

Rare sex chromosome aneuploidies: 49,XXXXY and 48,XXXY syndromes

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49,XXXXY and 48,XXXY syndromes are rare gonosomal aneuploidies in which the affected individuals present with characteristic facial and skeletal malformations, intrauterine growth retardation, and psychomotor retardation. Psychological, endocrinologic and orthopedic disorders constitute the major problems in the clinical follow-up. Sex chromosome abnormalities should especially be kept in mind in the evaluation of patients with micropenis, mental retardation and accompanying behavioral disturbances. Management mandates a multidisciplinary approach with pediatric endocrinology, pediatric surgery, orthopedics, psychiatry, and clinical genetic evaluations.

Key words: 49,XXXXY, 48,XXXY, gonosomal aneuploidy, hypogenitalism, micropenis, hip dysplasia.

Sex chromosome aneuploidies, among which 45,X, 47,XXY, 47,XXX and 47,XYY constitute the majority, are estimated to occur in 1/400 livebirths¹. 48,XXYY and X chromosome tetrasomies (48,XXXX in females and 49,XXXXY in males) are encountered rarely, the incidence of 49,XXXXY being 1 per 85,000 to 1 per 100,000 births^{2,3}.

49,XXXXY syndrome, first reported in 1960, was considered a Klinefelter variant until 1998, when it was delineated as a distinct phenotype^{3,4}. The main findings include hypogenitalism, multiple skeletal findings and mental retardation^{5,6}. There is often intrauterine growth retardation, and multiple malformations may accompany^{7,8}. Microcephaly, rounded face, midface hypoplasia, ocular hypertelorism, epicanthic folds, flat nasal bridge, upslanting palpebral fissures, bifid uvula, upturned nose, low-set ears, heart defects, genu valgum, pes cavus, fifth finger clinodactyly, and small genitalia with hypergonadotropic hypogonadism may be present^{1,3,9-14}. Micrognathia and cleft palate may be occasionally present, as well as cardiac malformations, usually patent ductus arteriosus⁹. Males with 48,XXXY syndrome can be of average or tall stature¹.

Intelligence quotient is usually between 20 to 60, with a mean value of 35. Significant delay in speech is present, while non-verbal skills are better preserved. The patients are reported to have a rather shy and friendly personality; however, occasional irritability and temper tantrums with low frustration tolerance may accompany¹⁰. Psychomotor problems constitute a major area of clinical follow-up in these patients, especially during adolescence, along with endocrinological follow-up.

Case Reports

Case 1

A 17-month-old male infant was referred for microcephaly and micropenis. His past history revealed an operation at two months of age for developmental hip dysplasia. He achieved head control at five months of age and could sit with support at six months. On physical examination, his weight was 7700 g (<3rd centile), length 74 cm (10th-25th centiles) and head circumference 43 cm (<3rd centile). Left-sided ptosis, bilateral epicanthic folds, narrow and upward slanted palpebral fissures

and limited lateral movement of the right eye, a short nose with anteverted nares, and a prominent philtrum were noted (Fig. 1). He also had bilateral clinodactyly of the fifth fingers and overriding toes. Stretched penile length of 2.5 x 1 cm and a hypoplastic scrotum were noticed in the genitourinary system examination. Left testis was palpable in the scrotum whereas the right testis was palpable along the upper border of the inguinal canal. There was also a sacral dimple. Basal levels of testosterone (T) and dihydrotestosterone (DHT) were less than 20 ng/dl (245-1600 ng/dl) and 23.9 pg/ml (<50 pg/ml), respectively. Following stimulation with human chorionic gonadotropin (HCG) for three days (3000 unit/m²/day), the level of T was 47 ng/dl and of DHT was 52.9 pg/ml (T/DHT ratio: 9, normal for this age). Karyotype analysis from peripheral blood lymphocytes revealed 49,XXXXY. Echocardiographic examination was normal. Cranial magnetic resonance imaging demonstrated ventricular dilatation, hyperintense nonspecific lesions on white matter, possibly indicating gliosis

or demyelination areas, and a thin corpus callosum. Abdominal ultrasonography showed an anechoic cystic lesion of 10x8 mm at the upper pole of the spleen. The patient was able to walk at 22 months of age and talk with sentences of two to three words at 2^{8/12} years of age. Toilet training was achieved at 2^{6/12} years.

