Chromosomal Abnormalities Associated with Neural Tube Defects (I): Full Aneuploidy

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SUMMARY

Fetuses with neural tube defects (NTDs) carry a risk of chromosomal abnormalities. The risk varies with maternal age, gestational age at diagnosis, association with other structural abnormalities, and family history of chromosome aberrations. This article provides an overview of chromosomal abnormalities associated with NTDs in embryos, fetuses, and newborn patients, and a comprehensive review of numerical chromosomal abnormalities associated with NTDs, such as trisomy 18, trisomy 13, triploidy, trisomy 9, trisomy 2, trisomy 21, trisomy 7, trisomy 8, trisomy 14, trisomy 15, trisomy 16, trisomy 5 mosaicism, trisomy 11 mosaicism, trisomy 20 mosaicism, monosomy X, and tetraploidy. NTDs may be associated with aneuploidy. Perinatal identification of NTDs should alert one to the possibility of chromosomal abnormalities and prompt a thorough cytogenetic investigation and genetic counseling. [*Taiwan J Obstet Gynecol* 2007;46(4):325–335]

Key Words: chromosomal abnormalities, full aneuploidy, neural tube defects

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 (omphalocele-exstrophy-imperforate anus-spinal defects) 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 (Meckel syndrome, median cleft face syndrome, Roberts syndrome, Jarcho-Levin syndrome and HARD [hydrocephalus, agyria, retinal dysplasia] syndrome), chromosomal abnormalities (trisomy 18, trisomy 13, triploidy and other structural abnormalities), teratogens (valproic acid, aminopterin/amethopterin and thalidomide), maternal diabetes, family history of NTDs, thermolabile mutation in the *MTHFR* gene, and others [1]. There is considerable evidence that genetics contributes to the etiology of NTDs. Fetuses with NTDs carry a risk of chromosomal abnormalities. The risk varies with maternal age, gestational age at diagnosis, association with other structural abnormalities, and family history of chromosome aberrations.

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Chromosomal Abnormalities Associated with NTDs in Aborted Embryos

When the diagnosis of NTDs is made in aborted embryos, the percentage of aneuploidy can increase to over 70% [2–5]. Table 1 shows the reported incidence

Table 1. Incidence of chromosomal aberrations in aborted embryos with neural tube defects (NTDs)

Authors	Total NTDs*	Cases	Anencephaly/exencephaly/craniorachischisis*	Spina bifida*	Encephalocele*	Iniencephaly*
Byrne and Warburton [2]	6/6 (100%)	Aborted embryos: sixth to seventh developmental week	2/2† Trisomy 21 (one case) Triploidy (one case)	1/1† Triploidy (one case)	3/3 Mosaic trisomy 20 (one case) Monosomy X (one case) Trisomy 13 (one case)	1/1 Triploidy (one case)
McFadden and Kalousek [3]	26/32 (81.25%)	Aborted embryos: < ninth developmental week	0/2	15/17 Triploidy (10 cases) Trisomy 13 (four cases) Trisomy 16 (one case)	11/13 Monosomy X (five cases) Trisomy 14 (three cases) Triploidy (two cases) Trisomy 15 (one case)	
Coerdt et al [4]	5/7 (71.43%)	Aborted embryos: sixth to ninth developmental week	0/1	4/4 Trisomy 18 (two cases) Triploidy (one case) Monosomy X (one case)	1/2 Trisomy 7 (one case)	
Philipp and Kalousek [5]	8/8 (100%)	Embryos in missed abortions: < ninth developmental week	1/1 Trisomy 9 (one case)	3/3 Triploidy (two cases) Trisomy 14 (one case)	4/4 Monosomy X (one case) Trisomy 14 (one case) Triploidy (one case) Trisomy 21 (one case)	

