First Report of Two Rare Entities in a Family: 49,XXXXY and 45,X

Yavuz Şahin¹ Aysegül Özcan²

¹Department of Medical Genetics, Necip Fazıl City Hospital, Kahramanmaraş, Turkey

²Department of Medical Genetics, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey

Address for correspondence Yavuz Şahin, MD, Department of Medical Genetics, Necip Fazıl City Hospital, Kahramanmaraş, 46050, Turkey (e-mail: mdysahin@gmail.com).

J Pediatr Genet 2017;6:174–176.

Abstract

49,XXXXY and 45,X syndromes are sex chromosome aneuploidies in which the affected individuals present with hypergonadotropic hypogonadism, short or long stature, and skeletal malformations. Psychological, endocrinological, and orthopaedic disorders constitute the major problems in the clinical follow-up. We report a family with two rare entities: 49,XXXXY and 45,X. Sex chromosome abnormalities should especially be in mind in the evaluation of patients with micropenis, mental retardation, and hypergonadotropic hypogonadism. Management mandates a multidisciplinary approach with pediatric endocrinology, pediatric surgery, orthopaedics, psychiatry, and clinical genetic evaluations. To our knowledge, our cases are the first to report the sibling patients with 49,XXXXY and 45,X.

Keywords

- ▶ 49,XXXXY
- ▶ 45,X
- ▶ meiotic segregation

Introduction

Approximately half of all chromosomal anomalies comprise abnormal number of X and Y chromosomes, called sex chromosome aneuploidy, with a frequency of 1:400.¹ Among those, Klinefelter's syndrome (KS; 47,XXY) is the most common aneuploidy and affects approximately 1/500 male births.² On the other hand, total or partial absence of one sex chromosome, Turner's syndrome (TS) (45,X), has an incidence of 1:2,500 for live female births.³ However, rare syndrome variants with X and Y polysomy have been reported including 48,XXXY, 48,XXYY, and 49,XXXXY. This chromosomal disorder is caused by the nondisjunction of the X chromosome during meiosis I and meiosis II.⁴

The 49,XXXXY, considered as a severe variant of KS, is associated with a triad of mental retardation (MR), musculoskeletal malformation, and hypogonadism.⁵ Microcephaly, ocular hypertelorism, upslanting palpebral fissures, midface hypoplasia, flat nasal bridge, epicanthic folds, low-set ears, genu valgum, pes cavus, radioulnar synostosis, and genital abnormalities may be present.^{2,4–6} The intelligence quotient (IQ) of boys with 49,XXXXY ranges from 20 to 60. Other sex

chromosomal aneuploidy TS is associated with several morbidities such as short stature, primary gonadal deficiency, horseshoe kidney, and coarctation of the aorta.⁷

Herein, we present the phenotypic and chromosomal findings in a 12-year-old boy with 49,XXXXY and his 18-year-old sister with 45,X. Such family has never been reported in the literature previously.

Case Report

Case 1

A 12-year-old male was referred for intellectual disability and micropenis. Delivery was at term and the birth weight was 1,600 g. Marriage was consanguineous. His mother was 32 years old and his father was 33 years old. Notable findings in prenatal ultrasonography were intrauterine growth retardation, abnormal posture in lower extremities, and extensive edema. Patient history obtained from parents revealed unsupported sitting by 2 years and the first walk at 7 years. According to history, patient was treated for inward rotation of the foot and the knee cap and had benefit from the treatment. On physical examination, weight was 47 kg (75–90p), height was 152 cm (90p), and

received

October 11, 2016

accepted

December 15, 2016

published online

January 18, 2017

Copyright © 2017 by Georg Thieme Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0037-1598027>.
ISSN 2146-4596.

head circumference was 53 cm (50p). Broad forehead, slightly down slanted palpebral fissures, large and prominent nasal root, plump cheek structure, small ears located posteriorly, and micrognathia were the dysmorphic findings of the patient's face. Patient had eunuchoid body structure and truncal obesity. Slender fingers of both hands, big toes on both feet, inward looking patella, and narrow nail beds were detected. He has hypergonadotropic hypogonadism and micropenis. Complete blood counts, liver and renal function tests, and ions were within the normal range. Ophthalmoscopic and hearing evaluation was normal. Echocardiographic examination was normal. In the psychometric assessment, patient was defined as borderline mentally retarded (IQ: 80). Chromosomal analysis showed 49, XXXYY structure (→Fig. 1D). Informed consent was obtained from patient's family.

Case 2

An 18-year-old female, sister of patient 1, with delayed puberty and hypergonadotropic hypogonadism has applied for genetic evaluation. No information about prenatal history could be obtained, but the dorsal foot and hand edema was conspicuous in the natal history. Postnatal mental and motor developmental stages were normal. She weighed 62 kg (25 percentile), her height was 157 cm (<3 percentile), and her head circumference was 55 (50 percentile). Psychometric evaluation revealed normal intelligence. On physical examination, multiple nevus, metacarpal shortness, cubitus valgus, and short broad neck were noted. Ultrasonography examination

revealed a normal measurement of uterus. The heart was normal at echocardiographic evaluation. Chromosomal analysis showed 45,X structure (→Fig. 1C). Informed consent was obtained from patient's family.

