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A rare sex chromosome aneuploidy: 49,XXXXY syndrome with pulmonary atresia and ventricular septal defect

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Abstract

Background: 49,XXXXY is a rare sex chromosome aneuploidy syndrome, which is associated with facial dysmorphism, hypogonadism, mental retardation and a combination of cardiac, skeletal and other malformations.

Case characteristics: We present here a case of 45-days-old male child having 49,XXXXY with pulmonary atresia and ventricular septal defect.

Conclusion: The presence of congenital heart defects in subjects with 49,XXXXY syndrome suggests special attention be given to the cardiac evaluation.

Keywords

49,XXXXY; sex chromosome aneuploidy; cardiac anomalies; developmental delay

Introduction

The 49,XXXXY syndrome, is a rare sex chromosomal aneuploidy with an incidence of 1 in 85,000 male births. 49,XXXXY syndrome, first reported in 1960, was considered a Klinefelter variant until 1998, when it was delineated as a distinct phenotype [1]. Clinical manifestations of 49,XXXXY include intellectual deficit, hypogonadism, remarkable facial dysmorphism (hypertelorism, large flat nose with a depressed nasal curvature, upslanting palpebral fissures, epicanthus, prognathism, folded-over ears, short neck) and other dysmorphic characteristics (cubitus valgus, flat feet, clinodactyly of the fifth finger, joint laxity) appear frequently. Congenital heart defects (arterial canal) as well as skeletal defects (radioulnar synostosis, epiphyseal dysplasia, coxa valga, kyphoscoliosis, hip and knee dislocation), cerebral (hypoplastic corpus callosum, arhinencephaly) and renal defects (renal hypoplasia) can also be present. Axial hypotonia is often seen in children. Strabismus or severe and progressive myopia can occur which can lead to declining vision. Behavioral problems such as shyness can also become apparent [2]. In this paper we reported a case of 49,XXXXY with pulmonary atresia and ventricular septal defect (PA-VSD) and discuss the clinical course.

Case Presentation

A 45-days-old male baby was admitted to the department of pediatric cardiology due to multiple congenital anomalies and episode of bronchopneumonia. The proband was the first living baby born to

non-consanguineous couple. His parents were healthy and the age of his father and mother were 33 and 27-year-old respectively. Mother had one first trimester abortion earlier. The baby was born after full-term normal delivery, with birth weight of 1900 g, length of 48 cm and head circumference of 31 cm. After birth, facial dysmorphism, hypoxia and cardiac systolic murmur were noted. Echocardiography showed PA, duct dependent pulmonary circulation and had multiple muscular VSD with right to left shunt (Fig. 1).

He had a dysmorphic face including microcephaly, hypertelorism, downward slant, short palpebral fissures, low-set dysplastic ears, megalocornea, micrognathia, short neck, pectus excavatum, short sternum, large open anterior fontanelle, cleft palate with central fissure, laryngomalacia, umbilical hernia, simian crease, pes planus, hypoplastic scrotum, micropenis, clinodactyly and hypotonia of the muscles (Fig. 2).

The oxygen saturation in room air breathing varied from 70 - 75%. Liver, renal function and electrolytes were all within normal ranges. X-ray studies of both upper extremities did not reveal radio-ulnar synostosis or other anomalies. Based on these findings proband was referred to Centre for Genetic Studies & Research for clinical cytogenetics workup. The karyotype was analysed on peripheral blood lymphocytes cultured for 72 h in Roswell Park Memorial Institute (RPMI)1640 with phytohaemagglutinin, antibiotic, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) and fetal bovine serum (FBS). After GTG banding, the karyotype was confirmed as 49,XXXXY in all the cells examined (Fig. 3a). Fluorescent in-situ hybridization (FISH) study was performed on metaphase chromosome from cultured peripheral blood sample of this patient to confirm the presence of X and Y chromosome using CEP X/Y localized to p11.1-q11.1 of both X and Y chromosomes from Vysis Inc., USA. Probe hybridization showed four signals (green) for X chromosome and one signal (orange) for Y chromosomes in all the cells suggestive of sex chromosome pentasomy (Fig. 3b).

