrome and myelomeningocele in a family. *J Med Genet* 1993;30:83–4.
65. Nye JS, Balkin N, Lucas H, Knepper PA, McLone DG, Charrow J. Myelomeningocele and Waardenburg syndrome (type 3) in patients with interstitial deletions of 2q35 and the *PAX3* gene: possible digenic inheritance of a neural tube defect. *Am J Med Genet* 1998;75:401–8.
66. Hol FA, Hamel BC, Geurds MP, Mullaart RA, Barr FG, Macina RA, Mariman EC. A frameshift mutation in the gene for *PAX3* in a girl with spina bifida and mild signs of Waardenburg syndrome. *J Med Genet* 1995;32:52–6.
67. Shim SH, Wyandt HE, McDonald-McGinn DM, Zackai EZ, Milunsky A. Molecular cytogenetic characterization of multiple intrachromosomal rearrangements of chromosome 2q in a patient with Waardenburg's syndrome and other congenital defects. *Clin Genet* 2004;66:46–52.
68. Kujat A, Veith VP, Faber R, Froster UG. Prenatal diagnosis and genetic counseling in a case of spina bifida in a family with Waardenburg syndrome type I. *Fetal Diagn Ther* 2007;22:155–8.
69. Zlotogora J, Lerer I, Bar-David S, Ergaz Z, Abeliovich D. Homozygosity for Waardenburg syndrome. *Am J Hum Genet* 1995;56:1173–8.
70. Aymé S, Philip N. Possible homozygous Waardenburg syndrome in a fetus with exencephaly. *Am J Med Genet* 1995;59: 263–5.
71. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001;153:961–8.
72. Omtzigt JG, Los FJ, Grobbee DE, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 1992;42(4 Suppl 5):119–25.
73. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; 324:674–7.
74. Källén AJ. Maternal carbamazepine and infant spina bifida. *Reprod Toxicol* 1994;8:203–5.
75. Matalon S, Schechtman S, Goldzweig G, Ornoy A. The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. *Reprod Toxicol* 2002;16:9–17.
76. Chen CP. Maternal diabetes and neural tube defects: prenatal diagnosis of lumbosacral myelomeningocele, ventriculomegaly, Arnold-Chiari malformation and foot deformities in a pregnancy with poor maternal metabolic control, and review of the literature. *Genet Couns* 2005; 16:313–6.
77. Mills JL, Baker L, Goldman AS. Malformations in infants of diabetic mothers occur before the seventh gestational week: implications for treatment. *Diabetes* 1979;28:292–3.
78. Ray JG, Vermeulen MJ, Meier C, Wyatt PR. Risk of congenital anomalies detected during antenatal serum screening in women with pregestational diabetes. *QJM* 2004;97:651–3.
79. Chang TI, Loeken MR. Genotoxicity and diabetic embryopathy: impaired expression of developmental control genes as a cause of defective morphogenesis. *Semin Reprod Endocrinol* 1999;17:153–65.
80. Phelan SA, Ito M, Loeken MR. Neural tube defects in embryos of diabetic mice: role of the *Pax-3* gene and apoptosis. *Diabetes* 1997;46:1189–97.
81. Fine EL, Horal M, Chang TI, Fortin G, Loeken MR. Evidence that elevated glucose causes altered gene expression, apoptosis, and neural tube defects in a mouse model of diabetic pregnancy. *Diabetes* 1999;48:2454–62.
82. Chang TI, Horal M, Jain SK, Wang F, Patel R, Loeken MR. Oxidant regulation of gene expression and neural tube development: insights gained from diabetic pregnancy on molecular causes of neural tube defects. *Diabetologia* 2003;46:538–45.
83. Pani L, Horal M, Loeken MR. Polymorphic susceptibility to the molecular causes of neural tube defects during diabetic embryopathy. *Diabetes* 2002;51:2871–4.
84. Pani L, Horal M, Loeken MR. Rescue of neural tube defects in Pax-3-deficient embryos by p53 loss of function: implications for Pax-3-dependent development and tumorigenesis. *Genes Dev* 2002;16:676–80.
85. Loeken MR. Free radicals and birth defects. *J Matern Fetal Neonatal Med* 2004;15:6–14.
86. Loeken MR. Current perspectives on the causes of neural tube defects resulting from diabetic pregnancy. *Am J Med Genet C Semin Med Genet* 2005;135:77–87.
87. Scialli AR; for the Public Affairs Committee of the Teratology Society. Teratology public affairs committee position paper: maternal obesity and pregnancy. *Birth Defects Res A Clin Mol Teratol* 2006;76:73–7.
88. Waller DK, Mills JL, Simpson JL, Cunningham GC, Conley MR, Lassman MR, Rhoads GG. Are obese women at higher risk for producing malformed offspring? *Am J Obstet Gynecol* 1994;170:541–8.
89. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. *JAMA* 1996; 275:1093–6.
90. Shaw GM, Todoroff K, Schaffer DM, Selvin S. Maternal height and prepregnancy body mass index as risk factors for selected congenital anomalies. *Paediatr Perinat Epidemiol* 2000;14:234–9.
91. Shaw GM, Quach T, Nelson V, Carmichael SL, Schaffer DM, Selvin S, Yang W. Neural tube defects associated with maternal periconceptional dietary intake of simple sugars and glycemic index. *Am J Clin Nutr* 2003;78:972–8.
92. Werler MM, Louik C, Shapiro S, Mitchell AA. Prepregnant weight in relation to risk of neural tube defects. *JAMA* 1996;275:1089–92.
93. Watkins ML, Scanlon KS, Mulinare J, Khoury MJ. Is maternal obesity a risk factor for anencephaly and spina bifida? *Epidemiology* 1996;7:507–12.
94. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. *Pediatrics* 2003;111:1152–8.
95. Hendricks KA, Nuno OM, Suarez L, Larsen R. Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. *Epidemiology* 2001;12:630–5.
96. Anderson JL, Waller DK, Canfield MA, Shaw GM, Watkins ML, Werler MM. Maternal obesity, gestational diabetes, and central nervous system birth defects. *Epidemiology* 2005;16:87–92.