Klinefelter Syndrome in Association with Tetralogy of Fallot and Congenital Diaphragmatic Hernia

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Abstract

Keywords

- Klinefelter syndrome
- tetralogy of Fallot
- congenital diaphragmatic hernia

Klinefelter syndrome (KS) is the most common sex chromosomal aneuploidy in males. Major cardiovascular and diaphragmatic anomalies are uncommon in this syndrome. Here we report an infant with KS who had tetralogy of Fallot and congenital diaphragmatic hernia, all of which were identified prenatally and managed successfully after birth. Microarray analysis did not reveal any deletions or duplications other than the additional X-chromosome, to account for the additional abnormalities in this infant. To the authors' knowledge, this is the first such report of major cardiac and diaphragm anomaly occurring together, in an infant with KS.

Introduction

Klinefelter syndrome (KS), the most common sex chromosomal anomaly in males, is characterized by the presence of an additional X-chromosome (47 XXY). The incidence of KS is approximately 1 in 500 male live births. Only approximately 25% of men with KS are diagnosed during their life time, with fewer than 10% being diagnosed before the onset of puberty.¹ KS is the most common genetic cause of male infertility. Typical KS phenotype includes eunuchoid body habitus, feminine distribution of body fat and hair, gynecomastia, and micropenis. They may also have learning disabilities, along with language and speech delays. Major cardiac anomalies are uncommon in KS. There are isolated reports of anomalies such as atrial septal defect, mitral valve prolapse, and hypertrophic cardiomyopathy described in patients with this syndrome. Tetralogy of Fallot, the most common cyanotic congenital heart disease, has no known association with KS as is the major diaphragmatic anomaly, congenital diaphragmatic hernia (CDH). This latter condition with a reported incidence of 2.3 per 10,000 live births² has been

reported in association with other genetic syndromes, but rarely with KS. In this report, we describe a case of KS in whom both tetralogy of Fallot and CDH were coexistent in the same patient.

Case Report

RH was born premature at 31 weeks' gestational age via vaginal delivery with a birth weight of 1.6 kg. He was born to nonconsanguineous parents. The mother had pregestational diabetes mellitus and was on insulin during the pregnancy. She was 37-years-old and gravida 3, with a history of two previous spontaneous early first-trimester abortions. There was no family history of any known metabolic or genetic disorders. RH was suspected to have a congenital heart defect and CDH by second-trimester fetal ultrasound performed at the referring physician's office. The mother had an amniocentesis after the abnormal ultrasound, which identified the fetus to have KS by karyotype, 47, XXY. Soon after birth, RH was intubated for respiratory failure. Investigations performed after birth confirmed the diagnoses of CDH, tetralogy

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of Fallot with severe pulmonary stenosis, and KS. Echocardiogram showed severe subvalvar, valvar, and supra-valvar pulmonary stenosis with severe hypoplasia of the branch pulmonary arteries. He had dysmorphic facial features consisting of hypertelorism, epicanthal folds, long philtrum, bilateral posteriorly rotated and hypoplastic ears, micrognathia, clinodactyly of the fifth fingers and toes, broad thumbs, overlapping fifth digit in the feet, and syndactyly of the second and third toes bilaterally. Microarray analysis performed in the neonatal period confirmed the presence of extra X-chromosome but did not show any deletion or duplication that could account for his multiple congenital anomalies. Biochemical evaluation of the patient after birth showed no abnormalities. The renal and liver function panels were normal. Hormonal (testosterone) evaluation was not done in this infant as no major hormonal abnormalities are anticipated at this age.

At 3 days of life, the patient underwent surgical repair of the CDH. On day 15 of life, he developed hypercyanotic spells with persistent hypoxemia, secondary to severe right ventricular outflow obstruction. These tetralogy of Fallot-related cyanotic spells responded to esmolol infusion. This medication was continued until his cardiac surgery on day 30 of life, when he underwent placement of a right modified Blalock-Taussig shunt. This shunt surgery was done when he attained weight of 2 kg. He was discharged home at 2 months of age. At discharge, he was feeding independently and was not requiring supplemental respiratory support. At 12 months of age, he underwent elective complete repair of tetralogy of Fallot with a transannular patch, without any postoperative complications. During the last follow-up at 2 years of age, he has mild degree of global developmental delay, his length was 84 cm (19th percentile), weight of 10.4 kg (10th percentile), and microcephalic with a head circumference measured at 18 months of 43.5 cm (< 5th percentile).

Discussion

KS is a common sex chromosomal anomaly in males and is associated with motor and cognitive dysfunction and behavioral problems, along with vascular and endocrine/metabolic disease. It is rarely associated with congenital diaphragmatic or cardiovascular anomalies. Both tetralogy of Fallot and CDH, relatively infrequent major congenital anomalies in the general population are rarely reported in KS.

In 1964, Gautier and Nouaille reported two cases of KS associated with tetralogy of Fallot, among a study of Barr's corpuscle in 210 infants with congenital heart disease.³ Since then there has not been any report of such an association in the literature. The association between KS and mitral valve prolapse has been reported.⁴ Recently, Pasquali et al demonstrated increase in left ventricular diastolic dysfunction, impaired cardiopulmonary performance, chronotropic incompetence, and increased intima-media thickness in children and young adults with KS.⁵ There are also few case reports of CDH in patients with KS. Taheri and Kadir reported a case of diaphragmatic hernia diagnosed prenatally in a fetus,

who was postnatally found to have KS.⁶ Valdez et al reported a case in which CDH and KS were diagnosed prenatally.⁷

In a recent review on CDH by Wynn et al, the cause of approximately 80% of CDH cases was unknown with no genetic abnormalities, demonstrating our limited understanding of the genetic etiologies of CDH as well as suggesting nongenetic, non-Mendelian, or multifactorial etiologies for CDH.⁸ In addition to single-gene mutations in GAT4, GATA6, MYH10, ZFPM2/FOG2, and DIPS1, other rare single-gene mutations have also been reported with some patients with CDH. In a large review of patients with tetralogy of Fallot by Rauch et al, 22q11.2 deletion was found to represent the most frequent genetic diagnosis, followed by Down's syndrome.⁹ Atypical proximal deletions in 22q11.2 as well as mutations in TBX1, NKX2.5, and JAG1 were found far less frequent in tetralogy of Fallot in that series. Neither CDH nor tetralogy of Fallot has any known consistent association shown with KS. The coexistence of both of these rare congenital anomalies in our patient is possibly incidental rather than associated with a common genetic factor. It is possible that he also has another genetic disorder that could explain his multiple congenital anomalies and dysmorphic features so whole exome sequencing is being considered. Syndromes to consider include Fryns syndrome, which is a genetic condition that causes diaphragmatic hernia in up to 90% of cases, renal malformations, and cardiac disease (atrial septal defect, ventricular septal defect, and aortic arch anomalies). Fryns syndrome is inherited as an autosomal recessive disorder, but the underlying gene is unknown at this time. Other possible conditions include Pallister-Killian syndrome, Donnai-Barrow syndrome, and Cornelia de Lange syndrome. However, he did not have many of the other features of these disorders.

KS is not reported to be associated with a higher risk for premature birth. Presence of prematurity, along with major diaphragmatic hernia, posed a challenge in the management of tetralogy of Fallot in this child in the neonatal period. Even though most patients with this cardiac anomaly undergo single-stage repair, situations such as this still warrant a two-stage repair that includes an initial palliation in the form of an aortopulmonary shunt followed by a complete repair at approximately 1 year of age.

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Conflict of Interest

None.

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