The proband was confined to a neonatal intensive-care unit observation for 5 days. At 1 year of age, the child underwent cardiac catheterisation with an attempt to perforate the atretic pulmonary valve; but the hypoplastic right ventricular infundibulum did not permit perforation of pulmonary atresia (Fig. 4). So he underwent aorto-pulmonary shunt at 1 year of age. On a subsequent follow up at 2 years of age he has oxygen saturation of 80%, developmental age of 1 year and has speech delay.

Discussion

The previous reports describing children with 49,XXXXY syndrome have emphasized the 'classic triad' of mental retardation, radio-ulnar synostosis and hypogonadism [1]. At present, it is well-known that 49,XXXXY syndrome is a distinct clinical entity characterized by a variety of genital, skeletal, facial, and cardiac abnormalities. This patient did not have radioulnar synostosis, but had other typical features and cardiac defects with 49,XXXXY syndrome. Congenital cardiac defects in 49,XXXXY syndrome are infrequent with 14 % prevalence of which patent ductus arteriosus (PDA) is the most commonly observed defect [3]. Ventricular and atrial septal defect (ASD) and VSD with infundibular pulmonary stenosis (IPS) have also been reported in association with 49,XXXXY syndrome. In our patient, the cardiac diagnosis was mid-muscular VSD with vulvar pulmonary atresia. The clinical phenotype changes as the person grows to an adult. Therefore, certain features present in children are not necessarily present in adults and vice-versa. In new-borns with this syndrome, below average lengths and weights are reported at birth [1]. Our patient had a low birth weight and failed to catch-up growth thereafter. Treatment

depends on the features in each affected person and is often managed by a multidisciplinary team. Patients have an essentially normal life expectancy but will need to attend regular medical visits [2].

49,XXXXY is the outcome of non-disjunction of the X chromosome during both meiosis I and meiosis II. Such successive non-disjunction theoretically produces an egg with four X chromosomes, which, when fertilized by a Y bearing sperm, results in an embryo with 49,XXXXY syndrome [4,5]. However, the occurrence of this syndrome does not appear to be related to maternal age. Parental origin has been reported in five cases of 48,XXXY. In two of these cases, the origin was successive non-disjunction in formation of the sperm (XpXpYp) fertilizing a normal female oocyte (Xm) and the other three cases showed XmXmXmYp, indicated double non-disjunction events during oogenesis [1]. Unfortunately, the parents of the child in our report were not willing to support us to observe the parental origin.

Conclusion

49,XXXXY syndrome is a genetic entity with distinctive facial features, mental retardation, and development delay. Even though initial reports of 49,XXXXY syndrome were described as a triad that included radioulnar synostosis, this was absent in our patient and so it need not be included as a diagnostic triad. Considering the near normal life expectancy in this syndrome, a long term follow-up is needed by a multidisciplinary team.

