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CASE REPORT

Case report of 49, XXXXY syndrome: first case in Oman

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ABSTRACT

Background: The incidence of sex chromosome aneuploidies is 1:400. Klinefelter syndrome is considered to be the most common type of sex chromosome aneuploidy, manifested as variants, such as 48,XXXY, 48,XXYY and 49,XXXXY. Nondisjunction of the X chromosome during meiosis I and II is considered as the cause of this type of aneuploidy. The classic clinical presentation of Klinefelter Syndrome is a triad of hypogonadism, mental retardation, and musculoskeletal anomalies.

Case Presentation: In this case report, we describe a 2-year-old male child identified postnatally to have low birth weight, congenital heart defect, inguinal hernia, facial dysmorphism, and genital organs anomalies. Chromosomal analysis revealed a karyotype of 49,XXXXY and the comparative genomic hybridization (CGH) array analysis revealed a 155,065 kilo base pair duplication on chromosome Xp22.33q28 (168,546, −155,233,731) X4.

Conclusion: 49,XXXXY karyotype is considered as the rarest sex chromosome aneuploidy syndrome. To our knowledge, this study is the first report of a patient with 49,XXXXY syndrome from Oman.

Keywords: Aneuploidy, dysmorphism, 49, XXXXY, Klinefelter syndrome.

Introduction

49,XXXXY syndrome was first described by Fraccaro et al. (1), and it is the rarest and most severe phenotype of Klinefelter syndrome, with an incidence of 1:85,000 to 1:100,000 male births (2,3). It is characterized by a triad of hypogonadism, mental retardation, and musculoskeletal manifestations (4). In this study, we present the case of a 2-year-old male child with a karyotype of 49,XXXXY; the first such occurrence to be reported from Oman.

Case Presentation

A 2-years old male patient with dysmorphic features, congenital cardiac defect, abnormal genitalia, and inguinal hernia, was referred for genetic evaluation and work up. Antenatally, he was found to have intrauterine growth retardation and was delivered vaginally at term with a birth weight of 2.2 kg. The patient required resuscitation and phototherapy for jaundice. He was born to 31-year old mother and 28-year old father in a non-consanguineous union. The patient had three older siblings who were normal.

Post-delivery, the patient was noted to have a murmur during a physical examination. Echocardiography indicated a ventricular septal defect (perimembranous VSD). He was then started on anti-failure medications with regular follow ups at Cardiology Outpatient Department. The patient underwent VSD repair and right inguinal hernia repair post-delivery. The patient history obtained from the mother revealed delayed developmental milestones, e.g. inability to walk and sit without support, delayed speech, and inability to hold objects with both hands.

On physical examination, the patient profile was as follows: weight—9.2 kg (90th percentile), height—77 cm (5th percentile), and head circumference—47 cm (<3rd percentile). The patient was observed to have short stature, generalized hypotonia, microcephaly, frontal bossing, hirsutism, low-set posteriorly rotated dysplastic ears, deep-seated eyes, hypertelorism, bluish sclera, synophrys, up-slanting palpebral fissures, flat depressed nasal bridge, prominent nasal tip, saddle-shaped nose, wide smooth philtrum, micrognathia, short neck, and bilateral large first toes (Figure 1). Genital

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organ examination revealed bilateral undescended testes, micropenis, and small scrotum. An abdominal X-ray noted bowel loop dilatation down to the rectum projecting over the right lower pelvis (Right sided inguinal hernia). A chest X-ray reported cardiomegaly with plethoric lung fields. Chromosomal analysis of a peripheral blood sample from the patient revealed a karyotype of 49,XXXXY and comparative genomic hybridization (CGH) array analysis revealed a 155,065 kilo base pair duplication on chromosome Xp22.33q28 (168,546, −155,233,731) X4 (Figures 2 and 3).

Discussion

49, XXXXY syndrome is one of the rarest sex chromosome aberrations. It affects almost 1 in 85,000 to 1 in 100,000 new-born males (5). Such an aberration occurs as a result of nondisjunction of the X chromosome during meiosis I and meiosis II (1). Sometimes, it is named as a variant of Klinefelter syndrome and has been reported to have a more complex clinical phenotype (6,7).

Figure 1. *(A and B). Facial phenotypes of the patient: Note frontal bossing, hirsutism, low-set posteriorly rotated dysplastic ears, deep-seated eyes, hypertelorism, bluish sclera, synophrys, up-slanting palpebral fissures, flat depressed nasal bridge, prominent nasal tip, saddle-shaped nose, wide smooth philtrum, micrognathia, and short neck.*

Having additional copies of the X chromosome and, therefore, an extra dosage of genes contributes to abnormal growth pathways and organ development (3,6). 49, XXXXY is usually not an inherited condition, with a recurrence rate of almost 1% (1,4).

Antenatally, some fetuses with the condition might develop intrauterine growth restriction, as well as low birth weight post-delivery (1,7,8). In the current case, intrauterine growth restriction was one of the main findings in the antenatal period.

Usually, individuals with 49, XXXXY syndrome present with cognitive problems and developmental delay. Developmental dyspraxia is the main attributer to language and motor impairment (6,8). Hypotonia and lack of coordination can contribute to delay in the development of motor skills, such as standing, sitting, and walking. In our patient, milestone delays were clearly observed and documented. For instance, the child was unable to walk or sit without support at one year and 4 months of age, had speech delays and demonstrated an inability to hold objects with both hands.

Males with 49, XXXXY present with distinctive facial features like micrognathia, hypertelorism, up-slanting palpebral fissure, low nasal bridge with epicanthic folds, and low-set ears with up-slanting eyes (1,4). Most of these characteristics were identified in our patient, with additional features, such as frontal bossing, bluish sclera, and synophrys was also observed.