**Aneuploidy cases/total cases; †one case with anencephaly, spina bifida, and triploidy.*

of chromosomal abnormalities associated with NTDs in aborted embryos. Table 2 shows the characteristics of aborted embryos with NTDs. Byrne and Warburton [2] reported the incidence of 1.02% of NTDs in spontaneous abortions, a rate about 10 times higher than in term births. In their study of 879 spontaneous fetal losses occurring before 28 weeks' gestation, six embryos and three fetuses had NTDs. All of the six embryos had chromosomal abnormalities. Triploidy occurred in two embryos, one with anencephaly and spina bifida, and the other with iniencephaly. One embryo had exencephaly, cleft lip and palate, and trisomy 21 [t(21q;21q)]. Three embryos had encephaloceles, of which one had mosaic trisomy 20, one had monosomy X, and one with trisomy 13 [t(13q;13q)]. McFadden and Kalousek [3] reported the incidence of 6.7% of NTDs in spontaneously aborted embryos, a rate markedly higher than the 0.155% of NTDs in births observed in British Columbia, Canada. In their study of 569 embryos at the developmental age of less than 9 weeks, 38 embryos had NTDs of which 32 had cytogenetic analysis. Of the 32 embryos, 26 (81.25%) were cytogenetically abnormal. Of the two embryos with anencephaly, none had aneuploidy. Of the 13 embryos with encephalocele, 11 had aneuploidy, including monosomy X (five cases), trisomy 14 (three cases), trisomy 15 (one case), and triploidy (two cases). Of the five embryos with classical spina bifida, three had aneuploidy, including triploidy (two cases) and trisomy 16 (one case). Of the 12 embryos with caudal neural tube overgrowth, all had aneuploidy, including triploidy (eight cases) and trisomy 13 (four cases). McFadden and Kalousek [3] suggested that the frequency of NTDs in embryos differs from that observed in fetuses and newborn infants. They found that there was a predominance of encephalocele and caudal NTDs in embryos. In fetuses and newborn infants, the common observed NTDs are spina bifida and anencephaly. Coerdt et al [4] recognized NTDs in nine out of 91 intact first-trimester embryos following spontaneous or induced abortion. In their study, five of the seven NTD embryos cytogenetically analyzed had aneuploidy, including trisomy 18 (two spina bifidas), trisomy 7 (one encephalocele), triploidy (one spina bifida), and monosomy X (one spina bifida). The other two embryos (one with craniorachischisis and one with encephalocele) were cytogenetically normal. In a study of missed abortion of 99 embryos with a complete embryoscopic evaluation at the developmental age of less than 9 weeks, Philipp and Kalousek [5] found that 10 embryos had NTDs. All of the eight NTD embryos cytogenetically analyzed in this study had aneuploidy, including triploidy (two spina bifidas and one encephalocele), trisomy 14 (one spina bifida and one encephalocele), trisomy 9 (one anencephaly), monosomy X (one encephalocele), and trisomy 21 (one encephalocele).

Chromosomal Abnormalities Associated with NTDs in Fetal and Newborn Patients

Chromosomal abnormalities have been reported in 2.5–10.26% of fetal and newborn patients with common NTDs [6–11]. Chromosomal abnormalities occur in 0.66–5.56% of anencephaly [6–8,10,11], 4.38–17.31% of spina bifidas [6–8,10–14], and 2.08–12.29% of encephaloceles [8,10,11,15]. Table 3 shows the reported incidence of chromosomal abnormalities associated with NTDs in fetal and newborn patients. Trisomy 18, trisomy 13, and triploidy are the most common chromosomal abnormalities associated with NTDs, and there is a predominance of spina bifida (Table 3).

Full Aneuploidy

Numerical chromosomal abnormalities associated with NTDs include trisomy 18, trisomy 13, triploidy, trisomy 9, trisomy 2, trisomy 21, trisomy 7, trisomy 8, trisomy 14, trisomy 15, trisomy 16, trisomy 5 mosaicism, trisomy 11 mosaicism, trisomy 20 mosaicism, monosomy X, and tetraploidy [16].

