CASE REPORT

Fetal Jacob Syndrome (47XYY): An Uncommon Association of Fetal Pulmonary Atresia with Ventricular Septal Defect

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Abstract

Jacob syndrome is a sex chromosome aneuploidy comprising of an extra Y choromosome usually diagnosed late in postnatal life or never diagnosed throughout the life. Its prenatal diagnosis is usually accidental due to lack of specific fetal phenotype. The case presented here is that of a prenatally diagnosed Jacob syndrome associated with pulmonary atresia and ventricular septal defect (PA-VSD) which is an uncommon fetal phenotype, not reported in the literature so far.

Keywords: 47XYY, Fetal ultrasound, Genetic counseling, Jacob syndrome, PA-VSD, Prenatal diagnosis, Pulmonary atresia with VSD, Sex chromosomal aneuploidy.

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Introduction

Jacob syndrome is a sex chromosome aneuploidy comprising of an extra Y choromosome affecting 1 out of 1,000 males. It is diagnosed late in postnatal life or never diagnosed throughout the life.[1,2] Prenatal diagnosis is usually accidental due to lack of specific fetal phenotype. Only a handful of prenatal cases have been reported with phenotype pertaining to increased nuchal translucency, skeletal, brain, and heart abnormalities or as an accidental pickup on cell-free DNA testing.[3,4] The case presented here is prenatally diagnosed Jacob syndrome associated with pulmonary atresia with ventricular septal defect (PA-VSD) which is an uncommon phenotype not reported in the literature so far.

Case Description

A 29-year-old low risk primigravida was scanned at 32 weeks for a routine well-being wherein following findings were documented: Normal four chamber view of the heart with a large subaortic VSD with overriding aorta ("Y" sign) seen in five chamber view, only two vessels in the three vessel view and an atretic pulmonary valve were noted. Major aorto pulmonary collaterals (MAPCAs) arising from the descending aorta were seen in the longitudinal view. Findings suggested PA-VSD with MAPCA (Figs 1A to C). Normal male genitalia with bilateral testes *in situ* were seen. Fetal face suggested mild hypertelorism. No other major anomalies were found. The patient had missed her anomaly scan in view of the ongoing COVID pandemic. Nondirective genetic counseling was done keeping in view the advance gestation and high association of PA-VSD with 22q11.2 microdeletion. Amniocentesis was done for chromosomal microarray and karyotype which revealed 47,XYY (Jacob syndrome) (Figs 1D and 2). The prognosis of Jacob syndrome with underlying cardiac defect was explained to the parents who then decided to continue the pregnancy expectantly. A full term vaginal delivery was carried out and postnatal echocardiography confirmed the findings. Parents opted against pediatric cardiologist interventional management. The child expired at 4 months age.

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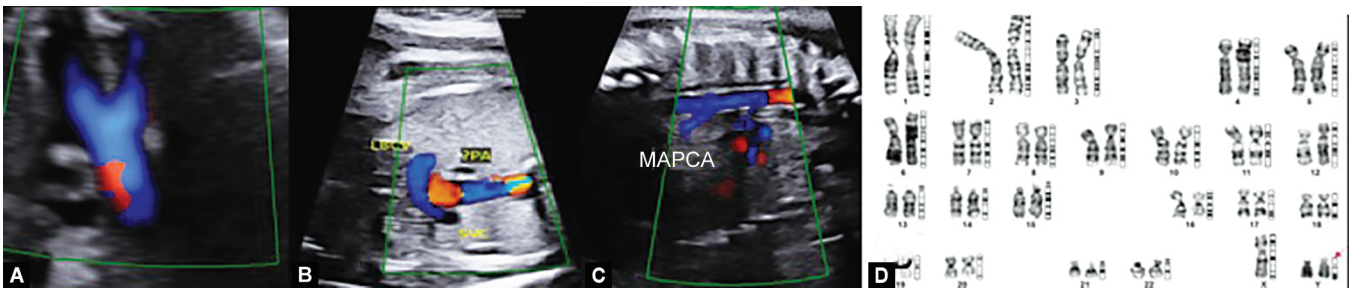
Discussion

