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Case Report

Down-Klinefelter syndrome (48,XXY,+21) in a neonate associated with congenital heart disease

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ABSTRACT. Double aneuploidy is considered a rare phenomenon. Herein, we describe a case of double aneuploidy 48,XXY,+21 in a neonate with congenital heart defects. The 28-day-old neonate male (23-year-old mother and 24-year-old father) was admitted to a neonatal intensive care unit owing to congenital heart disease. Echocardiography showed a complete atrioventricular septal defect with Rastelli type B and significant left ventricular failure, moderate atrioventricular valve regurgitation, right-sided heart failure, and preserved systolic function. Cytogenetic analysis of the newborn showed double aneuploidy 48,XXY,+21. The maternal karyotype was 46,XX,inv(9)(p11q13) and the paternal was 46,XY. Characteristics associated with Down syndrome

are observed in newborns; on the other hand, children under 10 months of age and neonates may show little or no signs of the Klinefelter syndrome. According to this study, there seem to be differences between the frequency of congenital heart disease among patients with Down-Klinefelter and Down syndrome. At about 11 months of age, the child died after undergoing heart surgeries. The early cytogenetic study is important for better diagnosis and management of the disease.

Key words: Double Aneuploidy; Down-Klinefelter syndrome; 48,XXY,+21; Congenital heart defects

INTRODUCTION

The occurrence of more than one chromosomal abnormality in the same person is considered to be a rare phenomenon (Gerretsen et al., 2009). Down syndrome (DS) is a human chromosomal disease with high incidence and affects one out of every 770 live births (Iliopoulos et al., 2004). Moreover, Klinefelter syndrome (KS), usually with the 47,XXY karyotype, is one of the most prevalent genetic diseases involving human sex chromosomes, and the incidence is estimated to be one in 500 male births (Visootsak and Grahan, 2006).

Developmental delay, single palmar crease, short stature, facial anomalies, hypotony and short hands are the main characteristics of DS. Besides, DS is commonly associated with cardiac and gastrointestinal defects, hypothyroidism, and celiac disease (Weijerman et al., 2008).

Pediatric cardiologists are acquainted with congenital heart defects in babies with DS. However, congenital heart diseases are only rarely reported in children with KS (Pierpont et al., 2007). This study aimed to report a case of a neonate with chromosomal double trisomy 48,XXY,+21, known as Down-Klinefelter syndrome.

CASE REPORT

The case described herein was a 28-day-old neonate male, the result of the second pregnancy (term pregnancy, 37 weeks) of non-consanguineous parents (first pregnancy, first-trimester miscarriage; 23-year-old mother; and 24-year-old father). During pregnancy, the mother had hypothyroidism and urinary tract infection in the first trimester. The infant was delivered by cesarean section due to severe oligohydramnios. Birth weight was 2985g, length was 46 cm, and head circumference was 34 cm. After birth, he showed a heart rate of 157 beats per minute, respiratory rate 56 breaths per minute, axillary temperature 35.5°C, oxygen saturation 99%, blood pressure 180 mmHg, and Apgar index 6/7.

Owing to congenital heart anomaly, the baby remained hospitalized for 33 days in a neonatal intensive care unit. The entrance examination revealed cyanosis and muscle hypotonia. Physical characteristics associated with DS such as epicanthic folds, excess nuchal fluid, micrognathia, small ears and nose, flat nasal bridge, brachycephaly, and hydrocele were noted.

After discharge, his weight was 3014 g, length 52 cm, and head circumference 35 cm. Chest X-rays showed signs of increased pulmonary blood flow. Echocardiography revealed complete atrioventricular septal defect (AVSD) with Rastelli type B and significant left ventricular failure, moderate atrioventricular valve regurgitation, right-sided heart failure, and preserved systolic function. At approximately 11 months of age, the child died after undergoing heart surgeries.

This study was conducted with approval from the Ethics Committee of Nicola Albano Neonatal Intensive Care Unit. The patient's parents signed an informed written consent before enrollment in the study, according to the ethical guidelines of the Declaration of Helsinki amended in 2008.

Cytogenetic analysis

Cytogenetic investigation of the neonate at 28 days revealed a case of double aneuploidy with the karyotype 48,XXY,+21 (Figure 1). Maternal cytogenetic studies showed a karyotype of 46,XX,inv(9)(p11q13), and for the father a normal 46,XY karyotype was evident.