Trisomy 18

Trisomy 18 can be associated with spina bifida, encephalocele, and anencephaly. Most of the reported NTDs associated with trisomy 18 are spina bifidas. Encephalocele and anencephaly have occasionally been reported. Claussen et al [17] observed encephalocele with mosaic trisomy 18 at 34 gestational weeks. Babini et al [18] reported one occipital encephalocele, Menashi et al [19] reported one anencephaly, Merrild et al [20] reported one anencephaly, Nisani et al [21] reported one anencephaly with cervical rachischisis, Ramos et al [22] reported one anencephaly, Seller [23] reported one encephalocele, Sepulveda et al [10] reported two encephaloceles, and Chen [24] reported one anencephaly in patients associated with trisomy 18. Moore et al [25] reported craniorachischisis, large omphalocele, and bilateral cleft lip and palate in a fetus with trisomy 18. van Maldergem et al [26] reported craniorachischisis, omphalocele, bilateral radial agenesis, and distal arthrogryposis in a fetus with trisomy 18. Grangé et al [27] reported occipital encephalocele, craniorachischisis, and cystic hygroma in a fetus with

Table 2. Clinical findings of embryos with neural tube defects (NTDs) and chromosomal aberrations in abortions or missed abortions

Authors	Maternal age (yr)	Developmental age (wk)	NTD	Karyotype	Associated anomalies
Byrne and Warburton [2]					
Case 3	45	7	Encephalocele	46,XX/47,XX,+20	
Case 4	22	6	Encephalocele	46,XY,-13,+t(13q;13q)	
Case 5	17	7	Exencephaly	46,XY,-21,+t(21q;21q)	Cleft lip and palate
Case 6	20	7	Encephalocele	45,X	
Case 7	23	6	Anencephaly, spina bifida	69,XXX	
Case 8	31	6	Iniencephaly	69,XXY	
Coerdt et al [4]					
Case 1	41	9	Spina bifida	47,XX,+18	Situs inversus, ventricular septal defect
Case 2	41	10	Spina bifida	47,XY,+18	Radial defect, a rudimentary thumb
Case 5	31	7–8	Encephalocele	47,XX,+7	Microcephaly, cleft lip and palate
Case 6	32	8–9	Spina bifida	69,XXY	Syndactyly, ventricular septal defect
Case 7	26	6	Spina bifida, iniencephaly	45,X	Median cleft lip and palate
Philipp and Kalousek [5]					
Case 2	37	8	Encephalocele	45,X	Microcephaly, retarded limb development
Case 3	25	6	Encephalocele	69,XXY	Retarded limb development
Case 4	26	8	Spina bifida	69,XXX	Microcephaly
Case 5	25	6	Anencephaly	47,XX,+9	Fusion of the face to the chest, retarded limb development
Case 6	38	6	Encephalocele	47,XX,+14	Retarded limb development
Case 7	31	7	Spina bifida	47,XX,+14	Microcephaly, facial anomalies, retarded limb development
Case 9	28	6	Spina bifida	69,XXY	Microcephaly, retarded limb development
Case 10	34	6	Encephalocele	47,XX,+21	Microcephaly, facial defects
Philipp et al [38]					
Case 7		6	Spina bifida	69,XXY	Microcephaly, rudimentary limb development
Case 8		6	Lumbosacral myelocele	69,XXY	Microcephaly, a dysplastic midface
Case 12		8	Lumbosacral myelocele	69,XXX	Retarded limb development
Case 15		6	Spina bifida	69,XXX	A dysplastic face, retarded limb development
Case 16		6	Spina bifida	69,XXY	Microcephaly
Case 17		6	Spina bifida	69,XXY	Microcephaly

Table 3. Incidence of chromosomal aberrations in fetal and newborn patients with neural tube defects (NTDs)

