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Short Communication

Double aneuploidy with Edwards–Klinefelter syndromes (48,XXY,+18) of maternal origin: Prenatal diagnosis and molecular cytogenetic characterization in a fetus with arthrogryposis of the left wrist and aplasia of the left thumb

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Abstract

Objective: To present the prenatal diagnosis and molecular investigation of the parental origin and mechanism of nondisjunction underlying an 48,XXY,+18 karyotype in a fetus with congenital abnormalities, and to review the literature.

Materials, Methods, and Results: A 42-year-old woman was referred for amniocentesis at 18 weeks of gestation because of advanced maternal age. Prenatal ultrasound revealed bilateral choroid plexus cysts. Amniocentesis revealed a karyotype of 48,XXY,+18. The parental karyotypes were normal. Level II ultrasound revealed a flexion contracture deformity of the left wrist with absence of the thumb. The pregnancy was terminated at 22 weeks of gestation. A 332 g male fetus was delivered with clenched hands, arthrogryposis of the left wrist, aplasia of the left thumb, micrognathia, low-set ears, hypertelorism, rocker-bottom feet, and a normal penis. Quantitative fluorescent polymerase chain reaction assays using polymorphic DNA markers showed a triallelic pattern with a dosage ratio of 1:1:1 (paternal:maternal:maternal) for chromosome 18-specific markers, and a monoallelic pattern of a single maternal allele for chromosome X-specific markers. The fetus inherited two copies of two different maternal alleles on chromosome 18, and two copies of a single maternal allele on chromosome X. The molecular result, along with the karyotype of 48,XXY,+18, was consistent with the occurrence of nondisjunction of chromosome 18 in a maternal meiosis I error and nondisjunction of chromosome X in a maternal meiosis II error or less likely a postzygotic mitotic error.

Conclusion: The present case provides evidence that abnormal separation of chromosomes 18 and X resulting in double aneuploidy may occur in different cell divisions, and such an occurrence is related to advanced maternal age.

Keywords: 48,XXY,+18; Double aneuploidy; Klinefelter syndrome; Nondisjunction; Parental origin; Trisomy 18

Introduction

The simultaneous occurrence of double aneuploidy involving Edwards syndrome (trisomy 18) and Klinefelter syndrome (47,XXY) is rare. To our knowledge, only 13 cases

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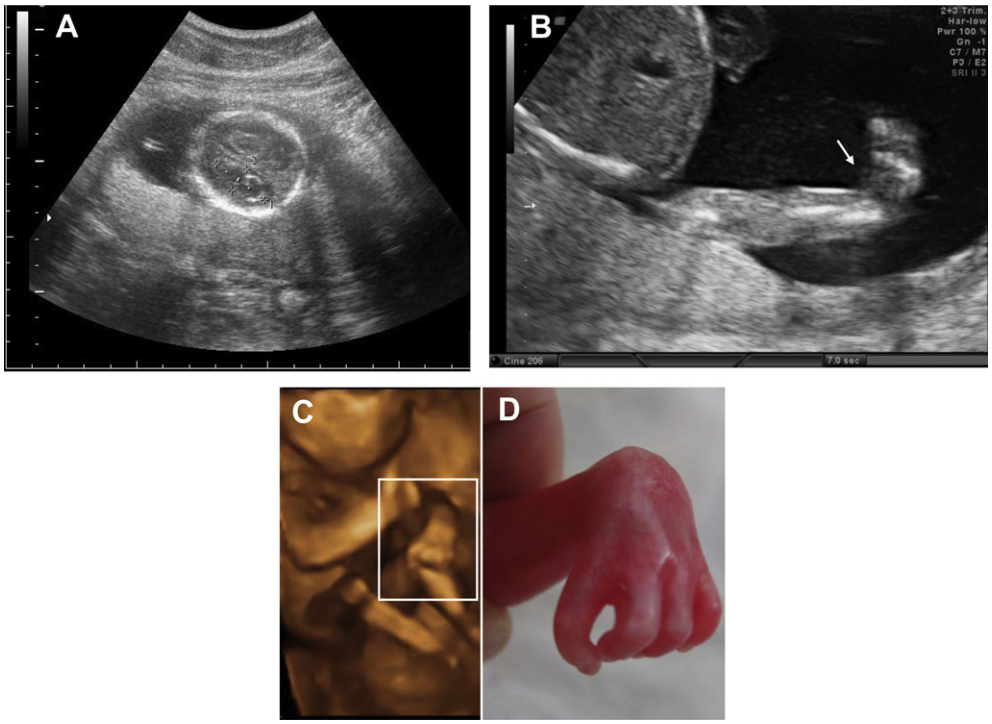

