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ORIGINAL ARTICLE

Dysmorphic features as an early presentation of rare sex chromosome aneuploidies

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ABSTRACT

Background: The 48,XXXY syndrome is a rare sex chromosome aneuploidy, presenting characteristic features such as prominent facial and skeletal malformations, intrauterine growth retardation, and psychomotor retardation. Psychological, endocrinological, auxological issues, and orthopedic disorders constitute the major problems in this syndrome, which require long-term clinical and biochemical follow-up.

Materials and Methods: In the present investigation, chromosomal analysis (standard chromosomal karyotyping) and fluorescence in situ hybridization (FISH) were performed according to the standard protocols.

Results: Here, we report a single affected individual (boy) having Saudi origin, suffering from rare sex chromosomal aneuploidy. The main presenting complaint is the obvious dysmorphic features associated with developmental delay, epicanthal folds, short nose, prominent philtrum, low seated ears, and overlapping toes. Chromosomal analysis and FISH revealed an extra two X chromosomes, thus causing the 48,XXXY syndrome.

Conclusion: Patients with facial dysmorphism, developmental delay, unexplained hypotonia, and accompanying behavioral disturbances must be tested for sex chromosome aneuploidies. Management and proper diagnosis require a multidisciplinary approach involving pediatric endocrinology, pediatric surgery, orthopedics, psychiatry, and clinical genetic evaluations. Considering 48,XXXY syndrome as a highly severe disorder, cytogenetic tests should be performed as the first diagnostic approach.

Keywords: Sex chromosome aneuploidies, 48,XXXY syndrome, XXXY syndrome, Klinefelter syndrome variant.

Introduction

Sex chromosomal aneuploidies (SCAs) are described as genetic conditions having variation in the number of chromosomes. The most common SCA is Klinefelter syndrome (KS) (1,2). The 47,XXY karyotype (gain in X chromosome) corresponds to 80%, while the 48,XXXY, 48,XXYY, and the 49,XXXXY correspond to the remaining 20%. Prevalence of 1/500 males has been reported in KS, while characteristic features include infertility, eunuchoidism, gynecomastia, small penis/testes, and hypergonadotropic hypogonadism (3).

48,XXXY syndrome is a rare genetic disorder, characterized by a sex chromosome aneuploidy, where males have two extra X chromosomes (4). The syndrome has diverse and severe phenotypic spectrum, including cognitive and behavioral problems, taurodontism, and infertility (4,5). The 48,XXXY, 48,XXYY, and 49,XXXXY share some particular features and are often characterized as "variants" of KS (47,XXY), but trisomy and tetrasomy of the X chromosome show a different phenotype with more severe clinical features (3).

This condition is not inherited and likely results from random errors in the cell division. Its prevalence is estimated as high as 1/17,000 to 1/50,000 male births (5,6). 48,XXXY syndrome can be from nondisjunction in the paternal sperm or nondisjunction in the maternal oocyte (5).

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48,XXXY is often compared with 47,XXY/KS due to shared features such as tall stature and hypogonadism. The 48,XXXY syndromes have additional features such as severe physical anomalies, congenital malformations, medical problems, and psychological features which can be presented earlier during infancy and fetal life (7,8).

In the study presented here, the infant belongs to Saudi consanguineous couple. The proband had facial dysmorphisms associated with motor delayed, generalized hypotonia, and micropenis. Treatment of 48,XXXY syndrome is different for each individual depending on the features observed and often involves the coordinated efforts of a multidisciplinary team of specialists. Future research should focus on the early presentation of sex chromosome aneuploidies, genotype–phenotype relationships, and the development of evidence-based treatments.

Materials and Methods

Human subject

In the present study, we clinically investigated a single affected individual (proband) from Saudi origin family. The proband underwent a comprehensive clinical evaluation by a general pediatrician, endocrinologist, and clinical geneticist. Written informed consent for publication of photographs and clinical results was obtained from the patients.

Cytogenetic analysis

Karyotyping

Standard chromosomal karyotyping was performed on the lymphocytes from peripheral blood.

The Giemsa Banding by trypsin, BPHS 400, 20 cells were counted at the metaphases. Ten cells of metaphases were analyzed and karyotyped showed the presence of three copies of chromosome (X) and one copy of chromosome (Y) in all metaphase examined.

