Neural tube defects (NTDs) may be associated with syndromes, disorders and maternal risk factors. This article provides a comprehensive review of the syndromes, disorders and maternal risk factors associated with NTDs, including DK phocomelia syndrome (von Voss-Cherstvoy syndrome), Siegel-Bartlet syndrome, fetal warfarin syndrome, cranietelencephal dysplasia, Czeizel-Losonci syndrome, maternal cocaine abuse, Weissenbacher-Zweymüller syndrome, parietal foramina (cranium bifidum), Apert syndrome, craniofacial syndrome, XX-agonadism with multiple dysraphic lesions including omphaloceles and NTDs, Fryns microphthalma syndrome, Gershoni-Baruch syndrome, PHAVER syndrome, periconceptional vitamin B6 deficiency, and autosomal dominant Dandy-Walker malformation with occipital cephalocele. NTDs associated with these 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 nonsyndromic multifactorial NTDs. Perinatal diagnosis of NTDs should alert doctors to the syndromes, disorders and maternal risk factors associated with NTDs, and prompt thorough etiologic investigation and genetic counseling.

Key Words: congenital malformations, disorders, 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, while less common types include amniotic band syndrome, limb–body wall complex, cloacal extrophy or omphalocoele–extrophy–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 genetic and environmental factors contribute to the etiology of NTDs. NTDs may be associated with maternal and fetal risk factors.

DK Phocomelia Syndrome (von Voss-Cherstvoy Syndrome)

DK phocomelia syndrome (OMIM 223340) or von Voss-Cherstvoy syndrome is characterized by phocomelia, thrombocytopenia, encephalocele, and urogenital malformations. Phocomelia usually involves only the upper limbs and is limited to radial anomalies. All reported...
cases of DK phocomelia syndrome have been sporadic, with both sexes affected by this syndrome and having normal chromosomes, except for a case described by Bamforth and Lin [1] with mosaicism for a deletion of 13q12 in the fibroblasts but with normal lymphocyte chromosomes. Lubinsky et al [2] reported consanguinity in DK phocomelia syndrome and suggested an autosomal recessive pattern of inheritance. Meningoencephalocele is the most characteristic central nervous system malformation associated with DK phocomelia syndrome [1–7]. A defect of the corpus callosum is another common brain anomaly [2,4,6].

Siegel-Bartlet Syndrome

Siegel-Bartlet syndrome, or craniofacial anomalies, cataracts, congenital heart disease, sacral neural tube defects and growth and developmental retardation (OMIM 608227), is postulated to have an autosomal recessive pattern of inheritance [8]. Siegel-Bartlet et al [8] reported two female sibs with sacral NTDs and tethered cord, congenital heart defects, bilateral hyperopia, rapid onset of cataracts, aphakic glaucoma, and abnormal facial features.

Fetal Warfarin Syndrome

Fetal warfarin syndrome is characterized by nasal hypoplasia, stippled epiphyses, chondrodysplasia punctata, and first-trimester prenatal exposure to the vitamin K antagonist, i.e. the anticoagulant warfarin (coumarin or Coumadin). Warfarin inhibits the synthesis of γ-carboxyglutamic acid, which is involved in clotting and calcification. Occasional central nervous system anomalies associated with fetal warfarin syndrome include microcephaly, hydrocephalus, Dandy-Walker malformation, and agenesis of the corpus callosum [9]. Tejani [10] reported nasal hypoplasia, occipital encephalocele, hydrocephalus, microphthalmia and persistent truncus arteriosus in a patient with warfarin syndrome. Warkany and Bofinger [11] reported occipital encephalocele and renal malformation in a patient with warfarin syndrome.

Czeizel-Losonci Syndrome

Czeizel-Losonci syndrome, or split hand with obstructive uropathy, spina bifida and diaphragmatic defects (OMIM 183802), is postulated to have an autosomal dominant pattern of inheritance with variable expressivity [15]. Czeizel and Losonci [15] reported a woman with right hydronephrosis, atresia of the ureter, cutaneous syndactyly of both hands and feet, lumbar spina bifida occulta, and thoracolumbar scoliosis. Her first child was a stillborn male with lumbosacral spina bifida cystica, hydrocephalus, split hand/split foot malformation, atresia of the right ureter, and hydronephrosis. Her second child was a liveborn male with split hand/foot malformation, megaureter, bilateral hydronephrosis, and a right diaphragmatic defect of Bochdalek type. Genuardi et al [16] reported a baby with split hand/split foot malformation, urinary tract obstruction, syndactyly, lumbosacral myelomeningocele, and radial and diaphragmatic defects, and suggested a case of Czeizel-Losonci syndrome.