Fig. 1. Prenatal ultrasound findings. (A) Choroid plexus cysts at 18 weeks of gestation. (B, C) Flexion contracture deformity of the left wrist with absence of the thumb (arrow and inset) at 22 weeks of gestation. (D) Corresponding findings for the left wrist and absence of the thumb at birth as compared with the three-dimensional ultrasound image in (C), inset.

have been reported [1–13]. Among these cases, three concern the prenatal diagnosis [9,10,13], and only one concerns the parental origin and cell stage of nondisjunction of the aneuploidy [11]. Here, we present our experience of the prenatal diagnosis and molecular investigation of the parental origin and the mechanism of nondisjunction underlying a 48,XXY,+18 karyotype in a fetus with congenital abnormalities. We also review the literature.

Materials, methods and results

A 42-year-old, gravida 3, para 1 woman was referred for amniocentesis at 18 weeks of gestation because of advanced maternal age. She had experienced one abortion and had a healthy 14-year-old daughter. Her husband was 43 years old. She and her husband were healthy, and there was no family history of congenital malformation. Prenatal ultrasound at 18 weeks of gestation revealed bilateral choroid plexus cysts in a singleton fetus with fetal biometry equivalent to 17 weeks (Fig. 1A). Cytogenetic analysis of cultured amniocytes revealed a karyotype of 48,XXY,+18 (Fig. 2). The parental karyotypes were normal. Level II ultrasound revealed a flexion contracture deformity of the left wrist with absence of the thumb (Fig. 1B).

The parents elected to terminate the pregnancy at 22 weeks of gestation. A 332 g male fetus was delivered with clenched hands, arthrogryposis of the left wrist, aplasia of the left thumb, micrognathia, low-set ears, hypertelorism, rocker-bottom feet, and a normal penis (Fig. 3). Postnatal cytogenetic analysis of the fetal tissues confirmed the prenatal diagnosis. Quantitative fluorescent polymerase chain reaction assays using polymorphic short tandem repeat markers showed a triallelic pattern with a dosage ratio of 1:1:1 (paternal:maternal:maternal) for chromosome 18-specific markers, and a monoallelic pattern of a single maternal allele for chromosome X-specific markers. The fetus had inherited two copies of two different maternal alleles on chromosome 18, and two copies of a single maternal allele on chromosome X. The molecular result, along with the 48,XXY,+18 karyotype, was consistent with the occurrence of nondisjunction of chromosome 18 in a maternal meiosis I error (mat MI) and nondisjunction of chromosome X in a maternal

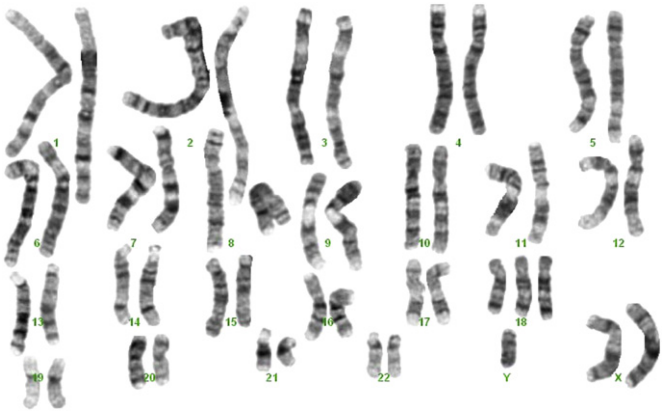

Fig. 2. 48,XXY,+18 karyotype.

