

Case Report



Double Trisomy 48,XXY,+21 in a Neonate with Congenital Heart Disease

Mahdi Bijanzadeh, MD, PhD^{1,2*}; Shahram Rajaei Behbahani, MD^{2,3}

¹Department of Medical Genetics, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

²Atherosclerosis Research Center, Ahvaz JundiShapur University of Medical Sciences, Ahvaz, Iran

³Division of Pediatric Cardiology, Department of Pediatrics, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Abstract

Double trisomy 48, XXY, +21 or Down-Klinefelter syndrome is a rare occurrence and presents clinical manifestation of trisomy 21 in early life and of Klinefelter syndrome after 10 months of age. The phenotypic and karyotyping characteristics of a 2-month-old boy were reported. He had mild clinical feature of Down syndrome and echocardiographic features of atrioventricular (AV) septal defects with severe pulmonary valve stenosis.

Keywords: Down syndrome, Chromosome abnormalities, Congenital heart disease, Double aneuploidy, Klinefelter syndrome

Cite this article as: Bijanzadeh M, Rajaei Behbahani S. Double trisomy 48,XXY,+21 in a neonate with congenital heart disease. Arch Iran Med. 2020;23(5):356–358. doi: 10.34172/aim.2020.26.

Received: October 17, 2018, Accepted: December 11, 2019, ePublished: May 1, 2020

Introduction

As an abnormal number of a genomic region copies, fetal aneuploidy is the most common mechanism of human chromosomal diseases. Along with other chromosomal aberrations, it affects 9 out of 1000 live births.¹

As the most common chromosomal disorder in humans, Down syndrome (trisomy 21) has an incidence of one in 770 live births; and Klinefelter syndrome (47, XXY), in which there is one extra X chromosome resulting in the karyotype is also the most common disorder of sex chromosomes in humans, with prevalence of one in 500 males.² About 45% of trisomy 21 patients are affected by congenital heart diseases (CHDs) and half of them have balanced complete atrioventricular (AV) canal (complete endocardial cushion defect), a complex condition that needs cardiac repair by open heart surgery.³

Double aneuploidy, the presence of two chromosomal abnormalities in the same individual, is a rare phenomenon and occurs because of two meiotic non-disjunctional events. Double aneuploidy of 48,XXY,+21 is the most commonly described double aneuploidy whose coincidence rate is estimated to lie in the range 0.27-0.7 × 10⁻⁵.^{4,5} After reviewing the available literatures, Shen et al revealed that since the first case reported by Ford et al in 1959, sixty-three cases of 48,XXY,+21 chromosome pattern were reported until 2012, and only 9 cases had CHD.² Following that, seven cases of 48, XXY,+21 were reported, out of whom one case presented CHD.⁶⁻⁹

In the current report, the clinical features of a 2-month-old infant who exhibited 48,XXY,+21 double aneuploidy

karyotype were presented.

Case Report

A 2-month-old male infant was referred for chromosomal analysis due to dysmorphic features suggestive of Down syndrome in cytogenetic laboratory of Shafa educational hospital, Ahvaz, Iran, on June 2018; informed consent was obtained from the patient's parent. He was the third child of consanguineous couple (second cousins). The mother was 39 years old and the father was 40. After 10 years of infertility and related medications, the couple has a healthy 7-year-old girl and a 5-year-old son.

His mother had no history of perinatal medically significant problems such as diabetes mellitus, systemic lupus erythematosus, infections, using alcohol and smoking, but she was using oral ranitidine and aluminum MGS for her gastritis. She did not carry out prenatal chromosomal trisomies screening as generally used for diagnosis of 13, 18 and 21 trisomies in Iran.

The proband was born after 41 weeks of gestation via caesarian section following an uncomplicated pregnancy and with post-partum cyanosis. He was born with 3350 g of weight, 52 cm of length and 34.5 cm of head circumference and had active crying and was fed normally. Now the patient and his family stay in Haftgel city of Khuzestan province, Iran and he is Lor, ethnically.