Fluorescence *in situ* hybridization

The fluorescence *in situ* hybridization (FISH) study was performed using Probe set: Xcen (Xp11.1-q11.1)/ LSI SRY (Yp11.3) for sex chromatin study according to standard methods.

Results

Clinical presentation

The proband belongs to a Saudi consanguineous family. The proband is a boy (age: 10 months), a product of preterm (34–35 weeks), and delivered to 47-years-old mother. The mother had no history of medical illness, yet the cesarean section was performed due to the breech presentation with APGAR score (Activity, Pulse, Grimace, Appearance, Respiration) 8 at 1 minute and 8 at 5 minutes. Weight at the time of birth was recorded 2,310 g (below the third centile), while the total length was 49 cm (on the 50th centile) and head circumference of 33 cm (between 10th and 25th centile) was observed. The patient was admitted to the neonatal intensive care unit with respiratory distress having the impression of respiratory distress syndrome for 19 days. The proband was then shifted to bilevel positive airway pressure (BiPAP) for 4 days, continuous positive airway pressure for 2 days, and then on the O2 nasal cannula. Cultures were prepared and antibiotics were started, upon admission, the proband was noticed to have minor dysmorphism and micropenis. Specific investigations revealed intraventricular hemorrhage grade I and decrease in G6PD enzyme activity. Finally, the proband was discharged from hospital in good condition without the O2 nasal cannula, on oral feeding, and asked for a regular follow-up.

Cytogenetic analysis

Chromosomal analysis and karyotyping from peripheral blood lymphocytes revealed 48,XXXY (KS variant) (Figure 1A). FISH analysis showed three copies of chromosome

(X) and one copy of chromosome (Y), respectively (Figure 1B and C).

Clinical follow-up

During the follow-up in the genetic clinic, the proband had features such as obvious dysmorphism, failure to thrive, and delay in achieving milestones. There was no history of abnormal movements, convulsion, or specific odors.

Examination of the proband at 10 months of age showed a total body weight of 6.3 kg (below the third centile), height 76 cm (between 50th and 75th centile), and head

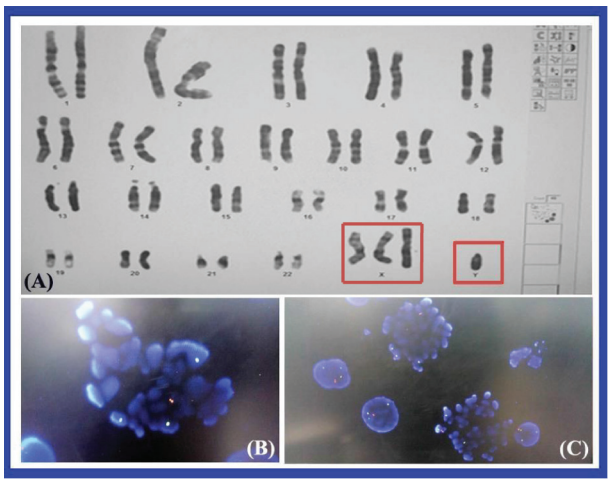

Figure 1. *(A) Chromosomal karyotype revealed three copies of chromosome (X) and one copy of chromosome (Y) in all metaphase examined (No. of cells Examined 200). (B and C) FISH analysis revealed three signals of chromosome (X) and one signal of chromosome (Y) in the examined interphase.*

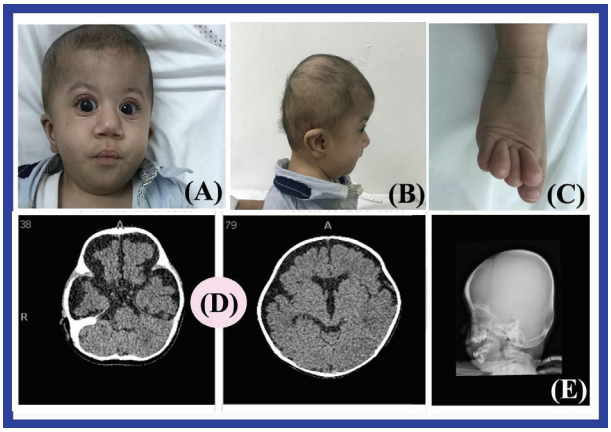

Figure 2. *(A) Proband suffering from 48,XXXY syndrome. Features include narrow and upward slanted palpebral fissures, epicanthic fold a short nose, and a prominent philtrum. (B) The proband having a characteristic low set ear. (C) Overlapping toes. (D) The brain MRI performed at the age of 10 months. (E) Radiological examination of the proband.*

circumference 43 cm (10th centile). He also displayed dysmorphic features including triangle face, narrow forehead, brachycephaly, upward slanting palpebral fissures, epicanthal folds, short nose, prominent philtrum, low seated ears, and overlapping toes (Figure 2A–C).