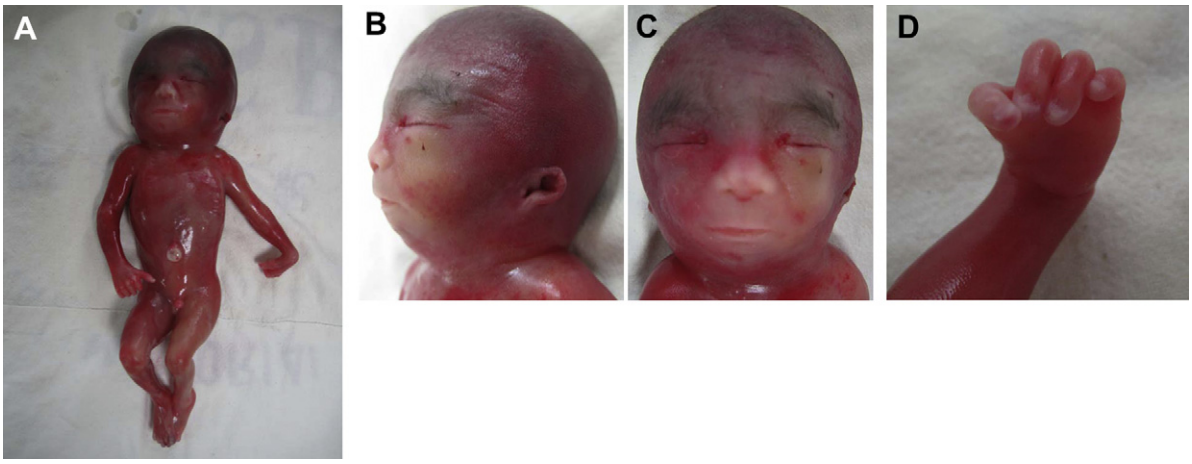

Fig. 3. (A) Whole-body view of the fetus at birth. (B, C) Craniofacial appearance of micrognathia, hypertelorism, and low-set ears. (D) Arthrogryposis of the left wrist with absence of the thumb.

meiosis II error (mat MII) or less likely a postzygotic mitotic error (PZM) (Table 1 and Fig. 4).

Discussion

The present case was detected viably in the second trimester and was associated with two aneuploidies involving Klinefelter syndrome and trisomy 18. Reddy [14] reported that double aneuploidies in liveborns usually contain sex chromosome abnormalities and/or common aneuploidies of trisomy 13, 18, and/or 21, including XXX/18, XXX/21, XXY/13, XXY/18, XXY/21, XYY/13, XYY/18, XYY/21, 13/18, 13/21, 18/21, 21/21, and XXYY, and that double aneuploidies in spontaneous abortions usually contained nonviable trisomies of trisomy 16, 8, 15, or 2, including 16/21, 2/16, 15/16, 2/18, 8/16, 13/16, and 16/22. Diego-Alvare et al [15] reported double aneuploidy in 2.18% of miscarriages (n = 321). In a study of 385 cases of double trisomy in spontaneous abortions, Micale et al [16] found that the most common double trisomies involving an autosome and a sex chromosome were X/Y,+21 (36 cases) and X/Y,+18 (33 cases), with the most common double trisomies involving two autosomes being 16/21 (7 cases), 15/16 (5 cases), 15/21 (4 cases), 18/21 (4 cases), and 21/22 (4 cases).

Table 1
Molecular results using polymorphic markers specific for chromosomes 18 and X[a].

Markers	Locus	Father	Mother	Fetus	Result
D18S535	18q12.3	143, 161	153, 157	153, 157, 161	mat MI
D18S878	18q22.1	174, 182	174, 186	174, 182, 186	
D18S1358	18q22.3	142, 142	138, 142	138, 142, 142	
DXS9903	Xp22.33	210	218, 226	218, 218	mat MII
DXS8378	Xp22.31	227	227, 231	231, 231	or PZM
DXS6806	Xq27.3	176	180, 184	180, 180	
DXS6814	Xp22.33 Yp11.3	163	163, 175	163, 175, 175	

mat MI = maternal meiosis I nondisjunction error; mat MII = maternal meiosis II nondisjunction error; PZM = postzygotic mitotic error.
[a] Alleles (base pair sizes) are listed below each individual.