Maternal Cocaine Abuse

Reported malformations associated with cocaine abuse during pregnancy include hypertelorism, midfacial flattening, neurobehavioral disorders, schizencephaly, callosal agenesis, porencephaly, NTDs, vascular occlusion, fetal myocardial calcification, renal agenesis, hydronephrosis, ambiguous genitalia, ileal atresia, and prune-belly syndrome [17]. Mahalik et al [18] found that nontoxic doses of cocaine caused exencephaly in mice. Bingol et al [19] found that cocaine abuse in human was significantly associated with congenital malformations (10% vs. 2% for the control group), including one exencephaly, one parietal encephalocele and one skull dysraphism with parietal bone defects. Heier et al
[20] found five central nervous system anomalies among 43 babies (12% vs. 0% for the control group) of cocaine-abusing mothers, including one towering encephalocele, one posterior encephalocele, one holoprosencephaly, one hypoplastic cerebellum and one spinal teratoma, and postulated that placental or cerebral artery vasoconstriction from cocaine in the first trimester results in the congenital malformations. Zimmerman et al [21] found that cocaine-induced vascular disruption in early mouse development was mediated by maternal production of oxygen free radicals. However, Shaw et al [22] found that periconceptional maternal use of cocaine did not increase the risk of NTDs (odds ratio, 0.74; 95% confidence interval, 0.40–1.4). Behnke et al [23] found that the incidence of structural brain anomalies in newborns exposed to cocaine was not significantly different from the control group (17/134 cocaine-exposed vs. 10/132 control; p = 0.119), and the identified brain anomalies included choroid plexus cysts, subependymal cysts, mildly altered ventricles, and a cyst of the third ventricle.

Weissenbacher-Zweymüller Syndrome

Weissenbacher-Zweymüller syndrome (WZS; OMIM 277610), or Pierre Robin syndrome with fetal chondrodysplasia, is characterized by congenital neonatal rhizomelic dwarfism, metaphyseal widening of the long bones, vertebral coronal clefts, micrognathia, cleft palate, depressed nasal root, hypertelorism, protruding eyes, and occasional sensorineural deafness [24]. Mutations in the COL11A2 gene (OMIM 120290) encoding the α2(XI) chain of type XI collagen have been associated with the autosomal dominant form of WZS [25] and the autosomal recessive form of WZS [24]. Ramer et al [26] reported identical twins with WZS and NTDs. The twins had small birth size, proximal radion production of oxygen free radicals. However, Shaw et al [22] found that periconceptional maternal use of cocaine did not increase the risk of NTDs (odds ratio, 0.74; 95% confidence interval, 0.40–1.4). Behnke et al [23] found that the incidence of structural brain anomalies in newborns exposed to cocaine was not significantly different from the control group (17/134 cocaine-exposed vs. 10/132 control; p = 0.119), and the identified brain anomalies included choroid plexus cysts, subependymal cysts, mildly altered ventricles, and a cyst of the third ventricle.

Parietal Foramina (Cranium Bifidum)

Parietal foramina (PFM; OMIM 168500), also known as foramina parietalia permagna, cranium bifidum occultum or hereditary cranium bifidum, is characterized by symmetrical oval defects in the parietal bone situated on each side of the sagittal suture and separated from each other by a narrow bridge of bone. PFM is an autosomal dominant disorder. PFM1 (OMIM 168500) is caused by mutations in the MSX2 gene (OMIM 123101) [27–30]. PFM2 (OMIM 609597) is caused by mutations or haploinsufficiency in the ALX4 gene (OMIM 605420) [30–32]. PFM3 (OMIM 609566) is associated with a locus on chromosome 4q21–q23 [33]. The MSX2 and ALX4 genes encode homeodomain transcription factors, which act as pleiotropic developmental regulators in vertebrates [34,35]. Mavrogiannis et al [30] concluded that PFM caused by mutations in ALX4 and MSX2 have similar prevalence and are usually clinical indistinguishable. PFM may be associated with NTDs [36–39]. Terrafranca and Zellis [36] reported a patient with cranium bifidum and cervical and lumbosacral spina bifida occulta. Aoyagi et al [37] reported a case of PFM complicated by meningocele through the foramina. Reddy et al [38] reported an atretic occipital encephalocele in a patient with PFM. Tekkök [39] reported triple NTDs in a boy with hydrocephalus, Chiari II malformation, cranium bifidum, a parieto-occipital encephalocele, a cervical myelomeningocele, and a thoracolumbar myelomeningocele.