Developmental and neurological examination

The proband showed underdeveloped features and gave characteristics of a 5-month-old baby. He could roll over, look around, brings hands to midline, sitting with support, while raised his head and smiled socially at an age of 3 months. He is fully conscious neurologically, interesting to surroundings, pupils 3 mm bilaterally equally reactive, normal extraocular muscle, symmetrical face, with generalized hypotonia and areflexia. Followed by 180° examination, the proband had a head lag and was unable to stand alone with positive Ragdoll Position. The brain computed tomography revealed a normal size, an enlarged extra-axial space, subarachnoid basal cisterns, no midline shift or deformity, and a normal ventricular system (Figure 2D).

Genital examination

The probands genitalia exhibited bilateral palpable testes in the scrotum, stretched penile length of 3 cm (10%), and no hyperpigmentation or hypospadias was observed. The serum follicular-stimulating hormones (FSH) and luteinizing hormones (LH) concentrations were within normal (0.526 and 0.1 mlU/ml) range, respectively. (FSH pre-pubertal normal value below 1 mIU/ml) , (LH pre-pubertal value below 0.2 mIU/ml). The testosterone level was (0.087 nmol/l) observed within the normal limit (0.22–2.9 nmol/l). Human chorionic gonadotropin (HCG) stimulation was performed according to standard procedures. The proband showed normal testosterone response for male and normal functioning testicle, which indicated that hypogonadism is an evolving process. The pre-stimulation testosterone: 0.087 nmol/l and post HCG stimulation testosterone: 2.8 nmol/l were under normal range. The proband did not reveal any other abnormalities such as respiratory, abdominal, cardiovascular, dysfunction, and different laboratory tests such as complete blood count, liver function test, renal function test, and serum electrolytes tests were within the normal level. The proband was also normal for metabolic screening through tandem mass spectrometry for 17 common inborn errors of metabolism in Saudi Arabia, serum ammonia, serum lactate, and venous blood gases. The skeletal survey reported brachycephalic skull, otherwise, no gross skeletal deformities were observed (Figure 2E).

Discussion

Sex chromosomes aneuploidies are characterized by having several phenotypic features, diverse neuropsychological findings, and thus represent a distinct group of disorders that may be recognized in relation to peculiar findings. Several clinical features such as dysmorphic, psychological, endocrinological, and orthopedic constitute the syndrome. The additional X chromosomes (although mostly inactive) cause a corresponding more severe phenotype, including severe dysmorphism, affect sexual development, developmental delay, and intellectual disability. Hence, the 48,XXXY syndrome is more severe in terms of clinical symptoms and presentation as compared to KS. Hypogonadism phenotype may include micropenis, cryptorchidism, scrotal hypoplasia, or hypergonadotropic hypogonadism (8–10).

Children with 48,XXXY syndrome commonly have developmental delay, mental retardation, failure to thrive, and endocrine problems with secondary bone complications. Therefore, regular and frequent follow-up with hormonal assessment is mandatory to prevent the mentioned complications.

Conclusion

In the present study, we emphasize a major problem in sex chromosome aneuploidies, and dysmorphic facial features. We suggest that the clinicians should consider the possibility of sex chromosome aneuploidies in patients presenting typical features of facial dysmorphism (Head bossing, low-set posteriorly rotated ears, pinched nose, long philtrum, depressed nasal bridge, epicanthal fold, micrognathia, micropenis, and digit abnormalities), developmental delay, and perform a standard chromosomal analysis.

Finally, we emphasize the need for longitudinal data, as such information will provide profile encompassing care recommendations and provide proper management of 48,XXXY patients. Increasing awareness, research based on molecular diagnosis is highly recommended in order

to elucidate the long-term outcome of these patients and achieving therapeutic goals.

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Ethical approval
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