CASE REPORT OLGU SUNUMU

Congenital Heart Disease in an Infant with 49,XXXXY Syndrome

49,XXXXY Sendromlu Bir Çocukta Konjenital Kalp Hastalığı

Mustafa Argun, Mustafa Ali Akin*, Selim Kurtoglu*, Dilek Sarıca*, Abdullah Özyurt, Özge Pamukcu, Ali Baykan

Erciyes Üniversity Faculty of Medicine, Department of Pediatric Cardiology, Kayseri, Turkey
*Erciyes Üniversity Faculty of Medicine, Department of Neonatology, Kayseri, Turkey

Abstract

49,XXXXY syndrome which is characterized with the addition of three extra X chromosomes to 46,XY is the rarest sex chromosome aneuploidy syndrome. Its classical findings were defined as a triad of mental retardation, hypogonadism and radioulnar synostosis. In 49,XXXXY syndrome, congenital heart defects like patent ductus arteriosus, atrial septal defect, ventricular septal defect, pulmonary stenosis, Fallot's tetralogy have been reported. We present a case diagnosed in the newborn stage with low birth weight, short stature, dysmorphic craniofacial findings and hypoplastic male genitalia who was found to have severe pulmonary hypertension and medium patent ductus arteriosus when admitted at 4 months of age with heart failure and who underwent transcathater ductus closure with Amplatzer Duct Occluder I. To our knowledge, our case is the first reported 49,XXXXY syndrome with patent ductus arteriosus closed with the transcathater route.

Öz

49,XXXXY sendromu, 46,XY'ye ekstra üç X kromozomu eklenmesi ile karakterize nadir görülen cinsiyet kromozom anöploidi hastalığıdır. Klasik bulguları mental retardasyon, hipogonadizm, radioulnar sinostozis triadı olarak tanımlanmıştır. 49,XXXXY sendromunda patent duktus arteriozus, atriyal septal defekt, ventrikuler septal defekt, pulmoner stenoz, Fallot tetralojisi gibi konjenital kalp defektleri bildirilmiştir. Yenidoğan döneminde düşük doğum ağırlığı, kısa boy, dismorfik kraniyofasiyal bulgular ve hipoplastik erkek genitalya ile tanısını koyduğumuz ve 4 aylık iken kalp yetersizliği kliniği ile kabul edildiğinde ciddi pulmoner hipertansiyonu ve orta büyüklükte patent duktus artriyozusu saptanarak, duktusu transkateter Amplatzer Duktal Okluder I ile kapattığımız olguyu sunuyoruz. Bildiğimiz kadarıyla bu olgu patent duktus artiyozusu transkateter kapatılan ilk 49,XXXXY sendromudur.

Keywords
49,XXXXY syndrome, congenital heart disease, transcathater ductus closure

Anahtar kelimeler
49,XXXXY sendromu, konjenital kalp hastalığı, transkateter duktus kapatma

Received/Geliş Tarihi : 23.07.2013
Accepted/Kabul Tarihi : 06.05.2014

DOI:10.4274/jcp.88597

Address for Correspondence/Yazışma Adresi: Mustafa Argun MD, Erciyes Üniversity Faculty of Medicine, Department of Pediatric Cardiology, Kayseri, Turkey
Phone: +90 533 682 62 66
E-mail: dr.margun@hotmail.com

Introduction

49,XXXXY syndrome is the rarest and most severe X chromosome aneuploidy defect with an approximate incidence of one in 85.000-100.000 male births (1). It was first described in 1960 by Fraccaro et al. (2). Its classical findings were defined as a triad of mental retardation, hypogonadism and radioulnar synostosis. 49,XXXXY syndrome is often considered variants of Klinefelter syndrome (47,XXY) because of some shared features as testicular dysgenesis and hypergonadotropic hypogonadism (3). Klinefelter syndrome is the most common disorder of sex chromosomes in humans, with a prevalence of one in 650 males (4). Male of 49,XXXXY syndrome are generally shorter, more

mentally handicapped, have distinctive facial features, and a higher incidence of congenital heart defects when compared to males with a Klinefelter syndrome (5-7). We present a case of 49,XXXXY syndrome with patent ductus arteriosus and briefly discuss congenital heart defects in 49,XXXXY syndrome.

Case

The patient was born to a 19-year-old healthy mother in her first pregnancy with C/S. Both his weight was 2.25 kg and his height was 43 cm were below the 3rd centile. Head circumference was 32.5 cm (3rd-10th centile). There were three degrees of consanguinity among parents and the pregnancy was uncomplicated. There was not another family member with choromosome abnormality.