Apert Syndrome

Apert syndrome (OMIM 101200) or acrocephalosyndactyly is characterized by craniosynostosis, midface hypoplasia, and syndactyly of hands and feet. Apert syndrome has an autosomal dominant pattern of inheritance and is caused by mutations in the FGFR2 gene (OMIM 176943), which encodes the fibroblast growth factor receptor-2 [40]. Waterson et al [41] reported a female infant with Apert syndrome and a frontonasal encephalocele. Lorenz et al [42] reported a male infant with Apert syndrome, bilateral parieto-occipital “encephalocele”, micropenis, and severe mental retardation. Gershoni-Baruch et al [43] reported a case of Apert syndrome with occipital encephalocele and absence of the corpus callosum. In a review of Apert syndrome, Cohen and Kreiborg [44] found that 30 patients had malformations of the corpus callosum and/or limbic structures and other frequent findings, including gyri abnormalities (eight cases), megalencephaly (seven cases), encephalocele (four cases), hypoplasia of cerebral white matter (four cases), pyramidal tract abnormalities (two cases) and heterotopic gray matter (two cases). Cohen and Kreiborg [45] found that 4% of Apert syndrome infants had a frank cloverleaf skull. The authors suggested that encephalocele is rarely found in Apert syndrome, and pseudoencephalocele in the frontal region may be confused with encephalocele, because the Apert calvaria at birth is characterized by a widely gaping midline defect. In a review of intracranial anomalies
detected by brain imaging studies in 30 patients with Apert syndrome, Quintero-Rivera et al [46] found non-progressive ventriculomegaly in 23 (76%), partially absent septum pellucidum in seven (23%), complete absent septum pellucidum in five (17%), hydrocephalus in four (13%), thinning of corpus callosum in four (13%), deficiency of septal leaflets in three (10%), agenesis of the corpus callosum in two (7%) and deficient corpus callosum in one (3%).

**Craniomicromelic Syndrome**

Craniomicromelic syndrome (OMIM 602558) is a lethal condition characterized by craniosynostosis, distinct facial anomalies, short limbs and intrauterine growth restriction, and has been postulated to have an autosomal recessive pattern of inheritance [47]. Baralle and Firth [48] reported a 29-week-gestation fetus with craniomicromelic syndrome, intrauterine growth restriction, ossification defects of the skull with posterior encephalocele, large fontanels with wide cranial suture, and absent phalanges and digital syndactyly.

**XX-Agonadism with Multiple Dysraphic Lesions Including Omphalocele and NTDs**

XX-agonadism with multiple dysraphic lesions including omphalocele and NTDs is unique and may represent a new syndrome [49,50]. Kennerknecht et al [49] reported a 19-week-gestation fetus with a 46,XX karyotype, normal female external genitalia, complete gonadal agenesis, omphalocele, a long encephalocele that extended from the occipital region to the upper third of the spine, and a dysraphic segment of the spine (spina bifida) below the encephalocele. Kennerknecht et al [49] suggested a new syndrome of XX-agonadism with multiple dysraphic lesions. Woo et al [50] reported an 18-week-gestation fetus with a 46,XX karyotype, normal female external genitalia, complete gonadal agenesis, omphalocele, a large occipital meningoencephalocele and spina bifida affecting the cervical spine, webbing of right upper limb, deformed right clavicle and right-sided ribs, absent interventricular septum, hypoplastic aorta, hypoplastic spleen, and single umbilical artery.

**Fryns Microphthalmia Syndrome**

Fryns microphthalmia syndrome (OMIM 600776) or anophthalmia-plus syndrome is characterized by anophthalmia/microphthalmia, facial clefting and sacral NTDs, and has been postulated to have an autosomal recessive pattern of inheritance [51]. Fryns et al [51] described a 17-week-gestation fetus with bilateral anophthalmia, bilateral cleft lip/cleft palate, macrostia, bilateral facial cleft, a large open sacral NTD, and uterus unicornis. Warburg et al [52] reported a female infant with anophthalmia-microphthalmia-oblique clefting and frontal encephalocele resembling the anophthalmia-plus syndrome. Makhoul et al [53] reported a male infant with anophthalmia-plus syndrome and sacral spina bifida. In a review of nine cases with Fryns microphthalmia syndrome, Makhoul et al [53] found frontal encephalocele in one case and sacral NTDs in two cases.