Figures

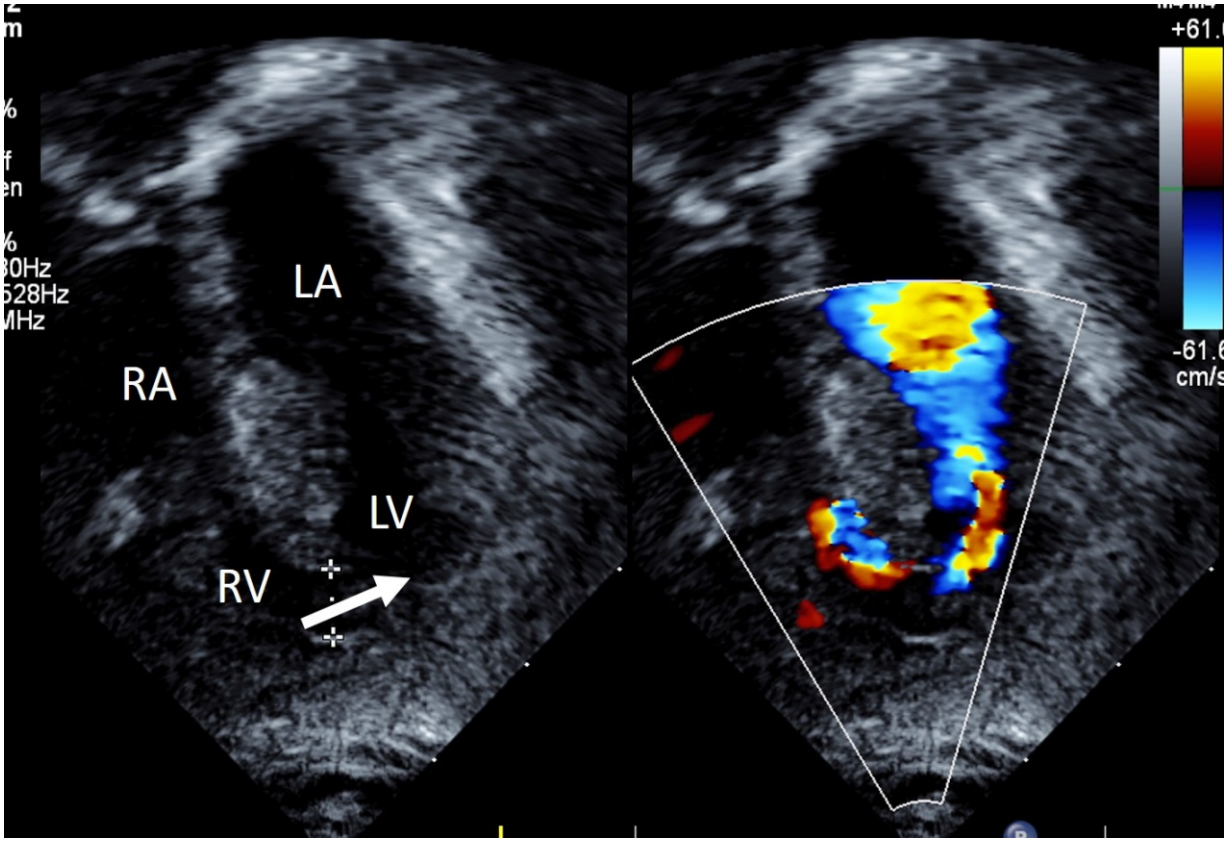

Figure 1: Apical four chamber view with color flow mapping on echocardiography showed large apical muscular ventricular septal defect shown with arrow.

RA: right atrium; LA: left atrium; LV: left ventricle; RV: right ventricle.

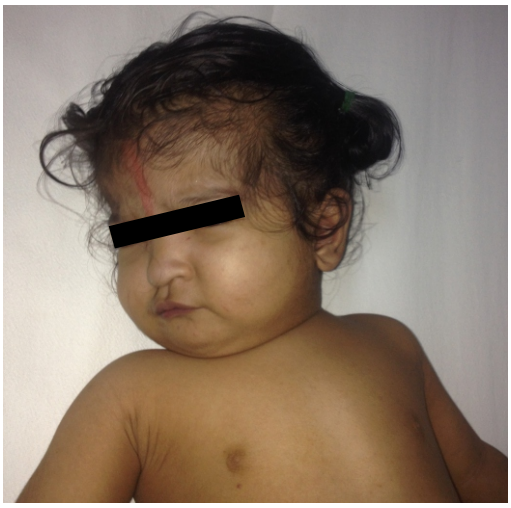

Figure 2: Facial features of the patient.