Authors	Total NTDs*	Cases	Anencephaly*	Spina bifida*	Encephalocele*	Iniencephaly*
Drugan et al [6]	4/39 (10.26%)	Fetuses with ultrasound anomalies or elevated maternal serum α-fetoprotein	1/18 (5.56%) del(13)(q13) (one case)	3/21 (14.29%) Trisomy 18 (two cases) 4p+ (one case)		
Babcook et al [12]		Prenatally detected myelomeningoceles		9/52 (17.31%) Trisomy 18 (five cases) Trisomy 13 (two cases) 69,XXY (one case) 8p+ (one case)		
Harmon et al [14]		Prenatally detected isolated NTDs (mean GW, 22)		7/43 (16.28%) Trisomy 18 (two cases) 69,XXX (two cases) 69,XXY (one case) t(13q;14q) (one case) inv Xq (one case)		
Hume et al [7]	6/100 (6%)	Prenatally detected NTDs	1/44 (2.27%) Supernumerary marker (one case)	5/62 (8.07%) Trisomy 18 (five cases)		
Kennedy et al [8]	13/200 (6.5%)	Fetuses with NTDs (mean GW, 19)	2/88 (2.27%) der(13)t(13;22)(q31.2;q13.3) (one case) Mosaic marker (one case)	10/98 (10.2%) Trisomy 18 (four cases) Trisomy 9 (one case) 69,XXX (one case) 45,X (one case) 46,X,rea(X) (one case) dup(3)(p21) (one case) der(13)t(11;13)(q23.1;q34) (one case)	1/14 (7.14%) t(11;14)(p15.1;q24.1) (one case)	
Babcook et al [13]		Open spina bifidas: live births + still births + terminations		6/45 (13.33%) Trisomy 18 (four cases) Trisomy 13 (two cases)		

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Table 3. *(continued)*

Authors	Total NTDs*	Cases	Anencephaly*	Spina bifida*	Encephalocele*	Iniencephaly*
Sepulveda et al [10]	10/144 (7%)	Fetuses with open NTDs: < 16 GW (4.8%) 16–24 GW (45.5%) > 24 GW (49.7%)	1/57 (1.75%) Trisomy 18 (one case)	6/66 (9.09%) Trisomy 18 (four cases) Trisomy 13 (two cases)	3/21 (14.29%) Trisomy 18 (two cases) Mosaic marker (one case)	0/11
Stoll et al [11]	9/360† (2.5%)	Live births + still births + terminations	1/152 (0.66%)	7/160 (4.38%)	1/48 (2.08%)	
Wen et al [15]		Records of infants/fetuses with encephalocele in the Texas Birth Defects Registry			9/134 (6.7%) del(1)(q42) (one case) Mosaic trisomy 8 (one case) inv 9q (one case) Trisomy 13 (one case) Trisomy 21 (one case) inv Y (one case) Triploidy (one case) Trisomy 18 (2 cases)	

**Aneuploidy cases/total cases; †eight cases had trisomy 18, one case had unbalanced translocation. GW = gestational weeks.*

trisomy 18. Donaldson et al [28] reported abdominal wall defect of thoraco-abdominoschisis extending from the neck to the pelvis, and craniorachischisis in a fetus with trisomy 18. Several studies have shown that NTDs occur in 6–11% of trisomy 18 cases [25,29,30]. Flannery and Kahler [30] reported three meningomyeloceles among 48 liveborn cases (6.25%) with trisomy 18. Moore et al [25] reported 85 patients with trisomy 18 evaluated at Indiana University School of Medicine from 1963 to 1986 and found that the frequency of NTDs in trisomy 18 cases was 7.06% (6/85). Seller [23], in a study of 38 mid-trimester fetuses with trisomy 18, found that 23.68% (9/38) had NTDs, including eight spina bifidas and one anencephaly. Chen [24], in a study of 89 consecutive cases of fetal trisomy 18 (mean gestational age at diagnosis: 23.5 weeks), found that 2.25% (2/89) had NTDs, including one anencephaly and one lumbosacral myelomeningocele.

Trisomy 13

Trisomy 13 can be associated with spina bifida, encephalocele, and anencephaly. Most of the reported NTDs associated with trisomy 13 are spina bifidas. Encephalocele and anencephaly have occasionally been reported. Byrne and Warburton [2] reported trisomy 13 in an aborted embryo with encephalocele. Phadke and Thakur [31] reported prenatal diagnosis of iniencephaly, alobar holoprosencephaly, and cyclopia in a fetus with mosaic trisomy 13. Halder et al [32] reported mosaic trisomy 13 in a fetus with iniencephaly, anencephaly, facial clefts, single umbilical artery, dilated right side of the heart and club foot. Several studies have shown that NTDs occur in about 8% of trisomy 13 cases [23,33,34]. Rodriguez et al [33] found three spina bifidas among 34 trisomy 13 patients (8.8%). Wyllie et al [34] found one meningocele and two encephaloceles among 36 trisomy 13 patients (8.33%). Seller [23], in a study of 25 mid-trimester trisomy 13 fetuses, found that 8% (2/25) had spina bifidas.

