

CASE REPORT

**DOUBLE ANEUPLOIDY 48,XXY,+21 ASSOCIATED WITH
A CONGENITAL HEART DEFECT IN A NEONATE**

Shu X, Zou C, Shen Z*

***Corresponding Author:** Zheng Shen, M.D., The Children's Hospital of Zhejiang University School of Medicine, 57 Zhugan Xiang, Hangzhou 310003, People's Republic of China; Tel.: +86-13575743518; Fax: +86-571-87033296; E-mail: shenzheng@tom.com

ABSTRACT

A neonate with a double aneuploidy associated with congenital heart defect (CHD) suffered from cyanosis after birth. He had typical features of Down syndrome (DS) including hypertelorism, slightly lowset ears with protruding pinna. Doppler echocardiography indicated complex congenital heart disease with an ostium secundum atrial septal defect, enlarged right ventricle, and mild tricuspid valve regurgitation. Further chromosomal analysis showed a karyotype of 48,XXY,+21: a double aneuploidy of DS and Klinefelter syndrome (KS). Until now, only seven cases of double aneuploidy associated with CHD defect have been reported.

Keywords: Double aneuploidy; Down syndrome (DS); Klinefelter syndrome (KS); 48,XXY,+21; Congenital heart defect (CHD).

INTRODUCTION

A chromosome abnormality reflects an atypical number of chromosomes or a structural abnormality in one or more chromosomes including autosomes and sex chromosomes. Trisomy 21, also named Down syndrome (DS), is caused by the presence of an additional autosome, affecting 1/700 live births

[1]. Klinefelter syndrome (KS) is a genetic condition in which humans have an extra X chromosome, resulting in a 47,XXY karyotype [2]. This karyotype exists in roughly between 1/500 to 1/1000 live male births, while most people do not show symptoms [3]. Though trisomy 21 and numerical sex chromosome anomalies are both common chromosome disorders, the cooccurrence of chromosomes 21 and X is rare [4]. Several cases of double aneuploidy of XXY and trisomy 21 have been published since the first report by Ford *et al.* [5] in 1959; only seven patients suffered from aneuploidy (DS + KS) associated with congenital heart defect (CHD) [5-7]. The effect of maternal age is certainly demonstrated in trisomy 21 and 47,XXY aneuploidy, respectively [4]. Herein, we described a case of 1-day-old boy who exhibited the karyotype of 48,XXY,+21 with CHD, who was born to young parents.

CASE REPORT

A 13-hour-old male infant, the first-born of a non consanguineous marriage to a 23-year-old father and a 21-year-old mother, presented cyanosis half an hour after birth. The baby was delivered by Cesarean section at a local hospital at 38 weeks' gestation because the ultrasound assessment showed the amniotic fluid was less than normal. He was gravida 3, para 1, and born without asphyxia history. His birth weight was 2750 g with an Apgar score of 10 at 1 min. Half an hour after birth, he exhibited cyanosis of the lips and face when taking a bath. He

* Department of Pediatrics, the Children's Hospital of Zhejiang University School of Medicine and Zhejiang Key Laboratory for Diagnosis and Therapy of Neonatal Diseases, Hangzhou, People's Republic of China