Structural congenital heart defects are found in 15% to 20% of cases of Klinefelter syndrome (8). Congenital heart defects like atrial septal defect (ASD), ventricular septal defect (VSD), Patent ductus arteriosus (PDA), Fallot's Tetralogy, and pulmonary stenosis have been reported (9,10). VSD/ASD with pulmonary hypertension was identified in the patient reported here.

Abnormal genital organ development at birth has been described in most reported cases in the literature (1–4,11,12). In addition, testosterone deficiency in individuals with this syndrome leads to

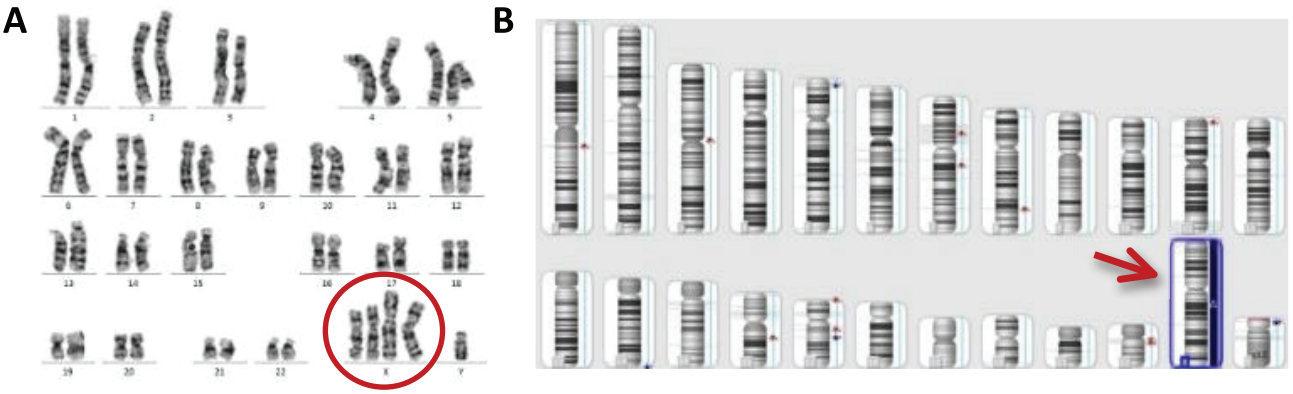

Figure 2. *Cytogenetic analyses of the index patient. (A) Karyotype showing 49, XXXXY profile. (B) Karyoview indicating increased dosage of chromosome X.*

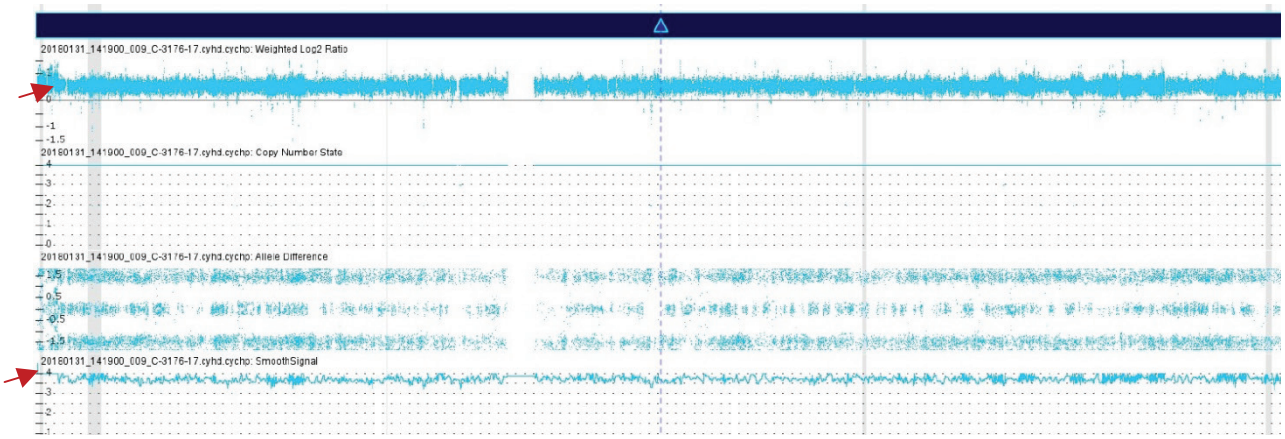

Figure 3. *aCGH Ideogram view showing the extra dosage of chromosome X (red Arrow).*

hypergonadotropic hypogonadism (3,6). In our patient, micropenis, undescended testes, and small scrotum were noted. In addition to all the presented features, he also exhibited short stature, brachydactyly, bilateral large first toes, and an inguinal hernia that was repaired surgically at the age of 1 year.

In conclusion, we report a case with 49, XXXXY syndrome, a variant of Klinefelter syndrome. To the best of author's knowledge, this is the first case reported in Oman with such a complex presentation. In clinical practice, sex chromosome abnormalities should usually be excluded first in cases presenting with developmental delays, short stature, congenital heart defect, and abnormal genitalia. Comprehensive multidisciplinary health care and early rehabilitation and educational interventional strategies are essential in managing such cases.

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List of Abbreviations

ASD	Atrial septal defect
GCC	Gulf Cooperation Council Countries Middle East
VSD	ventricular septal defect

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Declaration of conflicting interests

The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

Ethical approval was sought from the Royal Hospital Research Ethics Committee. Date October 2019.

Consent for publication

A written informed consent was obtained from the parents of the patient at the National Genetics Center in Oman for publication and accompanying images of the case report.

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