Jacob syndrome, also known as superman syndrome, is a sex chromosome aneuploidy characterized by an extra Y chromosome. The origin of this Y chromosome is paternal and results from nondisjunction in the second meiotic division (84% of cases) or a postfertilization mitotic error (16%). It does not result from increased parental age.[1] Fetal Jacob syndrome does not have a specific phenotype although a few structural associations have been reported.[1-3] Prenatal cases are usually picked up accidentally on cell free fetal DNA or karyotype/microarray offered for other indications.[4] The case presented highlights an uncommon association of pulmonary atresia with ventricular septal defect with Jacob syndrome in a male fetus. The mechanism of an extra Y chromosome in causing this cardiac defect is unclear. PA-VSD is reported to be associated with 22q11.2 deletion syndrome in 25% cases.[5] Association of PA-VSD with sex chromosomal abnormalities like Klinefelter syndrome (47XXY) has been reported but with Jacob syndrome (47XYY) is not yet reported.[5] In this case, 22q11.2 deletion syndrome was ruled out by microarray (Fig. 2). In such cases, parents need to be counseled about the prognosis and



Figs 1A to D: (A) Five-chamber view showing typical Y sign due to subaortic ventricular septal defect and overriding aorta; (B) Two-vessels in three-vessel view; (C) MAPCA arising from descending aorta; (D) Karyotype showing an extra Y chromosome, 47XYY

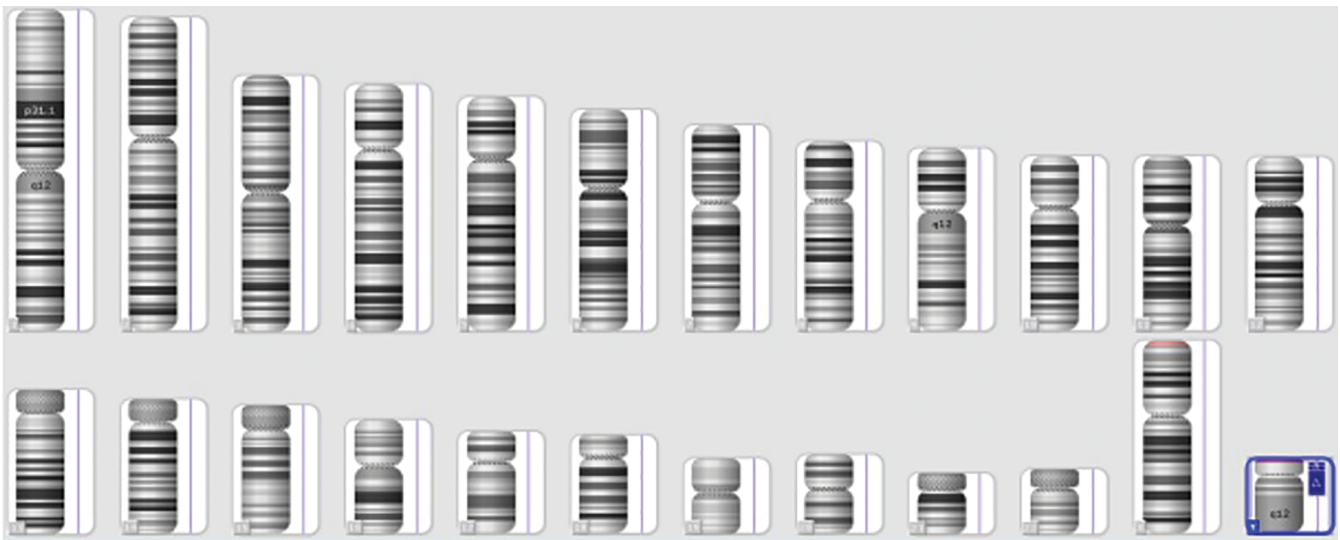


Fig. 2: Chromsomal microarray showing 47XYY-Jacob syndrome

management in context to cardiac defect and in context to the sex chromosomal abnormality. The risk of behavioral problems, autism, language problems, low IQ, and subfertility linked with the chromosomal abnormality were discussed. Parents' decision on continuing or terminating such pregnancies needs to be respected although advance gestation like in this case might be limiting. Risk of recurrence of Jacob syndrome is usually low.[1] Prenatal diagnostic procedure and early cardiac screening can be offered in subsequent pregnancies.

Conclusion

This case highlights an uncommon association of PA-VSD with Jacob syndrome (47XYY), which underscores importance of a microarray over limited Fluorescence *in situ* hybridization (FISH) for 22q11.2 deletion in such cardiac anomalies.

What is known?

It is known, that both entities are rare and PA-VSD is commonly associated with 22q11.2 deletion and uncommonly associated with Klinefelter syndrome (47XXY) in few cases.

What this case report adds?

This case brings an uncommon association of PA-VSD with Jacob syndrome (47XYY) and highlights the importance of chromosomal microarray over limited FISH in these cases.

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