**Gershoni-Baruch Syndrome**

Gershoni-Baruch syndrome, or omphalocele, diaphragmatic hernia and radial ray defects (OMIM 609545), is characterized by the association of diaphragmatic hernia, radial ray defects and multiple midline defects [54]. Gershoni-Baruch syndrome has been postulated to have an autosomal recessive pattern of inheritance [55]. Bird et al [5] reported a 26-week-gestation female fetus with Gershoni-Baruch syndrome and encephalocele. Franceschini et al [55] reported a 23-week-gestation female fetus with Gershoni-Baruch syndrome and thoraco-lumbar rachischisis, and a 9-week-gestation male sib with schisis defects.

**PHAVER Syndrome**

PHAVER syndrome (OMIM 261575) is characterized by the acronym PHAVER: Pterygia, Heart defects, Autosomal recessive inheritance, Vertebral defects, Ear anomalies and Radial defects [56]. Powell et al [56] reported two sibs with vertebral, radial, congenital heart and ear defects. One sib had limb pterygia and meningomyelocele.

**Periconceptional Vitamin B6 Deficiency**

An association of NTD risk with a low maternal blood level of vitamin B6 has been observed [57]. In a study of nutritional and genetic determinants of vitamin B and homocysteine metabolisms in NTDs, Candito et al [57] found that only the erythrocyte folate concentration \( (p = 0.005) \) and plasma vitamin B6 concentration \( (p = 0.020) \) were predictors. Candito et al [57] also
found that women prior to elective abortion for severe NTDs had significantly lower erythrocyte folate, plasma folate, vitamin B12 and vitamin B6 concentrations, and a higher homocysteine concentration than the controls. The authors suggested that increased consumption of vitamin B12 and vitamin B6 may provide additional protection against NTDs. Czeizel and Merhala [58] proposed bread fortification with folic acid, vitamin B12 and vitamin B6 in Hungary, based on the minimum requirement of 160 μg folic acid, 0.80 μg vitamin B12 and 880 μg vitamin B6 for 100 g flour, and the optimal requirement of 330 μg folic acid, 20 μg vitamin B12 and 3,000 μg vitamin B6 for 100 g flour, in an attempt to reduce NTDs and vascular diseases. The minimal requirement was accepted by Hungarian authorities in August 1998.

**Autosomal Dominant Dandy-Walker Malformation with Occipital Cephalocele**

Bassuk et al [59] reported a non-consanguineous Vietnamese kindred with isolated autosomal dominant occipital cephalocele over three generations. A similar Brazilian family with autosomal dominant atretic cephalocele with phenotype variability has been described [60]. Jalali et al [61] re-characterized this condition as autosomal dominant Dandy-Walker malformation with occipital cephalocele (ADDWOC). Jalali et al [61] performed genome-wide linkage analysis on members of the Vietnamese-American and Brazilian pedigrees and identified the ADDWOC causative locus on chromosome 2q36.1. Other families with ADDWOC have been reported in Spain [62] and in China [63]. Atretic cephalocele (OMIM 609222) is characterized by a skin-covered subscalp lesion containing meninges or remnants of glial or neural tissues [62]. Martínez-Lage et al [62] first reported familial occurrence of cephalocele in a family with three sibs having occipital atretic cephalocele. Bassuk et al [59] reported a clear pattern of autosomal dominant occipital cephalocele with incomplete penetrance and variable expressivity in a Vietnamese kindred, in which seven members spanning three generations had occipital atretic cephalocele. Carvalho et al [60] reported the clinical and imaging characteristics of a non-consanguineous Brazilian family with nonsyndromic autosomal dominant occipital cephalocele in six individuals over four generations. Zhao et al [63] reported a Chinese family with autosomal dominant occipital cephalocele over five generations in which 21 among 113 family members had subscalp encephalocele.

**Conclusion**

This article provides a comprehensive review of the syndromes, disorders and maternal risk factors associated with NTDs, including DK phocomelia syndrome (von Voss-Cherstvoy syndrome), Siegel-Bartlett syndrome, fetal warfarin syndrome, craniofacial clefts, cranial dysraphic lesions including omphalocele and NTDs, Fryns microphthalma syndrome, Gershoni-Baruch syndrome, PHAVER syndrome, periconceptional vitamin B6 deficiency, and autosomal dominant Dandy-Walker malformation with occipital cephalocele. 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 nonsyndromic multifactorial NTDs. Perinatal diagnosis of NTDs should alert doctors to the syndromes, disorders and maternal risk factors associated with NTDs, and prompt thorough etiologic investigation and genetic counseling.

**References**