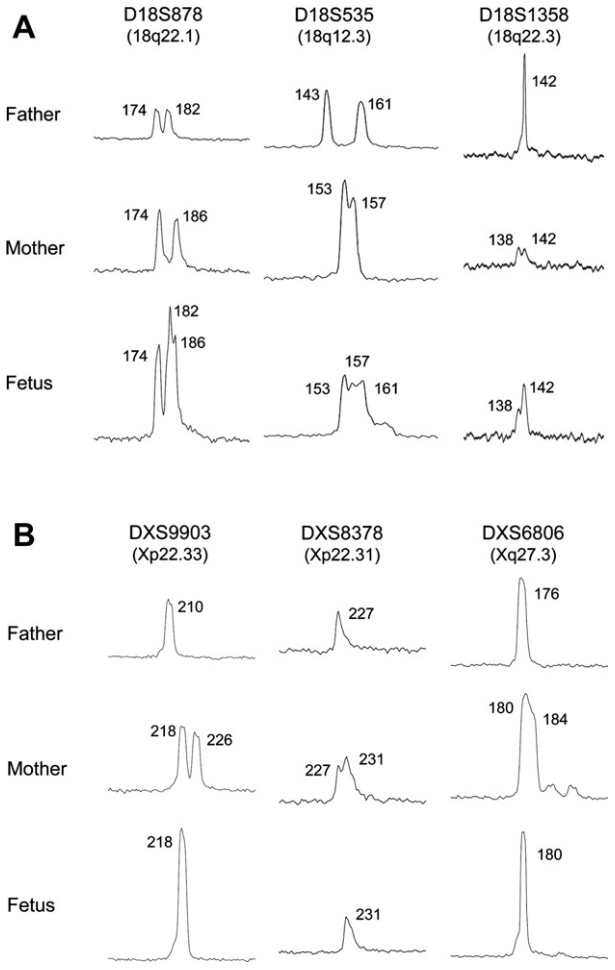

Fig. 4. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays show (A) two copies of two different maternal alleles for chromosome 18-specific markers, and (B) monoallelic pattern of a single maternal allele for the chromosome X-specific markers. For example, marker D18S535 shows three peaks (153 bp:157 bp:161 bp; maternal:maternal:paternal, respectively) of equal fluorescent activity indicating the occurrence of nondisjunction of chromosome 18 in a maternal meiosis I error (mat MI), the marker DXS9903 shows only one peak (218 bp) of maternal origin, indicating the occurrence of nondisjunction of chromosome X in a maternal meiosis II error (mat MII) or a postzygotic mitotic error (PZM).

Table 2
Clinical findings of reported cases with Edwards–Klinefelter syndromes (48,XXY,+18).

Authors	Karyotype	Maternal age (y)	Paternal age (y)	Major abnormalities and outcome	Parental origin of aneuploidy	Cell stage of nondisjunction	
						Chr. 18	Chr. X
Haylock et al [1]							
Case 2	48,XXY,+18	45	47	VSD, patent foramen ovale, left chylous pleural effusion, horseshoe kidney, facial dysmorphism, micrognathia, absent corpus callosum, clenched hands, neonatal death (16 d)	NA	NA	NA
Cohen and Bumbalo [2]							
	48,XXY,+18	21	35	Delivery at 40 wk, 2,670 g, facial dysmorphism, micrognathia, clenched hands, rocker-bottom feet, normal male genitalia, undescended testes, clinodactyly, total anomalous venous drainage, single atrium, signal ventricle, right ventricular hypertrophy, neonatal death (16 wk)	NA	NA	NA
Zellweger and Abbo [3]							
Case 1	48,XXY,+18	23	29	Delivery at 43 wk, 2,070 g, high-arched palate, VSD, PDA, facial dysmorphism, micrognathia, clenched hands, neonatal death (10 wk)	NA	NA	NA
Henchman et al [4]							
	47,XXY/48, XXY,+18	23	26	Delivery at 40 wk, 2,140 g, clinodactyly, VSD, PDA, enlargement of right kidney, facial dysmorphism, micrognathia, clenched hands, neonatal death (3 mo)	NA	NA	NA
Bach et al [5]							
	48,XXY,+18	23	23	Delivery at 42 wk, 2,700 g, facial dysmorphism, micrognathia, clenched hands, neonatal death (6 wk)	NA	NA	NA
Nielsen et al [6]							
	48,XXY,+18	42	50	Delivery at 41 wk, 2,000 g, VSD, syndactyly, facial dysmorphism, micrognathia, clenched hands, congenital diaphragmatic hernia, dilated renal tubules, neonatal death (21 h)	NA	NA	NA
Rogers et al [7]							
Case 1	48,XXY,+18	24	NA	Delivery at 30 wk, 640 g, micrognathia, bilateral cataracts, contracture of left wrist, generalized hirsutism, facial dysmorphism, clenched hands, neonatal death (4 h)	NA	NA	NA
Hanna et al [8]							
	48,XXY,+18	NA	NA	Gastroschisis, facial dysmorphism, clenched hands	NA	NA	NA
Van Ravenswaaij-Arts et al [9]							
	47,XY,+3/ 48,XXY, +18/46,XY	26	NA	Prenatal ultrasound at 31 wk: IUGR, polyhydramnios, bilateral cleft lip. Amniocentesis: 47,XY,+3/ 48,XXY,+18. Delivery at 38 wk, 1,746 g, bilateral cleft lip and palate, micropenis, cryptorchidism, ventriculomegaly, camptodactyly, an atrioventricular septal defect, hypoplasia of cerebellar vermis, facial dysmorphism, clenched hands, neonatal death (10 d)	NA	PZM (suspected)	PZM (suspected)
Komwilaisak et al [10]							
	48,XXY,+18	21	NA	Prenatal ultrasound at 33 wk: IUGR, polyhydramnios, single umbilical artery, micrognathia, bilateral club hands, clenched hands, rocker-bottom feet. Cordocentesis: 48,XXY,+18. Delivery at 38 wk, 2,200 g, microcephaly, bilateral cataracts, microtia, micropenis, undescended testes, two-vessel cord, facial dysmorphism, neonatal death (18 d)	NA	NA	NA
Li et al [11]							
Case 2	48,XXY,+18	NA	NA	NA	Maternal	MI	MI