First postnatal examination revealed an incomplete cleft palate, so when the patient was admitted to the neonatal service, other phenotypic features in the baby such as a dysmorphic face including hypertelorism, short palpebral fissure, flat nasal bridge, broad nose, dysplastic ears and micrognathia, short stature, clinodactyly, micropenis, unilateral cryptorchidism and small testis were noted (Figure 1). Neurologically, he was hypotonic. Echocardiography showed patent ductus arteriosus (PDA). Analysis of metaphase chromosome on peripheral blood cultures was performed. The cytogenetic analysis of the peripheral blood revealed 49,XXXXY in 30/30 cells counted (Figure 2). Although follow-up was planned following discharge, he was not brought to the hospital until this admittance.

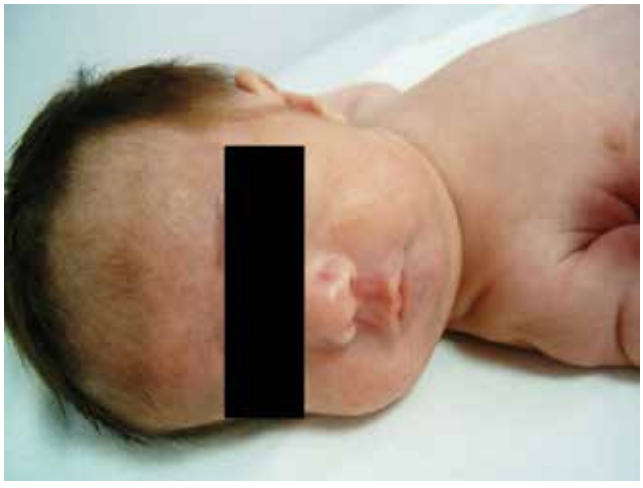

Figure 1. Clinical photograph demonstrates the dysmorphic face

Four-months-old male patient was admitted to our clinic because of tachypnea, cyanosis, convulsion and feeding difficulty. For the management of heart failure, anticongestive therapy and inotropic agent were administered.

Cranial magnetic resonance imaging (MRI) revealed bilateral dilated lateral ventricles and enlargement in the peripheral cerebrospinal fluid space (Figure 3).

Echocardiography showed PDA of moderate size. Angiography revealed the narrowest size of PDA with left-to-right shunt to be 2.5 mm. Hemodynamic parameters were as follows: main pulmonary artery pressure was 72/22 mean value being 57 mmHg.

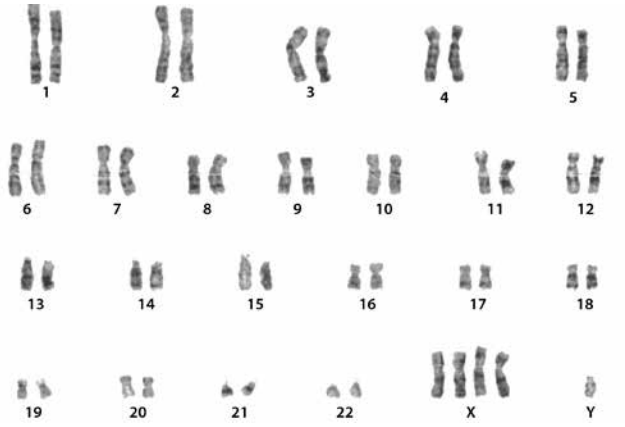

Figure 2. Choromosome analysis of the peripheral blood showing 49,XXXXY

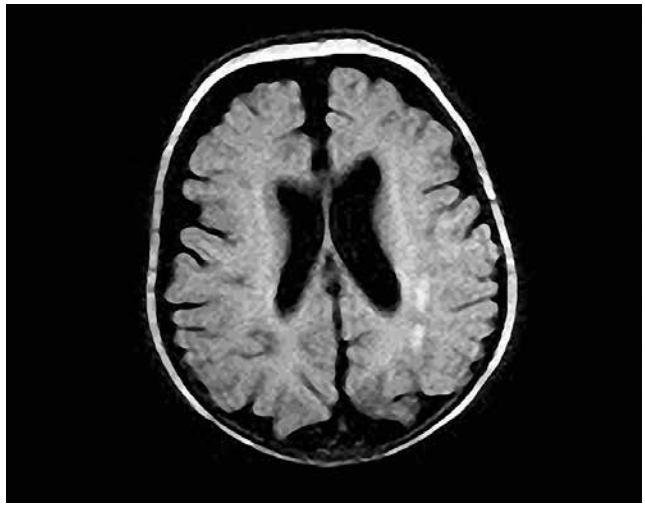

Figure 3. Cranial magnetic resonance showing bilateral dilated lateral ventricles and enlargement in the peripheral cerebrospinal fluid space