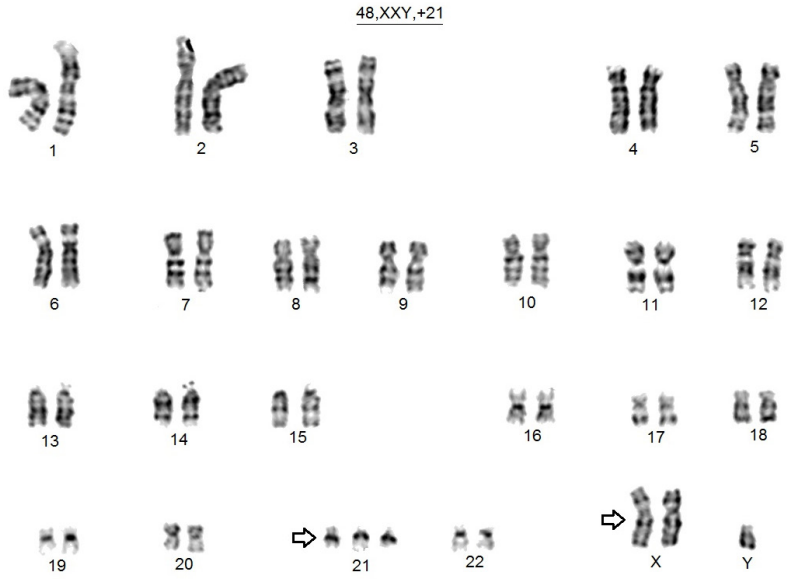

Figure 1. G-banding karyotype of the patient with double aneuploidy 48,XXY,+21.

The procedure was performed by peripheral blood culture with RPMI 1640 medium supplemented with 20% fetal bovine serum and phytohemagglutinin (Verma and Babu, 1995). G-banding of chromosomes was performed. The results were described according to the International System for Human Cytogenetic Nomenclature (Shaffer et al., 2013).

DISCUSSION

DS associated with KS was first reported by Ford et al. (1959). According to Jeanty et al. (2009), the incidence rate of the double aneuploidy 48,XXY,+21 is estimated to be one in 94,440 pregnancies. According to Kovaleva and Mutton (2005), the karyotype 48,XXY,+21 can be detected in 0.098% of neonates with DS. However, by multiplying the incidence rates of DS and KS, we estimated an incidence of one case in 350,000 pregnancies.

Our patient showed a 48,XXY,+21 karyotype, with a normal paternal result (46,XY) and a karyotype of 46,XX,inv(9)(p11q13) for the mother. The pericentric inversion of chromosome 9 is a chromosomal heteromorphism and often found in humans (Hsu et al.,

1987; Teo et al., 1995; Kim et al., 1999). According to Serra et al. (1990), couples with one partner being the bearer of this chromosome 9 inversion have three times greater chances of conceiving a child with DS than couples without it.

Our patient was referred for cytogenetic studies by presenting characteristics compatible with DS. However, he showed no characteristic of KS. According to previous reports, in Down-Klinefelter cases, newborns and children under the age of 10 months show little or no signs of KS; these characteristics appear around puberty. According to Jeanty and Turner (2009), the DS phenotype often prevails in patients with Down-Klinefelter, associated with the features of KS such as malformed genital organs and taller stature.

We compared the characteristics of our case with 10 other reports of double aneuploidy 48,XXY,+ 21 (Table 1) with congenital cardiac malformations. Among these, only 3 patients at the ages of 2 to 15 years old revealed features of KS. No sign of KS in patients was observed in neonates less than 10 months of age, which corroborates with the data presented in this study.

The cardiac malformation is a common congenital disability present in patients with DS, found in 40-60% of cases (Davidson, 2008). Among those born with congenital heart defects, approximately 5-10% showed DS characteristics (Paladini et al., 2000). Congenital heart defect is not a typical characteristic of patients with KS; however, some adults may occasionally suffer from the prolapsed mitral valve (Gerretsen et al., 2009).

It is known that AVSD is a common congenital heart defect in patients with DS (Marino et al., 1990; Parker et al., 2010). According to one study by Marino et al. (1990), complete AVSD is the most common type recorded in patients with DS.

In a review by Shen et al. (2012), of 63 cases of double aneuploidy 48,XXY,+21, only 15% of reports revealed some degree of congenital heart disease. According to our research, there seem to be differences between the frequency of congenital heart disease among patients with Down-Klinefelter and DS, because the incidence of heart disease in patients with DS can reach 60% of cases, according to the literature. It is important to analyze a greater number of cases to establish the correlation between congenital heart diseases and DS and KS.

Specific DS features described in other reports and presented in our review (Table 1) showed variation; however, all were typical of trisomy 21, such as hypotonia, flat nasal bridge, epicanthic folds, brachycephaly, low set ears, excess nuchal fluid, short neck, and heart defects. On the other hand, the specific characteristics reported for KS were genital malformation, epileptic seizures, and antisocial behavior.

The incidence of death in newborns with Down-Klinefelter syndrome has been little studied (Jeanty and turner, 2009). Kovaleva and Mutton (2005) studied 10 cases of 48,XXY,+21 in prenatal diagnosis and found two miscarriages, showing a mortality rate of about 20%. Furthermore, the authors stated that the risk for double aneuploidy 48,XXY,+21 would be considered age-dependent, and the average paternal age was 38 years, and maternal age was 33 years. Our report contradicts these data regarding maternal and paternal ages, being only 23 and 24 years, respectively.

