Case Report

A new 48, XXYY/47, XYY syndrome associated with multiple skeletal abnormalities, congenital heart disease and mental retardation

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While the XYY and XXYY syndromes have been several time described in patients, the combination of both syndromes in an individual is a rare event and may result in a severe phenotype. In the present observation, a boy with congenital scoliosis due to segmented thoracic hemivertebra associated with radioulnar synostosis and congenital heart disease is described. Chromosome G-banding and FISH analysis demonstrated a de novo mosaic karyotype 48, XXYY/47, XYY in this patient. To the best of our knowledge, this is the first report of a combination of XYY and XXYY syndromes.

Keywords: 48, XXYY/47, XYY syndrome, congenital heart disease, multiple skeletal abnormalities

Introduction

Both XYY and XXYY syndromes are fairly common chromosomal abnormalities, with a prevalence of 1:1,000 to 1:17,000 live male births in general population, respectively.[1-3] However, the combination of both syndromes in individuals is a rare event and may result in a more severe phenotype due to the compounding effects of the additional X and Y chromosomes.

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The XYY is seldom detected during childhood or even in the adult. It is now well recognized that the majority of XYY males are phenotypically normal. However, a pattern of variable abnormalities including skeletal abnormalities and behavioural problems have been described and can lead to clinical suspicion of the XYY syndrome. The XXYY syndrome was previously considered to be a variant of the Klinefelter syndrome with hypogenitalism problems. However, several specific clinical features including mental retardation and psychiatric problems, have been reported and now it is recognized as a distinct clinical and genetic entity.

While congenital heart disease and radioulnar synostosis have been reported in XXYY and XYY syndromes, respectively,[4,5] the occurrence of other congenital skeletal abnormalities such as hemivertebra is unusual in these syndromes. We herein report a boy showing XYY/XXYY syndrome associated with multiple skeletal abnormalities and congenital heart disease.

Case Report

A 12-year-old boy was referred for congenital skeletal abnormalities and heart disease associated with development delay and moderate mental retardation. The patient was a third child to healthy non consanguineous Caucasian parents. Birth weight and birth height were normal. He was born with congenital scoliosis due to segmented hemivertebra between the tenth and twelfth thoracic vertebrae and had an atrial septal defect which regressed spontaneously at the age of one year.

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At the age of 10 months, he developed bilateral synostosis of the proximal radius and ulna. The progression of the scoliosis and the poor cosmetic appearance indicated that an operation was necessary. At the age of 6 years, he underwent a surgical correction for the hemivertebra.

On our physical examination at 12 years of age, his height was 160 cm (75th centile), weight 68.6 kg (>97th centile) and his head circumference was 52 cm (10th centile). He had subtle minor facial dysmorphism, namely, slight hypertelorism, bilateral epicanthic folds, a flat nasal bridge and full lower lip, long philtrum [Figure 1a-c] and a high palate. He had moderate mental retardation and presented gynecomastia with truncal obesity [Figure 1d]. In addition, he had a scoliosis and presented limitation of supination at the elbows [Figure 1e and f].

X-ray examination of the spine and the upper limbs was performed. It showed a persistent scoliosis due to segmented hemivertebra between tenth and twelfth thoracic vertebrae [Figure 2a and b]. The radiography of the upper limbs showed synostosis of the proximal radius and ulna, associated with dislocation of both radial heads [Figure 2c and d].

Cytogenetic and FISH Studies

Standard karyotype with G-banding was performed on lymphocytes from patient's peripheral blood sample using conventional protocols. We used 500 resolution's level for banding characterization. Fluorescence *in situ* Hybridization (FISH) was performed on interphase using centromeric specific probes (Vysis) DXZ1 (green probe) and DYZ3 (red probe), which hybridize to the X and Y chromosomes, respectively. Hybridizations were done according to the manufacturer's recommendations.

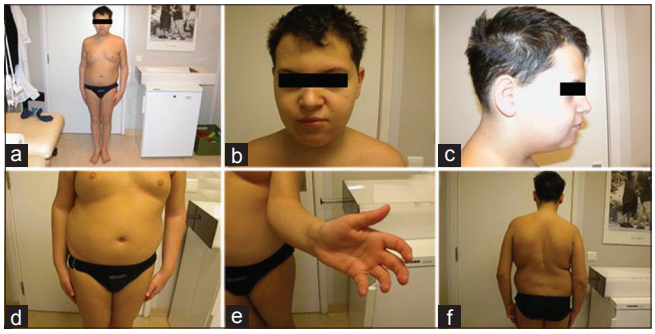

Figure 1: Full (a), frontal and lateral (b, c) views of the patient. (d) Note the gynecomastia and morbid obesity. (e) Limitation of supination. (f) Scoliosis

Results

The karyotype, performed on lymphocytes from peripheral blood, revealed the presence of 48, XXYY (67%)/47, XYY (33%) mosaic pattern. Figure 3 shows partial chromosome results (48, XXYY) with G-banding. Using FISH analysis, a total of 200 cells were examined and this analysis confirmed the previous result; 48, XXYY chromosomes were present in 74.5% and 47, XYY in 21.5% of the cells, respectively [Figure 4].