Amplatzer Duct Occluder (ADO) I is a cone shaped device made of nitilol wire mesh which is auto-expandable. 5x4 mm sized ADO-I device was placed via venous route under fluoroscopy (Figure 4). No complications occurred during or after percutaneous transcatheter PDA closure.

Discussion

49,XXXXY syndrome is the rarest and most severe X chromosome polysomy characterized with the presence of three extra X chromosomes in men (1). All four X chromosomes found in 49,XXXXY syndrome have maternal origin and originate from the non-separation of X chromosome both in meiosis I and meiosis II. That is, aneuploid oocytes are fertilized with normal male sperm (8).

One or more X chromosome added to 46,XY leads to testicular dysgenesis and hypergonadotropic hypogonadism, and these features have suggested that 49,XXXXY is a variant of Klinefelter syndrome (47,XXY) (4). Nevertheless, the two conditions have different etiologies as well as rather different clinical presentations. In summary, while body height is below average in 49,XXXXY syndrome, it is high in 47,XXY syndrome and mean adult height reaches 179-188 cm. While congenital malformations are very common in 49,XXXXY, they are rarely encountered in 47,XXY. Mental motor retardation are universal in 49,XXXXY and IQ is markedly low. Whereas in 47,XXY, mental and motor retardation is seen in only half of individuals and IQ is between 89 and 102. While 49,XXXXY is the rarest X chromosome aneuploidy syndrome seen in 1/85.000 males, 47,XXY is the most common chromosomal anomaly seen in humans with an incidence of 1/650 men (4).

Craniofacial features of 49,XXXXY syndrome include microcephaly, round face, upper slanted palpebral fissure, epicanthus, broad nasal bridge, micrognathia, prognathism, cleft palate, irregular dental implantation, malformed ears which are compatible with the findings in our case.

Figure 4. Angiography showing patent ductus arteriosus closure with Amplatzer Ductal Occluder I by transcathater.

Table 1. Accompanying congenital heart defects in our case and in cases with 49,XXXXY syndrome reported in the literature and treatment modalities of patent ductus arteriosus are reported

Case (Reporting researcher)	Accompanying congenital heart disease
Case 1 (Our report)	Patent ductus arteriosus (percutaneous closure)
Case 2 (5)	Atrial septal defect, ventricular septal defect
Case 3 (5)	Fallot's Tetralogy
Case 4 (5)	Patent ductus arteriosus (underwent ligation)
Case 5 (10)	Patent ductus arteriosus (closed spontaneously)
Case 6 (11)	None
Case 7 (11)	Patent ductus arteriosus (underwent ligation)
Case 8 (11)	None
Case 9 (12	None
Case 10 (13)	Patent ductus arteriosus (underwent ligation), atrial septal defect, mild pulmonary stenosis

Skeletal system abnormalities include short stature, proximal radioulnar dysostosis, vertebral anomalies, coxa valga, genu valgum, and pes planus (9). The height of the patient was below the 3rd percentile at birth and at 4 months of age and there was clinodactyly in the fifth finger.

Genital anomalies include hypoplastic male genitalia, micropenis, hypospadias, small testes, hypogonadism, and infertility. Compared with other chromosome aneuploidy syndromes (47,XXY, 48,XXYY and 48,XXXY), findings of hypogonadism are more prominent in 49,XXXXY syndrome because of the higher number of X chromosomes. Our case had hypoplastic male genitalia and unilateral cryptorchidism. As in the newborn case reported by Ng SF et al. (10), sometimes they can be presented with ambiguous genitalia as an advanced reflection of hypergonadotropic hypogonadism.

Seizures have been reported at a rate of 10-15% in 49,XXXXY syndrome (4). Our case had seizures controlled with three different antiepileptic. Hoffman TL et al. (11) have reported cerebral volume loss in various degrees, enlargement in the lateral ventricle, volume loss in the cerebellum and thinning in corpus callosum as cerebral MRI findings in 3 cases with 49,XXXXY syndrome. Brain MRI of our case revealed loss of brain white matter and enlargement in the lateral ventricle, which are compatible with the literature.