Table 2 (*continued*)

Authors	Karyotype	Maternal age (y)	Paternal age (y)	Major abnormalities and outcome	Parental origin of aneuploidy	Cell stage of nondisjunction	
						Chr. 18	Chr. X
Hou [12]							
	48,XXY,+18	21	NA	IUGR, polyhydramnios in late gestation. Delivery at 39 wk, 2,040 g, VSD, PDA, PS, facial dysmorphism, micrognathia, microcephaly, single umbilical artery, congenital diaphragmatic hernia, left renal hypoplasia, right hydronephrosis, clenched hands, clinodactyly, inguinal hernia, high-arched palate, cryptorchidism, a normal penis, alive at 15 mo	NA	NA	NA
Begam et al [13]							
	48,XXY,+18	NA	NA	Prenatal ultrasound at 34 wk: IUGR, choroid plexus cysts, cerebellar hypoplasia, ventricular septal defect, club feet, clinodactyly, pectus excavatum. Amniocentesis: 48,XXY,+18. Facial dysmorphism, clenched hands, neonatal death (2 d)	NA	NA	NA
Present case							
	48,XXY,+18	42	43	Prenatal ultrasound at 18 wk: choroid plexus cysts, prenatal ultrasound at 22 wk: a flexion contracture deformity of left wrist, absence of left thumb. Amniocentesis: 48,XXY,+18. Termination at 22 wk, 332 g, facial dysmorphism, micrognathia, arthrogryposis of left wrist, aplasia of left thumb, clenched hands, a normal penis	Maternal	MI	MII or PZM

Chr. = chromosome; IUGR = intrauterine growth restriction; MI = meiosis I nondisjunction error; MII = meiosis II nondisjunction error; NA = not available; PDA = patent ductus arteriosus; PS = pulmonary stenosis; PZM = postzygotic mitotic error; VSD = ventricular septal defect.