Triploidy

Triploidy can be associated with spina bifida, encephalocele, and anencephaly. Most of the reported NTDs associated with triploidy are spina bifidas. Several studies have shown that NTDs occur in 7–55% of triploid embryos and 7–35% of mid-trimester triploid fetuses [23,35–38]. Harris et al [35] found that 7.69% (2/26) of triploid embryos had NTDs, one with iniencephaly and thoracolumbar myelocele and the other with lumbosacral spina bifida. Seller [23], in a study of mid-trimester triploid fetuses, found that 23.08% (3/13) had spina bifidas. Jauniaux et al [36] reported five spina bifidas among 65 cases (7.69%) with triploidy diagnosed in the second trimester. Mittal et al [37], in a study of 20 triploid fetuses (mean gestational age, 20.4 weeks), found that seven (35%) had open NTDs, including six myeloceles and one encephalocele. Phillip et al [38] found that 55.56% (10/18) of triploid embryos had NTDs, including eight spina bifidas and two encephaloceles.

Trisomy 9

Trisomy 9 can be associated with spina bifida and anencephaly. Most reported NTDs associated with trisomy 9 are spina bifidas [8,9,39–43]. Anencephaly associated with trisomy 9 has only been observed in one case [5]. Phillip and Kalousek [5] reported trisomy 9 in an embryo with anencephaly at the sixth developmental week. Frohlich [39] reported the prenatal diagnosis of trisomy 9 by amniocentesis. The fetus was terminated at 19 weeks' gestation, with anophthalmia, bilateral corneal opacities, double outlet of right ventricle, ventricular septal defect, left congenital diaphragmatic hernia and a small closed lumbar meningocele. Benacerraf et al [40] reported the prenatal diagnosis of trisomy 9 by amniocentesis at 31 weeks' gestation in a fetus with prenatal sonographic findings of intrauterine growth restriction, polyhydramnios, microcephaly, mild cerebral ventriculomegaly, ventricular septal defect, a lumbosacral neural tube defect, clenched hands, and club feet. The baby was delivered at 41 weeks' gestation with neonatal death and the additional findings of cleft palate, microphthalmia, a horseshoe kidney, a bicornuate uterus, a persistent left superior vena cava, a dysplastic and stenotic pulmonary valve, a left unilobed lung, enlarged lateral ventricles, underdeveloped corpus callosum, right retinal dysplasia, coloboma, and optic nerve hypoplasia. Golden and Schoene [41] reported the prenatal diagnosis of trisomy 9 by amniocentesis at 33 weeks' gestation in a fetus with a lumbosacral myelomeningocele, ventricular septal defect, mild ventriculomegaly, microcephaly, rocker-bottom feet, and clenched hands. The baby was delivered at 41 weeks' gestation but died at age 23 days. Kennedy et al [8] reported the prenatal diagnosis of trisomy 9 in a fetus with meningocele, prominent cisterna magna, echogenic bowel, left upper quadrant calcification, single kidney, a two-vessel cord, truncus arteriosus, single coronary ostium, uni-lobed left lung, bi-lobed right lung, gut malformation, micrognathia, and low-set ears. Seller et al [42] reported a 14-week gestation abortus with a large cystic spina bifida in the lumbosacral region and trisomy 9. Chen et al [43] reported the prenatal diagnosis of trisomy 9 by amniocentesis at 19 weeks' gestation in a fetus with intrauterine growth restriction, left congenital diaphragmatic hernia, ascites, a horseshoe

kidney, a small bladder, and lumbosacral spina bifida. The fetus was terminated at 22 weeks' gestation with additional findings of camptodactyly and club feet.