Mild cyanosis, generalized hypotonia and simian crease were noted. Face appearance was overall suggestive of Down syndrome. He has low set and small ears, epicanthic folds, protruding tongue, upward sloping palpebral fissures

*Corresponding Author: Mahdi Bijanzadeh, MD, PhD; School of Medicine, Department of Medical Genetics, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 61355-33118, Khuzestan, Iran. Tel: +989161117707; Fax: +986133332036; Email: mbijanz@yahoo.com

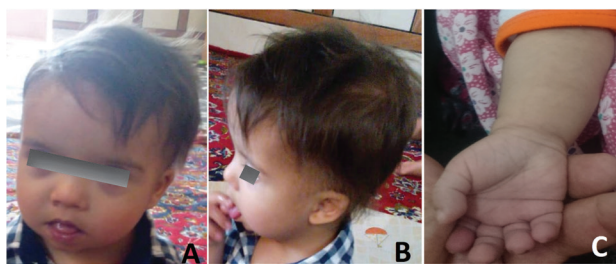


Figure 1. Frontal (A), Lateral (B) and Palmar (C) Views of the Patient. Face appearance showed low set and small ears, epicanthic folds, protruding tongue, upward sloping palpebral fissures, strabismus (A and B) and simian crease (C).

and strabismus. There was a loud systolic murmur in heart auscultation on mitral and pulmonary focal areas. The genitalia was normal. He showed no other malformation (Figure 1).

Cytogenetic study from peripheral blood cultures showed a complement of 48 chromosomes with two extra chromosomes X and 21 in the C and G groups. Chromosomal preparations obtained from peripheral blood cultures stimulated by phytohemagglutinin, were subjected to Giemsa banding and karyotyping result was 48,XXY,+21 (Figure 2) with no evidence of mosaicism.

The Doppler echocardiogram detection showed complete balanced AV canal presented by premium atrial septal defect (ASD1), large inlet ventricular septal defect (inlet VSD: 12 mm), common AV valve with regurgitation and significant pulmonary stenosis (PS) with 65 mm Hg pressure gradient as well as an additional secundum atrial septal defect or ASD2 (Figure 3). This complex CHD could be described as complete balanced AV canal plus tetralogy of Fallot. Clinically, coexisting PS could save the patient from pulmonary overflow and heart failure.

His development was delayed in all of the domains and he could not walk and talk, but he reacts normally to his parents.

Discussion

The incidence of trisomies is directly related to maternal age; this may play a more important role in the etiology of the most common double aneuploidy 48,XXY,+21.¹⁰ Kovaleva and Mutton reported a mean maternal age of 33 years and a mean paternal age of 38 years for the risk of 48,XXY,+21.⁵ In the current case, mother's and father's age of proband were 39 and 40 years respectively, which indicates this age dependent manner.

Aneuploidies are genetic disorders generally created due to meiotic non-disjunctional events. Considering history of our case's mother prominences old history of fertility inducer drugs during infertility period, compared to other teratogens such as histamine-2 blockers consumption.

Published cases of 48,XXY,+21 generally showed typical feature of Down syndrome and the Klinefelter syndrome characteristic feature not apparent until the pubertal

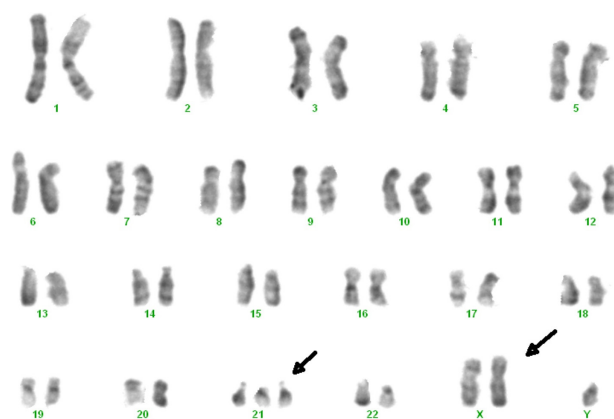


Figure 2. G-Banding Karyotype of the Patient. 48 chromosomes with two extra chromosomes X and 21 in the karyotype of patient.

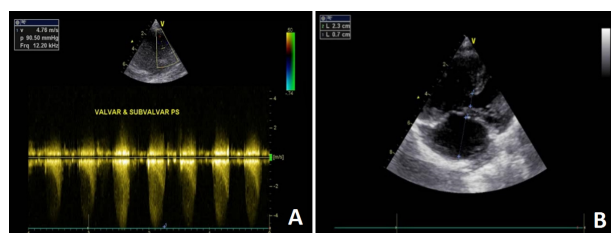


Figure 3. Echocardiogram Patterns of the Patient. (A) Four chambers view demonstrated large ASD1 and large inlet VSD. (B) Continuous-wave Doppler showed severe valvar and subvalvular pulmonary stenosis.

stage. According to the Down-Klinefelter case reports, neonates and infants younger than 10 months show few or no clinical appearance of Klinefelter syndrome.² The current case had features of trisomy 21, but not Klinefelter syndrome, which is consistent with other case reports. On the other hand, our proband had mild clinical feature of Down syndrome and it can be resulted from the presentation of X trisomy in the verge of trisomy 21.