The present case was associated with advanced maternal age, a maternal origin of double aneuploidy, and two different cell stages of nondisjunction. It has been shown that the extra chromosomes in double aneuploidy are almost always of maternal origin and are usually associated with advanced maternal age [11,15,16]. Zaragoza et al [17] reported maternal mat MII for 48,XX,+4,+14, mat MI for 48,XY,+15,+21, and mat MI or MII for 48,XX,+10,+15, and 48,XY,+15,+16 in spontaneous abortions. Park et al [18] reported mat MII for 48,XXX,+21 in a fetus terminated following prenatal diagnosis by amniocentesis. Chen et al [19] reported mat MII for 48,XXX,+18 in a liveborn. Li et al [11] reported mat MI for 48,XX,+16,+22, 48,XXY,+18, 48,XX,+15,+21, and 48,XX,+2,+5 in spontaneous abortions. Diego-Alvare et al [15] reported mat MI for 48,XX,+15,+22 and 48,XX,+8,+21, mat MII for 48,XXX,+18, and mat MI for trisomy 22 and mat MII for trisomy 18 respectively for 48, XY,+18,+22 in spontaneous miscarriages. In the present case, a mat MI error might have occurred for chromosome 18, and a mat MII error might have occurred for chromosome X, although a PZM could not completely be excluded. The present case adds to the report of Diego-Alvare et al [15] and provides evidence that nondisjunction events involving two different chromosomes can occur in different cell divisions.

Studies on the extra chromosome in trisomy 18 and Klinefelter syndrome have revealed a frequency of 91% of maternal origin for trisomy 18, and a frequency of 50% of maternal origin for Klinefelter syndrome [20,21]. The present case had a maternal origin in Klinefelter syndrome and trisomy 18. Infants or fetuses with a karyotype of 48,XXY,+18 can manifest typical abnormalities of trisomy 18 such as congenital heart defects, facial dysmorphism, clenched hands, arthrogryposis, congenital diaphragmatic hernia, ventriculomegaly, and cerebellar hypoplasia, and typical abnormalities of Klinefelter syndrome such as clinodactyly, inguinal hernia, and cleft palate (Table 2).

The present case manifested choroid plexus cysts, arthrogryposis of the left wrist, and absence of the left thumb in a male fetus on prenatal ultrasound. Both choroid plexus cysts and abnormal extremities have been associated with common aneuploidies [22,23]. Choroid plexus cysts occur in about 50% of fetuses with trisomy 18 [24]. Snijders et al [25] found a frequency of 8% for chromosome abnormalities in prenatally detected choroid plexus cysts, including trisomy 18 ($n = 121$) and trisomy 21 ($n = 18$), and a frequency of 1% for isolated choroid plexus cysts and 46% for nonisolated choroid plexus cysts with multiple anomalies. Trisomy 18 can be associated with arthrogryposis, overlapping fingers, rocker-bottom feet, and talipes. In a study of 89 cases with fetal trisomy 18, Chen [26] found that 23 cases (25.8%) had arthrogryposis of the wrist and/or ankle, with the left side being more common than the right side, and there was a male preponderance. The present case also had aplasia of the left thumb. Absence of the thumb may occasionally occur in trisomy 18. Chen [27] has reported that absence of the thumb occurs in only 1.1% (1/89) of cases with fetal trisomy 18.

In conclusion, we have presented a very rare occurrence of double aneuploidy (48,XXY,+18) of maternal origin in a male fetus with arthrogryposis of the left wrist and aplasia of the left thumb. Our presentation provides evidence that abnormal separation of chromosomes 18 and X resulting in double

aneuploidy may occur in different cell divisions, and such an occurrence is related to advanced maternal age.