At approximately 11 months of age, the child of this case report died after undergoing heart surgeries. Studies among patients with AVSD presented a survival rate of about 15% at 2 years old and 54% at 6 months (Clapp et al., 1990). Heart anomaly is highlighted as the main cause of death among syndromic patients, followed by gastrointestinal malformations and respiratory infection. Early cardiac surgery is the applied approach to avoid such consequences and is responsible for the substantial increase in life expectancy of these patients (Garrison et al., 2005; Weijerman et al., 2008).

Table 1. Features of the double aneuploidy cases of 48,XXY,+21.

Reference	Age	Characteristics of Down syndrome	Characteristics of Klinefelter syndrome	Congenital heart disease
This study	28 days	Epicanthic folds, muscle hypotonia, excess nuchal fluid, small ear and nose, flat nasal bridge, brachycephaly, and hydrocele.	None	Complete atrioventricular septal defect with Rastelli type B and significant left ventricular failure, moderate atrioventricular valve regurgitation, right-sided heart failure, and preserved systolic function.
Shu et al. (2013)	1 day	Anterior fontanelle and flat without broadening cranial suture, normal genitalia. On admission, showed hypertonia, tachypnea, and cyanosis. Hypertelorism and low set ears. Exudative lesions present in the lungs.	None	Atrial septal defect (ostium secundum), enlarged right ventricle, and mild tricuspid valve regurgitation.
Shen et al. (2012)	4 months	Simian crease, brachycephaly, flattened against the head, low-set ears, micropenis, flat facial profile, short, thick neck, low hair line, sandal gap sign, high palate, macrognathia, flat nasal bridge, hypertelorism, slanted palpebral fissures.	None	Ventricular septal defect with ductus arteriosus and large atrial septal defect. Tricuspid regurgitation and pulmonary hypertension.
Biselli et al. (2009)	3 months	Low weight and stature, flat nasal bridge, sandal gap sign, muscular hypotonia, brachycephaly, hypertelorism, epicanthic folds, slanted palpebral fissures, and Simian crease.	None	Interatrial communication.
Gerretsen et al. (2009)	14 months	Not described.	None	Double aortic arch. Small atrial septal defect, ostium secundum type.
Jeanty and Turner (2009)	Fetus	Short, thick neck, oblique palpebral fissures, and low nasal bridge.	None	Atrioventricular canal defect.
Akbas et al. (2008)	2 years	Flat nasal bridge, bilateral cryptorchidism, extra skin on the neck, flat face, high palate, micropenis, hypertelorism, low hair line, epicanthic folds, Simian crease, and macrognathia.	None	Atrioventricular septal defect. Pulmonary valve stenosis.
Efinski et al. (1974)	15 years	Low-set ears, muscular hypotonia, small penis, eyes slanted downward and inward, saddle nose, narrow shoulders, fissured large tongue, short neck, narrow palatal arch, and hypertelorism.	Epilepsy seizures and antisocial behavior.	Generalized cyanosis developed during exercise. A systolic murmur.
Erdtmann et al. (1971)	2 years	Brachycephalic head, hypoplastic nasal bone, loose skin, cone-shaped incisors and slight micrognathia, implanted low and malformed ears, bilateral epicanthus and small eyes, hypotrophic and slightly hypotonic	None	A surcharge of the right auricle. Ventricle compatible.

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Table 1. Continued.

Reference	Age	Characteristics of Down syndrome	Characteristics of Klinefelter syndrome	Congenital heart disease
		muscles, asymmetrical face, short neck with pterygium colli, and narrow palatal arch.		
Hecht et al. (1969)	8 years	Muscular hypotonia, mental retardation, growth retardation, epicanthic folds, umbilical hernia, spina bifida occulta, brachycephaly, slight nystagmus, Brushfield spots, hypoplasia of the middle phalanx of the 5th digit, furrowed tongue, absence of right 12th rib, small down-folded pinnae, sandal gap, and an upward slant to the palpebral fissures.	Hypospadias.	Mild aortic stenosis and chance of having pulmonary stenosis.
De Grouchy et al. (1965)	6 years	Bilateral epicanthic folds, hypertelorism, Simian crease, microcephaly, thick fissured tongue, bilateral clinodactyly of the 5th digits, brachydactyly and brachycephaly.	Undescended testis.	Cardiac anomalies.

This article describes a case of double trisomy 48,XXY,+21, with severe heart disease. According to the literature, the types of heart disease in Down-Klinefelter syndrome are varied. There seem to be differences between the incidence rate of congenital heart defects among patients with Down-Klinefelter and DS. More case studies are needed to establish better genotype-phenotype correlations. Early cytogenetic analysis proved to be an important tool for better diagnosis and management of Down-Klinefelter patients.

Conflicts of interest

The authors declare no conflict of interest.

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