Although Cyril et al⁴ and Eid et al¹⁰ did not report cardiac manifestation in their X, 21 double trisomy cases, Neu et al¹¹ reported an endocardial cushion defect of the AV canal type with large ASD and VSD. Down-Klinefelter case of Shen et al² had ASD and VSD with patent ductus arteriosus, pulmonary hypertension and mild tricuspid regurgitation. ASD and VSD are the common grounds of our case with the last two case reports.

Although prenatal trisomies screening currently became compulsory for all pregnant women in Iran, it was not carried out during the pregnancy of our case's mother. American College of Obstetricians and Gynecologists (ACOG) strongly recommended that all pregnant mothers implement Down syndrome screening tests.¹² Regarding familial problems, our proband was not prone to screening, which resulted in sustaining life without worried about termination of pregnancy.

Unlike Klinefelter syndrome, Down syndrome is well

known for CHD, occurring in 40%-50% of patients including AV, ventricular and isolated atrial septal defect and other anomalies.¹³ Our case suffered from AV canal and pulmonary stenosis too.

Authors' Contribution

MB conceived and designed the research and righted the manuscript. SRB selected the patient and analyzed the clinical data. MB analyzed the laboratory data. MB and SRB completed and revised the manuscript.

Conflict of Interest Disclosures

All authors declare that they have no conflict of interest.

Ethical Statement

Informed consent was obtained from the patient's parent. This research was approved by ethical committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Funding Sources

This work was supported by Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Acknowledgments

Authors thank the patient's parents for allowing them to use the data and Mrs. Beigporian, Mrs. Mahmoudi and Miss Esmaeili, technicians of Shafa educational Hospital for their technical collaboration.

References

1. Dierssen M, Herault Y, Estivill X. Aneuploidy: from a physiological mechanism of variance to Down syndrome. *Physiol Rev.* 2009;89(3):887-920. doi: 10.1152/physrev.00032.2007.
2. 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):1371-4. doi: 10.2169/internalmedicine.51.7097.
3. Goldmuntz E, Crenshaw M. Genetic aspects of congenital heart defects. In: Allen H, Shaddy R, Penny D, Feltes T, Cetta F, eds. *Moss and Adams' heart disease in infants, children and adolescents.* 9th ed. Philadelphia, PA: Lippincott; 2016:87-115.
4. Cyril C, Chandra N, Jegatheesan T, Chandralekha K, Ramesh A, Gopinath PM, et al. Down syndrome child with 48,XXY,+21 karyotype. *Indian J Hum Genet.* 2005;11(1): 47-8. doi: 10.4103/0971-6866.16296.
5. Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. *Am J Med Genet.* 2005;134A:24-32. doi: 10.1002/ajmg.a.30306.
6. Shu X, Zou C, Shen Z. Double aneuploidy 48,XXY,+21 associated with a congenital heart defect in a neonate. *Balkan J Med Genet* 2013;16(2):85-9. doi: 10.2478/bjmg-2013-0038.
7. Ramirez FF, Guerrero CP, Delgado CG, Jimenez ABM, Villegas CMA, Cervantes A. et al. Cytogenetic profile in 1,921 cases of trisomy 21 syndrome. *Arch Med Res.* 2015;46(6):484-9. doi: 10.1016/j.arcmed.2015.08.001.
8. Zhao W, Chen F, Wu M, Jiang S, Wu B, Luo H, et al. Postnatal identification of trisomy 21: An overview of 7,133 postnatal trisomy 21 cases identified in a diagnostic reference laboratory in China. *PLoS One.* 2015;10(7):1-13. doi: 10.1371/journal.pone.0133151.
9. Padilla CD, Cutiongco-de la Paz EM. Genetics and genomic medicine in the Philippines. *Mol Genet Genomic Med.* 2016;4(5):494-503. doi: 10.1002/mgg3.247.
10. Eid SS, Shawabkeh MM, Hawamdeh AA, Kamal NR. Double trisomy 48,XXY,+21 in a child with phenotypic features of Down syndrome. *Labmedicine.* 2000;40(4):215-8. doi: 10.1309/LMOZOOW7EAC06SZI.
11. Neu RL, Scheuer AQ, Gardner LI. A case of 48,XXY,21+ in an infant with Down's syndrome. *J Med Genet.* 1971;8:533-5. doi: 10.1136/jmg.8.4.533.
12. Farshbaf Khalili A, Shahnazi M, Hajizadeh K, Khaniani MS. Down syndrome screening methods in Iranian pregnant women. *J Caring Sci.* 2012;1(3):145-51. doi:10.5681/jcs.2012.021.
13. Rosenthal A. Cardiovascular malformations in Klinefelter's syndrome: report of three cases. *J Pediatr.* 1972;80(3):471-3.