Discussion

There is a considerable difference between the clinical characteristics of patients with the 48, XXYY karyotype and those with a 47, XYY. Classically, individuals from the first group display developmental delays, hypogonadism, gynecomastia, an increased prevalence of varicose veins and stasis dermatitis, autism spectrum disorders and aggressive behavioral problems.[6-8] In addition, mild to moderate mental retardation is a frequent, but not an obligate finding in the 48, XXYY syndrome, and congenital heart disease has been reported in a few cases.[6,9]

The XYY syndrome is a relatively frequent syndrome but seldom detected during childhood or even in adults. It is now recognized that the majority of XYY males

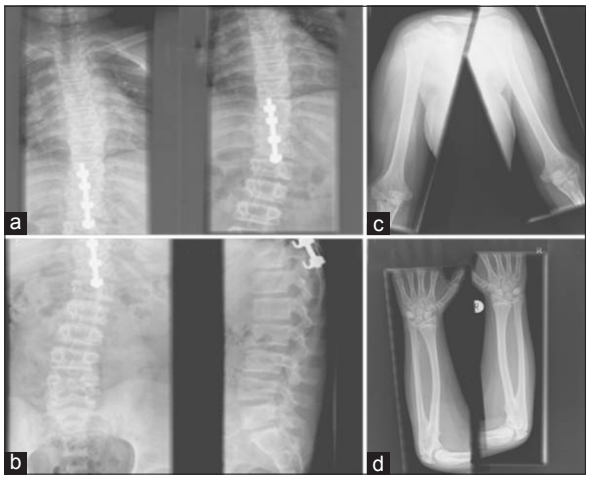

Figure 2: Postero-anterior radiographs of full spine (a, b). X-rays of left and right upper limbs (c, d)

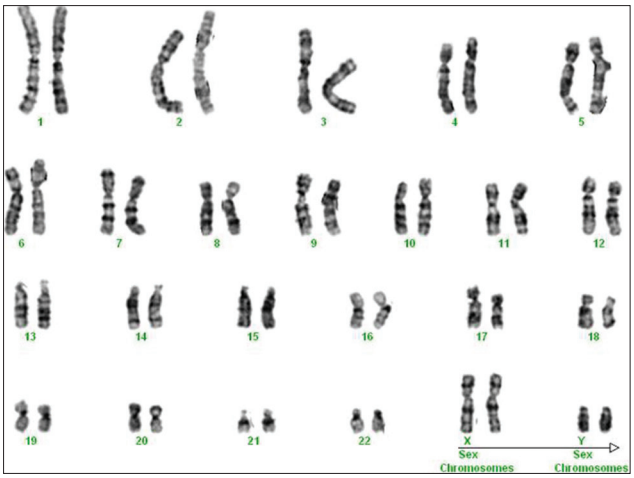

Figure 3: G-banding karyotype of peripheral lymphocytes showing 48, XXYY chromosomes (main cell line)

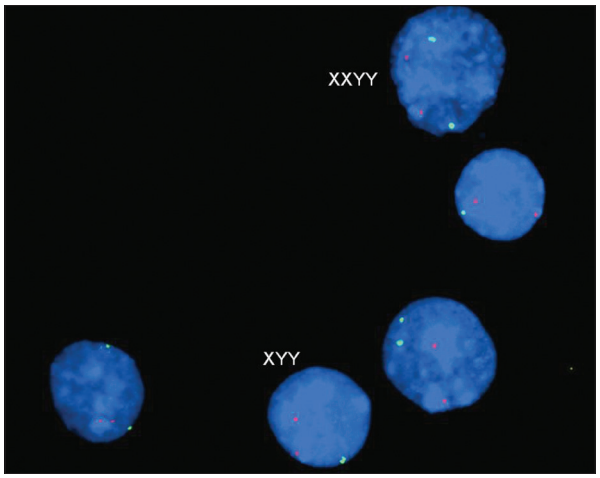

Figure 4: Interphase FISH with centromeric specific probes (Vysis) DXZ1 (green signal) and DYZ3 (red signal) showing XYY and XXYY lymphocyte nuclei

are phenotypically normal. Among the most common clinical features, tall stature, reduced IQ and poor motor coordination have been reported together with various quite non-specific dysmorphic features associated with minor skeletal abnormalities such as radioulnar synostosis.[4,10] The 47, XYY aneuploidy is always from paternal origin and results from nondisjunction in the second meiotic division or post zygotic mitosis. Fertilization of an X egg by a YY sperm would result in a conceptus with 47, XYY. However, the parental origin of the additional sex chromosomes is not well established in 48, XXYY patients. It can be paternally derived, resulting from nondisjunction at the first and second meiotic division during spermatogenesis.[2,11] One can speculate that the additional X chromosome can be maternally derived, resulting from either meiotic nondisjunction during gametogenesis, or from mitotic nondisjunction in the developing zygote, as in Klinefelter patients.[12]

The present patient had a combination of both XYY and XXYY features including mental retardation, congenital heart disease and radioulnar synostosis. Nevertheless, the hemivertebra which is a failure of vertebral formation carrying a risk of causing progressive scoliosis have not yet been reported in 47, XYY and 48, XXYY syndromes. Our patient presented mental retardation which could be attributed mainly to the polysomy, and probably to a skewed X inactivation as it has been previously reported.[13] Our case is a very rich observation, gathering the main typical features of 47, XYY and 48, XXYY syndromes with additional and unusual skeletal abnormalities. Its association should lead to cytogenetic studies. Surprisingly, this is the first report of a combination of XYY and XXYY syndromes.

Acknowledgements

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