Acknowledgments

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References

[1] Haylock J, Fitzgerald M, Danks D, Dennet X. Two cases of the 18-trisomy syndrome, one in combination with an XXY karyotype. Hum Chromos Lett 1963;9:15.
[2] Cohen MM, Bumbalo TS. Double aneuploidy: trisomy-18 and Klinefelter's syndrome. Am J Dis Child 1967;113:483–6.
[3] Zellweger H, Abbo G. Double trisomy and double trisomic mosaicism. Am J Dis Child 1967;113:329–37.
[4] Henchman DC, Grey J, Campbell JB, Nance S. Klinefelter's syndrome with mosaicism trisomy-18. Aust Paediatr J 1970;6:142–5.
[5] Bach C, Toublanc JE, Gautier M. Une observation de double aneuploidie chromosomique: trisomie 18 et XXY]. Ann Génét 1973;16:61–6 [in French].
[6] Nielsen J, Vetner M, Holm V, Askjær AS, Reske-Nielsen E, Žižka J. Klinefelter's syndrome and trisomy 18 in a newborn boy. Clin Genet 1978;13:259–64.
[7] Rogers RC, Phelan MC, Pulliam L, Albies K. Double aneuploidy. Proc Greenwood Genet Ctr 1986;5:49–57.
[8] Hanna JS, Neu RL, Lockwood DH. Prenatal cytogenetic results from cases referred for 44 different types of abnormal ultrasound findings. Prenat Diagn 1996;16:109–15.
[9] Van Ravenswaaij-Arts CMA, Tuerlings JHAM, Van Heyst AFJ, Nijhuis JG, Niehof J, Smeets DFCM. Misinterpretation of trisomy 18 as a pseudomosaicism at third-trimester amniocentesis of a child with a mosaic 46, XY/47, XY,+3/48, XXY,+18 karyotype. Prenat Diagn 1997;17:375–9.
[10] Komwilaisak R, Ratanasiri T, Komwilaisak P, Luengwattanawanit S. Three-dimensional ultrasonographic findings of the rare chromosomal abnormality 48, XXY/+18: a case report. J Med Assoc Thai 2004;87:198–203.
[11] Li QY, Tsukishiro S, Nakagawa C, Tanemura M, Sugiura-Ogasawara M, Suzumori K, et al. Parental origin and cell stage of non-disjunction of double trisomy in spontaneous abortion. Congen Anom Kyoto 2005;45: 21–5.
[12] Hou J- W. Double aneuploidy: trisomy 18 and XXY in a boy. Chang Gung Med J 2006;29(4 Suppl.):6–12.
[13] Begam M, Bekdache GN, Murthy SK, Mirghani HM. Double aneuploidy of trisomy 18 and Klinefelter syndrome: prenatal diagnosis and perinatal outcome. J Perinat Med 2010;38:565–6.
[14] Reddy KS. Double trisomy in spontaneous abortion. Hum Genet 1997; 101:339–45.
[15] Diego-Alvarez D, Ramos-Corrales C, Garcia-Hoyos M, Bustamante-Aragones A, Cantalapiedra D, Diaz-Recasens J, et al. Double trisomy in spontaneous miscarriages: cytogenetic and molecular approach. Hum Reprod 2006;21:958–66.
[16] Micale M, Insko J, Ebrahim SAD, Adeyinka A, Runke C, Van Dyke DL. Double trisomy revisited – a multicenter experience. Prenat Diagn 2010; 30:173–6.
[17] Zaragoza MV, Jacobs PA, James RS, Rogan P, Sherman S, Hassold T. Nondisjunction of human acrocentric chromosomes: studies of 432 trisomic fetuses and liveborns. Hum Genet 1994;94:411–7.
[18] Park VM, Bravo RR, Shulman LP. Double non-disjunction in maternal meiosis II giving rise to a fetus with 48, XXX,+21. J Med Genet 1995; 32:650–3.
[19] Chen C-P, Chern S-R, Yeh L-F, Chen W-L, Chen L-F, Wang W. Prenatal diagnosis and genetic analysis of double trisomy 48, XXX,+18. Prenat Diagn 2000;20:750–3.
[20] Nicolaidis P, Petersen MB. Origin and mechanisms of non-disjunction in human autosomal trisomies. Hum Reprod 1998;13:313–9.
[21] Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. Hum Mol Genet 2007;16: R203–8.
[22] Chen C- P. Prenatal sonographic features of fetuses in trisomy 13 pregnancies. I. Taiwan J Obstet Gynecol 2009;48:210–7.
[23] Chen C- P. Prenatal sonographic features of fetuses in trisomy 13 pregnancies. III. Taiwan J Obstet Gynecol 2009;48:342–9.
[24] Snijders RJM, Shawa L, Nicolaides KH. Fetal choroid plexus cysts and trisomy 18: assessment of risk based on ultrasound findings and maternal age. Prenat Diagn 1994;14:1119–27.
[25] Snijders RJM, Farrias M, von Kaisenberg C, Nicolaides KH. Fetal abnormalities. In: Snijders RJM, Nicolaides KH, editors. Ultrasound markers for fetal chromosomal defects. New York: Parthenon Publishing Group; 1996. p. 1–62.
[26] Chen C-P. Arthrogryposis of the wrist and ankle associated with fetal trisomy 18. Prenat Diagn 2005;25:423–5.
[27] Chen C- P. Aplasia and duplication of the thumb and facial clefts associated with fetal trisomy 18. Am J Med Genet 2006;104A:960–3.