Karyotype analysis was performed on parents and found to be normal (→Fig. 1A, B).

Discussion

Sex chromosome aneuploidies have been previously associated with pre- and post natal growth deficiency, neurocognitive delays, hypogenitalism, musculoskeletal abnormalities, dysmorphic features, and cardiovascular anomalies, but these findings are not as serious as chromosomal aneuploidies. Sex chromosome aneuploidies usually share many common phenotypic features, fertility problems, and neuropsychological findings, but they also can be distinguished with various features. Among these, 45,X, known as Turner's syndrome, the most common sex chromosome abnormality in female with a frequency of 1/2,500 to 3,000 live-born, is characterized with short stature, gonadal dysgenesis, short and webbed neck, low posterior hairline, broad chest, widespread nipples, cubitus valgus, short fourth and fifth metacarpals, multiple pigmented nevi, primary amenorrhea, lack of secondary sexual characteristics, and cardiovascular and renal anomalies.⁷ In our case, primary amenorrhea, short stature, multiple pigmented nevi, cubitus valgus, shortness of the fourth and fifth metacarpals, and short stature were present. Patient's mental motor development stages were completely normal.

Fig. 1 (A–D) Karyotype of the patients and parents (GTG banding, ~400–450 bands).

On the other hand, the 49,XXXXY, one of the rarest sex chromosome disorders, has been associated pre- and postnatal growth deficiency, neurodevelopmental delay with MR, hypogonadism with micropenis, cryptorchidism, scrotal hypoplasia, and skeletal and facial abnormalities.⁵ Similar to KS, tall stature is one of the most important physical evidence seen in 49,XXXXY syndrome. In spite of the fact that our patient was in the prepuberty period and her height was in 90 percentile, we believe that it will rise above 90 percentile with the puberty.

While no obvious dysmorphic evidence accompanies the 48,XXYY syndrome, anomalies such as joint abnormalities, muscle weakness, dental problems, and gynecomastia are commonly seen.⁸ In our case, the patient had mild dysmorphic features, foot deformities, and truncal obesity. While MR is rare in KS, it can be seen in 48,XXYY syndrome that the learning difficulties are present in almost all cases. In our patient, there were significant delays in the mental and motor development stages. Also, the patient's aggressive behavior was consistent with the previously defined psychiatric symptoms in this syndrome.

49,XXXXY and 45,X are usually not hereditary. Recurrence rate is approximately 1%. In 49,XXXXY patients, the extra X chromosomes are known to be maternal origins, and spawn from a double nondisjunction during meiosis I and II.⁴ There is no evidence between maternal age and 49,XXXXY.⁹ Consanguineous marriage of parents and sex chromosome aneuploidies in both siblings together brought out the thought of a defect in the genes responsible for the segregation of sex chromosomes. Consideration of exceptional cases of segregation failure may improve our finding out the mechanism of nondisjunction. Such study will illuminate our knowledge about the mechanisms of the aneuploidies.

In conclusion, we report a family with two rare entities: 49,XXXXY and 45,X. In routine clinical practice, sex chromosome abnormalities should especially be in mind in the evaluation of patients with MR, short or long stature, micropenis, and fertility problems. Management mandates include a comprehensive, multidisciplinary evaluation, such as pediatric neurology, pediatric endocrinology, pediatric surgery, orthopaedics, and psychiatry, and clinical genetic evaluations.

Conflict of Interest

None.

References

- 1 Nielsen J, Wohler M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Hum Genet* 1991;87(1):81–83
- 2 Visootsak J, Graham JM Jr. Klinefelter syndrome and other sex chromosomal aneuploidies. *Orphanet J Rare Dis* 2006;1:42. Doi: 10.1186/1750-1172-1-42
- 3 Lippe B. Turner syndrome. *Endocrinol Metab Clin North Am* 1991; 20(1):121–152
- 4 Peet J, Weaver DD, Vance GH. 49,XXXXY: a distinct phenotype. Three new cases and review. *J Med Genet* 1998;35(5):420–424
- 5 Linden MG, Bender BG, Robinson A. Sex chromosome tetrasomy and pentasomy. *Pediatrics* 1995;96(4 Pt 1):672–682
- 6 Pallister PD. 49,XXXXY syndrome. *Am J Med Genet* 1982;13(3): 337–339
- 7 Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; 351(12):1227–1238
- 8 Tartaglia N, Ayari N, Howell S, D'Epagnier C, Zeitler P. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome. *Acta Paediatr* 2011;100(6):851–860
- 9 Ng SF, Boo NY, Wu LL, Shuib S. A rare case of ambiguous genitalia. *Singapore Med J* 2007;48(9):858–861