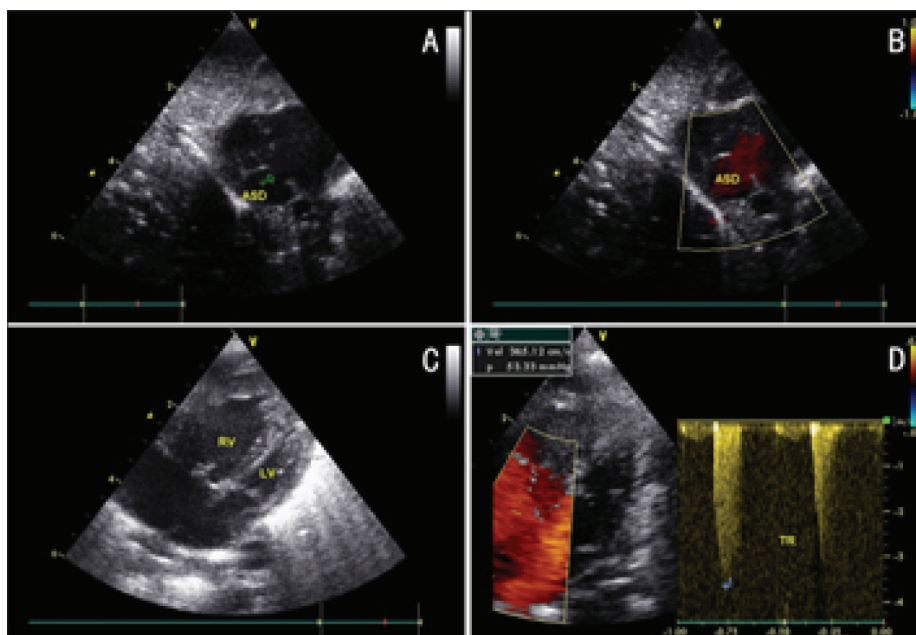


Figure 1. Doppler sonogram showing (A) and (B) an ostium secundum atrial septal defect (diameter 0.6 cm, bidirectional shunt flow and C an enlarged right ventricle, (D) mild tricuspid valve regurgitation.

was immediately administered oxygen inhalation using head hood and medicine treatment through an intravenous injection. He was transferred to our hospital due to the fact that his symptoms did not improve after therapy. On the way to our hospital, he was administered oxygen inhalation through a nasal catheter, and the cyanosis was relieved.

Physical examination showed that the child was 50 cm in height and his head circumference was 33.5 cm. The boy's anterior fontanelle was patent and flat without broadening cranial sutures. The genitalia were normal immature male. On admission, he presented with tachypnea, cyanosis and slight hypertonia. The features of DS including hypertelorism, slightly lowset ears with protruding pinna, were obvious.

Chest radiography showed exudative lesions in the lungs. Two-dimensional echocardiography indicated complex CHD with the presence of an ostium secundum atrial septal defect (diameter 0.6 cm, bidirectional shunt flow), enlarged right ventricle and mild tricuspid valve regurgitation (Figure 1). Cytogenetic study performed on peripheral blood samples using standard procedures revealed a complement of 48 chromosomes with two extra chromosomes in the G group. Fifty metaphases from PHA-stimulated peripheral blood lymphocytes

demonstrated a karyotype of 48,XXY,+21 according to the International System for Human Cytogenetic Nomenclature (ISCN) (2009) (Figure 2). There was no evidence of mosaicism and the diagnosis of double aneuploidy involving chromosome 21 and X was made. Chromosomal karyotypes of the parents were unknown due to their refusal to be tested, and they were counseled accordingly.

DISCUSSION

Double aneuploidy, the existence of two chromosome anomalies in the same person, is rare, which can involve autosomes (chromosome 13, 18 or 21) and sex chromosomes. The causes of aneuploidy are not well-documented, however, it is known that the most common chromosomal mechanism is meiotic non disjunction. The cause of non disjunction is also uncertain. Non disjunction can occur during meiosis I when the chromosome pairs fail to separate or during meiosis II when chromatids fail to separate. Generally, the mother contributes the extra chromosome 21 in 85.0% and the father in 15.0%, of cases. However, the extra X chromosome is contributed by the parents contribution in 50.0% of cases.