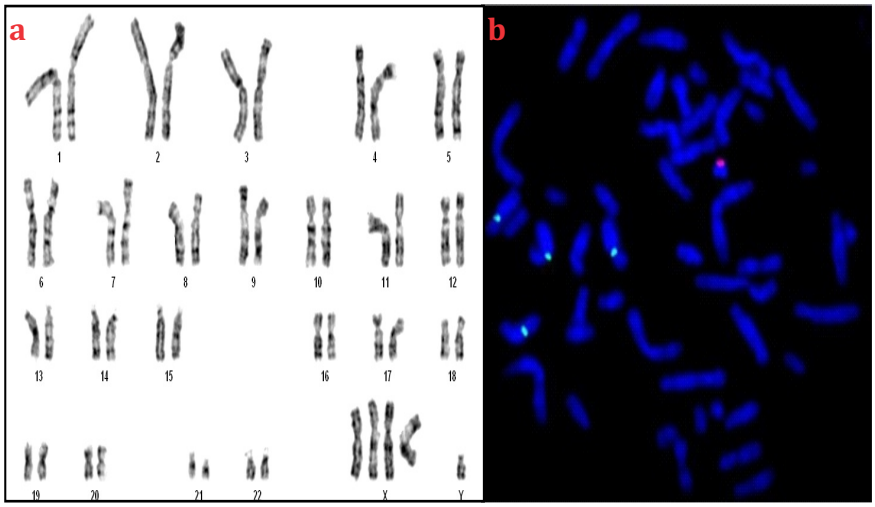

Figure 3: a). Karyotype of a male with 49,XXXXY chromosomal constitution. b) Fluorescent in situ hybridization analysis revealed four signals (green) for X chromosome and one signal (orange) for Y chromosome in all the cells analysed.

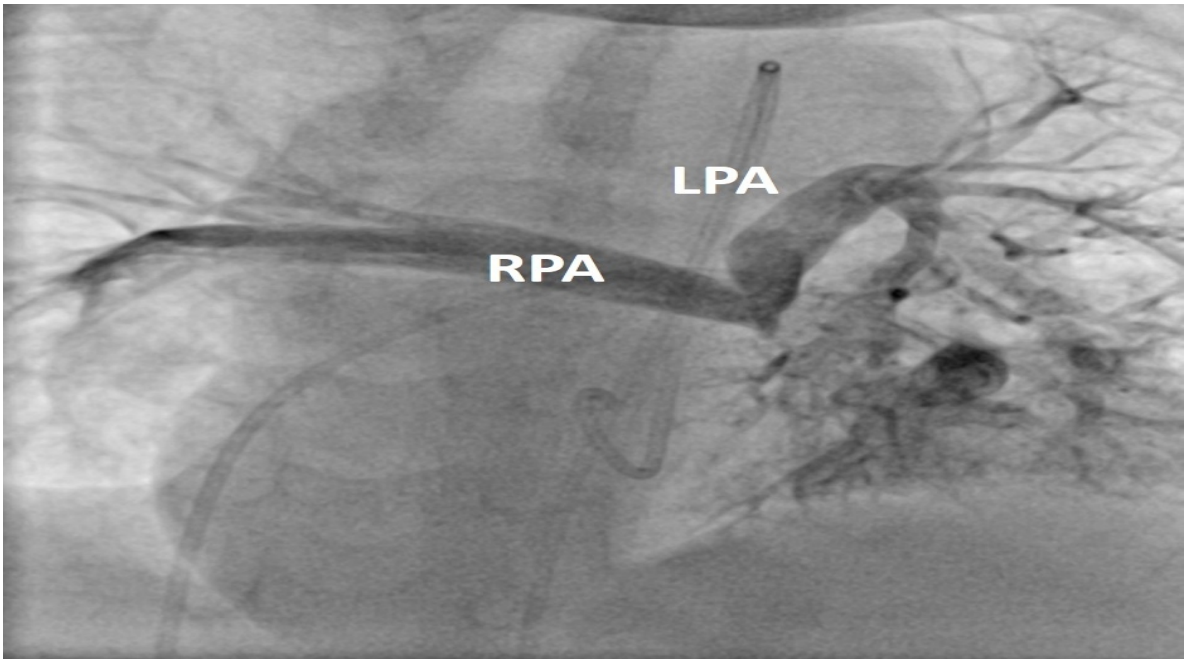

Figure 4: Pulmonary vein wedge angiography during cardiac catheterization from left pulmonary vein showed hypoplastic small confluent pulmonary arteries.

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