It is known that diabetes incidence is increased in Klinefelter and other X chromosome polysomy syndromes. Kim et al. have reported accompanying diabetes in an 18-year-old case with 49,XXXXY syndrome. Our case had normal routine biochemical values, including blood glucose level (12).

In 49,XXXXY syndrome, congenital heart defects like PDA, atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis (PS), Fallot's Tetralogy have been reported (5,10-13). Among these, PDA is the most frequently reported congenital heart defect which was present in the first case reported by Fraccaro and also in our case (2,5). In compliance with the literature we have reached (5,10-13), accompanying congenital heart defects reported in cases with 49,XXXXY syndrome and the way PDA is treated are shown in (Table 1). According to this, incidence of congenital heart defects is seen to be higher (60%) than 14% previously reported by Karsh RB et al. (8). Although PDA was of moderate size in our case, systolic pressure of the pulmonary artery was only 8 mmHg lower than the systolic pressure in the aorta. Because there was no pulmonary disease to explain pulmonary hypertension, there may be a tendency for PDA related pulmonary hypertension in these patients as well as a contribution of micrognathia related obstruction in the upper airways. In previously reported cases with 49,XXXXY syndrome, either PDA had closed spontaneously or surgical ligation had been performed. To our knowledge, our case is the first reported 49,XXXXY syndrome with PDA closed with the transcatheter route.

49,XXXXY syndrome is usually not hereditary. Recurrence rate is approximately 1%. No association has been reported with maternal age (10). Cautionary findings in prenatal ultrasonography are intrauterine growth retardation, abnormal posture in lower extremities, cystic hygroma and micropenis. Definite diagnosis is made with chromosome analysis in the amniotic fluid (13).

In conclusion, in 49,XXXXY syndrome which is distinguished from Klinefelter syndrome with many clinical findings, care should be taken regarding short stature, craniofacial features, hypogonadism findings, mental retardation, skeletal system malformations and particularly accompanying cardiac defects and necessary treatment should be started before pulmonary hypertension develops in the patients.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1. Kleczkowska A, Fryns JP, Van den Berghe H. X-chromosome polysomy in the male. The Leuven experience 1966-1987. Hum Genet 1988;80:16-22.
2. Fraccaro M, Kaijser K, Lindsten J. A child with 49 chromosomes. Lancet 1960;2:899-902.
3. Simşek PÖ, Ütine GE, Alikaşifoğlu A, Alanay Y, Boduroğlu K, Kandemir N. Rare sex chromosome aneuploidies: 49,XXXXY and 48,XXXY syndromes. Turk J Pediatr 2009;51:294-7.
4. Tartaglia N, Ayari N, Howell S, D'Epagnier C, Zeitler P. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klienfenter syndrome. Acta Paediatr 2011;100:851-60.
5. Peet J, Weaver DD, Vance GH. 49,XXXXY: a distinct phenotype. Three new cases and review. J Med Genet 1998;35:420-4.
6. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet 2004;364:273-83.

7. Visootsak J, Graham JM Jr. Klinefelter syndrome and other sex chromosomal aneuoploidies. Orphonet J Rare Dis 2006;1:42.
8. Karsh RB. Congenital heart disease in 49,XXXXY syndrome. Pediatrics 1975;56:462-4.
9. Guzel AI, Demirhan O, Pazarbasi O, Yuksel B. Parenteral origin and cell stage errors in X-chromosome polysomy 49,XXXXY. Balkan J Med Genet 2009;12:45-50.
10. Ng SF, Boo NY, Wu LL, Shuib S. A rare case of ambiguous genitelia. Singapore Med J 2007;48:858-61.
11. Hoffman TL, Vossough A, Ficicioglu C, Visootsak J. Brain magnetic resonance imaging finding in 49,XXXXY Syndrome. Pediatr Neurol 2008;38:450-3.
12. Kim HJ, Kim D, Shin JM, Chung HK, Lee G. 49,XXXXY syndrome with diabetes mellitus. Horm Res 2006;65:14-7.
13. Hou JW. 49,XXXXY syndrome. Chang Gung Med J 2004;27:551-4.
14. Sezgin I, Ruhi HI. Chromosome disorders and genetic counseling. Türkiye Klinikleri J Pediatr Sci 2005;1:36-41.