Our patient is an infant, who exhibited typical DS features with a 48,XXY,+21 karyotype, born at

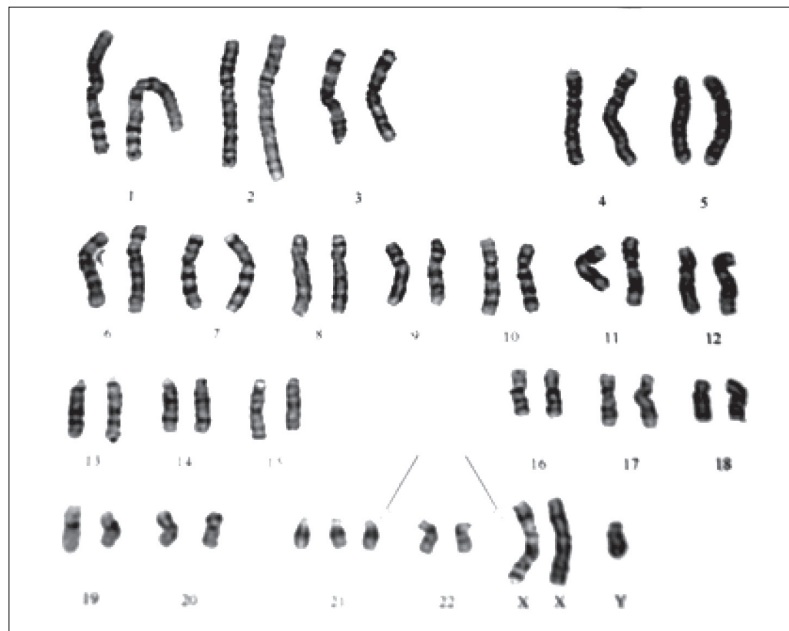


Figure 2. Karyotype of the infant with 48,XXY,+21. The arrows indicate the extra chromosome and X.

term to a 21-year-old mother and 23-year-old father. It is evident that the risk for trisomy 21 in offspring increases with maternal age, and the maternal age effect was also demonstrated in the 47,XXY aneuploidy [4]. A previous study also suggests women aged 20 through 24 years have the lowest prevalence rate of DS (1/1400 births), and for women aged 35 years, the rate is approximately 1/350 births, and for women over 45 years old, the rate rises to 1/25 births [5-6]. Thus, maternal age-related factors seem to play a more important role in the etiology of 48,XXY, +21

than genetic predisposition. Kovaleva and Mutton [4] reported that the double aneuploidy of 48,XXY,+21 is age-dependent, with a mean maternal age of 33 and a mean paternal age of 37.9. However, in our case, the parents were very young. From the published cases, we can conclude that the paternal ages are remarkably different in patients with a double aneuploidy of 48,XXY,+21 associated with CHD (Table 1) [7-13]. The exclusion of advanced maternal age as risk factor for chromosomal non disjunction in the present case suggests the existence of other risk factors.

Table 1. Characteristics of the double aneuploidy 48,XXY,+21 with congenital heart defect.

Sex-Age	Characteristics of CHD	Parental Ages		References
		Mother	Father	
M-8	mild aortic stenosis with possible coexistent pulmonary stenosis	26	29	8
M-15	a systolic murmur and generalized cyanosis developed during exercise	NA	NA	9
M-2	atrioventricular septal defect with pulmonary stenosis	25	28	10
M-14 months	a small atrial septal defect, a double aortic arch	36	NA	14
M-3 months	interatrial communication	13	24	11
Fetus	atrioventricular canal defect	33	39	12
M-4 months	large atrial and ventricular septal defect with patent ductus arteriosus, pulmonary hypertension and mild tricuspid regurgitation	30	32	13
M-1 day	ostium secundum atrial septal defect, enlarged right ventricle, mild tricuspid valve regurgitation	21	23	this study

NA: not available.

The occurrence of double aneuploidy of DS combined with KS is unclear, not to mention the double aneuploidy associated with CHD. Approximately 65 cases of double aneuploidy of XXY and trisomy 21 have been published since 1959, and there are only eight cases associated with CHD [12-14], including our case (Table 1). It is well known that 40.0-50.0% of patients with DS and half the patients with KS have CHD [15]. The incidence of cardiovascular anomalies in patients with 48,XXY,+21 karyo-type is not clear. To the best of our knowledge, only eight case reports of CHD in these patients have been published (Table 1). These patients have less vascular anomalies than the general population, probably because of an increased inhibition of vascular endothelial growth factor, whose genes are located on chromosome 21 [16].