Trisomy 2

Trisomy 2 has been described in a fetus with encephalocele, spina bifida, and iniencephaly [44]. Seller et al [44] reported the postnatal diagnosis of trisomy 2 using the tissue of umbilical cord in a 13-week gestation male fetus with an open occipital encephalocele continuous with cervical and complete thoracic spina bifida aperta, iniencephaly, scoliosis of the cervical and upper thoracic spine, and kyphosis of the lower thoracic spine. Additional findings included a central cleft palate, fused kidneys, and left heart hypoplasia. The mother was 41 years old. Fluorescence *in situ* hybridization analysis of the skin confirmed trisomy 2. The association of NTDs with trisomy 2 is likely due to the duplication of 2p. Doray et al [45] reviewed 64 cases with partial trisomy 2p and found that 15 cases (23.44%) had NTDs, including spina bifida, anencephaly and encephalocele. Lurie et al [46] suggested that the common triplicated region of chromosome 2p associated with NTDs is the band 2p24. Chromosome 2p24 contains the two genes *GDF7* (growth/differentiation factor 7) and *DDEF2* (development and differentiation enhancing factor 2) that are important for neural tube development. *GDF7* is involved in the generation of a discrete class of commissural interneurons in the spinal cord [47], and *DDEF2* is involved in cell communication and structure [48].

Trisomy 21

Trisomy 21 has occasionally been associated with spina bifida, anencephaly, and encephalocele. Two reports suggested no increased risk of NTDs in infants with trisomy 21 [49,50]. Källén et al [49], in a study of 5,581 infants with Down syndrome registered in programs of congenital malformations in France, Italy and Sweden, found an approximately 300 times increased risk for annular pancreas, cataracts and duodenal atresia, an approximately 100 times increased risk for megacolon and choanal atresia, 10–30 times increased risks for esophageal, anal and bowel atresia, preaxial polydactyly, and omphalocele, 3–5 times increased risks for cleft palate, cleft lip/palate, and limb deformities, but no increased risks for NTDs, hydrocephaly, microtia, renal agenesis or severe dysgenesis, and hypospadias or polydactyly, other than preaxial polydactyly, in Down syndrome infants. Among the 5,581 Down syndrome infants, there were only four spina bifidas, giving an NTD incidence of 0.72 per 1,000 infants with Down syndrome. Torfs and Christianson [50], in a study of a population of close to 2.5 million infants born from 1983 to 1993 and registered in the California Birth Defects Monitoring Program, compared the structural birth defects among 2,894 Down syndrome infants with that of 2,490,437 infants without Down syndrome and found no increased risk for NTDs in Down syndrome infants. Among the 2,894 Down syndrome infants, there was only one encephalocele, giving an NTD incidence of 0.35 per 1,000 infants with Down syndrome. Barkai et al [51] observed an increased prevalence of Down syndrome in the offspring of 493 mothers in Israel with an index pregnancy with NTD, and an increased prevalence of NTD in the offspring of 516 mothers in Ukraine with an index pregnancy with Down syndrome. However, recent studies did not support the findings of Barkai et al [51] and found no association between families at risk of NTDs and those at risk of Down syndrome [52–54]. James et al [55] and Hobbs et al [56] found that mothers of Down syndrome infants have an increased frequency of common *MTHFR* 677C → T and *MTRR* 66A → G polymorphisms, and elevated levels of plasma homocysteine. Al-Gazali et al [57] reported abnormal folate metabolism and genetic polymorphism of the folate pathway in a child with trisomy 21 and cervical meningomyelocele. Molecular analysis of the *MTHFR* gene in that case revealed homozygosity for the mutant 677C → T polymorphism in both the mother and the child. Guéant et al [58] suggested that both NTDs and Down syndrome are influenced by the same genetic determinants for one-carbon metabolism of folate, vitamin B12, and genetic polymorphism of methylenetetrahydrofolate reductase, methionine synthase, methionine synthase reductase or transcobalamin. Whether folate and homocysteine metabolism and gene polymorphism play a role in the etiology of Down syndrome, and whether preconception intake of folate and vitamin B12 is effective in the prevention of Down syndrome remain unclear, and further studies are required for verification [59,60].