Case 2

A 14^{10/12}-year-old mentally retarded male adolescent with aggressive mode of behavior and weak social relations was referred for a recently recognized gait disturbance. Mental and motor developmental stages were delayed. He had been followed for primary hypothyroidism and was on Na-L-thyroxine therapy. He weighed 51.3 kg (25th-50th centiles) and his height was 156 cm (10th-25th centiles). On physical examination, pes planus, genu valgum particularly on the right side, and increased degree of lordosis were noted (Fig. 2). Stretched penile length of 6.5 x 1.5 cm with testicular volume of 3 ml and pubarche stage 3 were noted on



Fig. 1. Patient 1 with 49,XXXXY syndrome. Left-sided ptosis, bilateral epicanthic folds, narrow and upward slanted palpebral fissures, a short nose with anteverted nares, and a prominent philtrum are noted.



Fig. 2. Hip roentgenography of Patient 2. Genu valgum particularly on the right side is noted.

the genitourinary system examination. Both testes were palpable in the scrotum. Karyotype analysis from peripheral blood lymphocytes revealed 48,XXXXY. Echocardiographic evaluation was normal except for a mitral valve insufficiency. Follicle stimulating hormone (FSH) levels of 28.2 mIU/ml (1.37-13.58 mIU/ml) and luteinizing hormone (LH) levels of 12.66 mIU/ml (1.14-8.75 mIU/ml) were measured. Testosterone level was 76.6 ng/dl (245-1600 ng/dl), consistent with hypergonadotropic hypogonadism. Osteoporosis was noted in the skeletal survey and a decreased bone density was determined (z-score,-3.09).

Discussion

Sex chromosome aneuploidies usually share many phenotypic features and neuropsychological findings, and they represent a distinct group of disorders that may be recognized in relation to peculiar findings. Psychological, endocrinologic and orthopedic disorders constitute the major problems in the clinical follow-up.

Hypogonadism may present as micropenis, cryptorchidism, scrotal hypoplasia or hypergonadotropic hypogonadism^{1,3,11-13}. Micropenis describes an abnormally small penis with a normal configuration. It constitutes a sign, rather than a diagnosis. A phallic length, which is 2.5 or more standard deviations below the mean, should be considered as abnormal. The underlying endocrinological etiologies are classified as hypogonadotropic hypogonadism, primary hypogonadism, androgen insensitivity, or idiopathic. The cause may be hormonal, testicular, end organ resistance, or iatrogenic¹⁵. Both of our patients had hypogonadism and micropenis.

It is known that decreased bone mineral density occurs in 25% of patients with Klinefelter syndrome, and it possibly reflects the decreased bone formation and increased bone resorption. There seems to be an inverse relationship between the extent of the bone deficit and serum testosterone levels in Klinefelter syndrome, which suggests that osteoporosis in these patients is the result of hypogonadism rather than being of genetic origin¹⁶. Our second patient had osteoporosis, with a Z-score of -3.09, which was thought to be a result of hypogonadism.

The patients have low-normal intelligence with lower performance in verbal tests. Language delay constitutes a major concern for the

families. Patients are described behaviorally as having a quiet, sensitive and reserved personality; however, increased incidence of anxiety, depression and substance abuse is reported, which may be associated with the language difficulty⁹. Management of these patients should include psychoeducational as well as speech therapy.

Both of our patients suffered from hip dysplasia, the first patient being operated at two months of age. The second patient suffered from genu valgum and bilateral acetabular dysplasia. Features consistent with epiphyseal dysplasia were described in chromosomal aneuploidies¹⁷. Dysplasia of the right hip along with the sex chromosome aneuploidy and behavior disturbances with aggressiveness were formerly described in a 37-year-old obese man¹⁸.

The extra X chromosomes are known to be maternal in origin, rising from a double non-disjunction during meiosis I and II¹⁹⁻²¹. There is no apparent association with advanced maternal age^{3,19-20}.

In conclusion, we emphasize the major problems in sex chromosome aneuploidies, as well as minor dysmorphic facial features. Sex chromosome abnormalities should especially be kept in mind in the evaluation of patients with micropenis, mental retardation and accompanying behavioral disturbances. Management mandates a multidisciplinary approach with pediatric endocrinology, pediatric surgery, orthopedics, psychiatry, and clinical genetic evaluations.

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