In conclusion, DS-KS syndrome is an extremely rare condition. We present a case of 48,XXY,+21 karyotype with typical features of DS, whose parents were very young. Together with the other seven cases of double aneuploidy associated with CHD, the maternal ages are different, which do not support the maternal age effect.

ACKNOWLEDGMENTS

The authors would like to thank the patient and family for allowing us to use these data.

Declaration of Interest. This study was supported by the National Natural Science Foundation of China (Grant No. 81000267) and Zhejiang Province, PRC, innovation team for early screening and intervention of birth defects. (Grant No. 2010R50045). The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

- Mégarbané A, Ravel A, Mircher C, Sturtz F, Grattau Y, Rethoré MO, *et al.* The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of Down syndrome. *Genet Med.* 2009; 11(9): 611-616.
- Jacobs PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature.* 1959; 183(4547): 302-303.
- Maiburg M, Repping S, Giltay J. The genetic origin of Klinefelter syndrome and its effect on spermatogenesis. *Fertil Steril.* 2012; 98(2): 253-260.
- Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. *Am J Med Genet A.* 2005; 134A(1): 24-32.
- Ford CE, Jones KW, Miller OJ, Mittwoch U, Penrose LS, Ridler M, *et al.* The chromosomes in a patient showing both mongolism and Klinefelter syndrome. *Lancet.* 1959; 1(7075): 709-710.
- Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. *JAMA.* 1983; 249(15): 2034-2038.
- Iliopoulos D, Poultides G, Peristeri V, Kouri G, Andreou A, Voyiatzis N. Double trisomy (48,XXY,+21) in monozygotic twins: case report and review of the literature. *Ann Genet.* 2004; 47(1): 95-98.
- Hecht F, Nievaard JE, Duncanson N, Miller JR, Higgins JV, Kimberling WJ, *et al.* Double aneuploidy: the frequency of XXY in males with Down's syndrome. *Am J Hum Genet.* 1969; 21(4): 352-359.
- Efinski D, Duma H, Apostolovski B, Sofijanov N, Ristevski B, Darkovski S. Klinefelter's and Down's syndrome in an adolescent with abnormal EEG. *Clin Genet.* 1974; 5(2): 81-85.
- Akbas E, Soylemez F, Savasoglu K, Hallioglu O, Balci S. A male case with double aneuploidy (48, XXY, +21). *Genet Couns.* 2008; 19(1): 59-63.
- Biselli JM, Machado FB, Zampieri BL, Alves da Silva AF, Goloni-Bertollo EM, Haddad R, *et al.* Double aneuploidy (48,XXY,+21) of maternal origin in a child born to a 13-year-old mother: evaluation of the maternal folate metabolism. *Genet Couns.* 2009; 20(3): 225-234.
- Jeanty C, Turner C. Prenatal diagnosis of double aneuploidy, 48, XXY,+21, and review of the literature. *J Ultrasound Med.* 2009; 28(5): 673-681.
- Shen Z, Zou CC, Shang SQ, Jiang KW. Down-Klinefelter syndrome (48,XXY,+21) in a child

- with congenital heart disease: case report and literature review. *Intern Med.* 2012; 51(11): 1371-1374.
14. Gerretsen MF, Peelen W, Rammeloo LA, Koolbergen DR, Hruda J. Double aortic arch with double aneuploidy – rare anomaly in combined Down and Kline-felter syndrome. *Eur J Pediatr.* 2009;168(12): 1479-1481.
 15. Pierpont ME, Basson CT, Benson DW Jr, Gelb BD, Giglia TM, Goldmuntz E, *et al.*; American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation.* 2007;115(23): 3015-3038.
 16. Greene AK, Kim S, Rogers GF, Fishman SJ, Olsen BR, Mulliken JB. Risk of vascular anomalies with Down syndrome. *Pediatrics.* 2008; 121(1): e135-e140.