Trisomy 8 and mosaic trisomy 8

Longo and Maccani [61] reported a case of myelomeningocele associated with trisomy 8. Mosaic trisomy 8 has been associated with spina bifida [16].

Trisomy 7

Trisomy 7 has been described at the seventh or eighth developmental week in an embryo with encephalocele, microcephaly, and cleft lip and palate [4].

Trisomy 14

Trisomy 14 has been described at the sixth developmental week in an embryo with encephalocele and retarded

limb development, and at the seventh developmental week in an embryo with spina bifida, microcephaly, facial anomalies, and retarded limb development [5], and in three embryos with encephalocele [3]. McDermott and Cross [62] reported an infant with complete trisomy 14 with a *de novo* 13/14 translocation, thoracolumbar meningomyelocele, horseshoe kidneys, absence of radii and thumbs, cleft lip, a ventricular septal defect, and neonatal death.

Trisomy 15

Trisomy 15 has been described in an embryo with encephalocele [3].

Trisomy 16

Trisomy 16 has been described in an embryo with spina bifida [3].

Mosaic trisomy 5

Mosaic trisomy 5 has been associated with encephalocele [15].

Mosaic trisomy 11

Mosaic trisomy 11 has been associated with anencephaly [16].

Mosaic trisomy 20

Mosaic trisomy 20 has been associated with encephalocele [2] and anencephaly [16].

Monosomy X

Monosomy X has been described in embryos with encephalocele [2,5]. Coerdt et al [4] reported an embryo with spina bifida, iniencephaly, and median cleft lip and palate at the sixth developmental week. Kennedy et al [8] reported a fetus with the karyotype of 45,X and abnormal sonographic findings of lumbosacral meningocele and Arnold-Chiari malformation. Halder et al [32] reported mosaic monosomy X in a fetus with iniencephaly, cystic hygroma, congenital diaphragmatic hernia, and hydrops fetalis. Monosomy X is the single most common aneuploidy in spontaneous abortion. Philipp and Kalousek [63] found that 24 out of 108 (22.22%) embryos in missed abortions had monosomy X. However, only a single case of encephalocele could be observed among the 24 monosomy X embryos.

Tetraploidy

Tetraploidy has been described in infants with spina bifida [64–66]. Pitt et al [64] reported a 15-day-old tetraploid (92,XXYY) infant born to a 27-year-old mother. The infant manifested facial dysmorphism, positional limb defects, urinary tract abnormalities, hydrocephalus, and sacral meningomyelocele. Scarbrough et al [65] reported a small-for-date tetraploid (92,XXXX) infant born to a 19-year-old mother. The infant manifested hypotonia, scaphocephaly, bilateral anophthalmia, facial dysmorphism, a lumbosacral meningomyelocele, arachnodactyly, craniosynostosis, Arnold-Chiari malformation, and cerebellar hypoplasia and died at 2 days of age. Shiono et al [66] reported a 15-month-old tetraploid (92,XXXX) infant born to a 35-year-old mother. The infant manifested micro-turricephaly, a prominent but narrow forehead, microphthalmia or anophthalmia, limb anomaly, sacral meningomyelocele, and mental retardation.

Conclusion

This article provides an overview of chromosomal abnormalities associated with NTDs in embryos, fetuses, and newborn patients, and a comprehensive review of numerical chromosomal abnormalities associated with NTDs, such as trisomy 18, trisomy 13, triploidy, trisomy 9, trisomy 2, trisomy 21, trisomy 7, trisomy 8, trisomy 14, trisomy 15, trisomy 16, trisomy 5 mosaicism, trisomy 11 mosaicism, trisomy 20 mosaicism, monosomy X, and tetraploidy. NTDs may be associated with aneuploidy. Perinatal identification of NTDs should alert one to the possibility of chromosomal abnormalities and prompt a thorough cytogenetic investigation and genetic counseling.

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