Infertility in a new 46, XX male with positive SRY confirmed by fluorescence in situ hybridization: a case report

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Summary

The 46, XX male syndrome (de la Chapelle syndrome or 46, XX testicular disorder of sex development) is a rare form of sex reversal with complex mechanisms leading to a large spectrum of clinical manifestations ranging from ambiguous genitalia in the newborn to normal male phenotype. Therefore, diagnosis is established either pre- or early postnatal, or in adult life due to male infertility. In some cases, subtle clinical signs during childhood and puberty may be overlooked. A 28-year-old married man presented with azoospermia without erectile dysfunction. Between 9-14 years he was examined for the small testes and under-masculinized external genitalia but the diagnosis was not further clarified. At presentation, hormonal laboratory evaluation revealed hypergonadotropic hypogonadism. Chromosome analysis showed a 46, XX karyotype and translocation of SRY (testis-determining factor) from chromosome Y to chromosome X was identified by fluorescence in situ hybridization (FISH). Despite early subtle clinical signs of abnormal sexual development in this new 46, XX male syndrome, medical investigations were triggered by infertility.

Key words: 46, XX male; Infertility; Hypogonadism; Fluorescence in situ hybridization; Karyotype.

Introduction

Chromosomal anomalies are seen in about 10% of infertile men leading to testicular dysgenesis and oligo- or azoospermia. The 46, XX male syndrome is associated with infertility but also testosterone insufficiency. Due to major consequences on health and social life of the affected individuals, efforts have to be made towards an early diagnosis of the disease.

Case Report

In April 2005, a 28-year-old married man was referred to the outpatient service of the Department of Endocrinology of the University of Medicine and Pharmacy Cluj-Napoca with primary infertility and azoospermia. Between three and six years the patient was treated for stuttering and a minor form of anxiety. At the age of nine he was medically examined for underdeveloped external genitalia and small bilateral testes were noted. However, the diagnosis was not further clarified and therapy with human chorionic gonadotropin in a total dose of 6000 IU was administered.

At the age of 28, the patient claimed no erectile dysfunction and stated he had a normal sex life, with sexual intercourse two-three times a week. He and his wife were childless after three years of unprotected sexual activity. Physical examination revealed a height below the 5th percentile of normal height (1.67 m, body mass index = 23.0 kg/m^2) and a female distribution of fat mass. The testes were small and firm, the pubic hair had a female distribution and the patient had bilateral minor diffuse gynecomastia. An intelligence score of 85 was established. Testicular ultrasound revealed bilateral small testes (right and left testes: 2.8 and 1.6 ml, respectively). Osteopenia (T score L_1-L_4 = –2.1 SD, T score femoral neck = –1.3 SD, T score total hip = –1.1 SD) was detected by dual X-ray absorptiometry (DPX-NT, GE, USA). The serum total testosterone was 11.57 nmol/l (normal range 9.9-27.8 nmol/l), free testosterone 0.031 nmol/l (normal range 0.019-0.145 nmol/l), FSH 43.96 mU/ml (normal range 1.5-12.4 mU/ml) and LH 25.31 mU/ml (normal range 1.7-8.6 mU/ml) suggesting hypergonadotropic hypogonadism. On conventional chromosome analysis a 46, XX karyotype was found (Figure 1). Analysis of metaphases and interphases of 46, XX cells using fluorescence in situ hybridization (FISH) showed a translocation of the SRY gene from the distal short arm of chromosome Y to chromosome X (Figure 2). The diagnosis was therefore of infertility and azoospermia secondary to testicular dysgenesis and SRY positive 46, XX male syndrome. Hormone replacement therapy with 40 mg testosterone undecanoate daily was initiated. An ongoing pregnancy was achieved by the patient's wife through sperm donation.

Discussion

In humans, the 46, XX male syndrome is a rare form of gonadal dysgenesis caused by an aberrant balanced or unbalanced Y-to-X interchange during paternal spermatogenesis leading to the translocation of Y-specific loci to the paternal X chromosome. Also, a chromosome Y-to-autosome translocation is possible [1]. In our patient, FISH evidenced a Y-to-X translocation.

The Y-chromosome gene, SRY, is the first gene involved in testis development [2]. Proof that this is the most important or even only Y chromosomal gene required for sex determination came from the production of mice transgenic for the mouse SRY gene who developed testes and external male genitalia but the testes were smaller than in

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Fig. 1

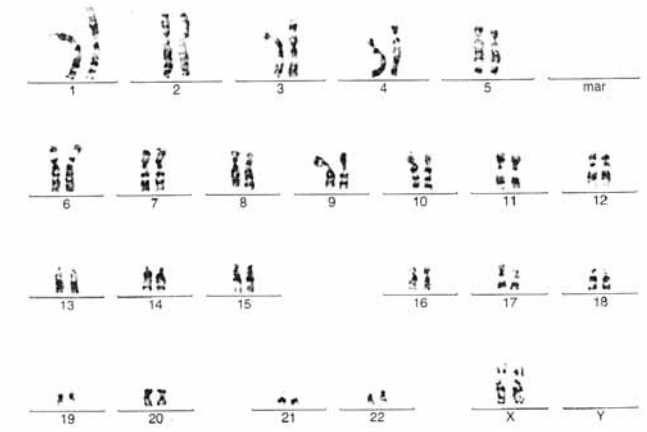

Fig. 2

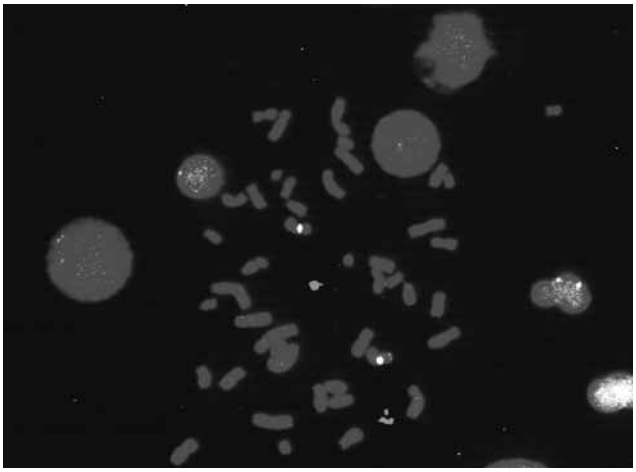

Figure 1. — 46, XX karyotype of a 28-year-old male with infertility.
Figure 2. — Fluorescence in situ hybridization (FISH) of metaphases and interphases of 46, XX cells with specific probe for the SRY gene revealed the presence of a translocation of the SRY gene from the distal short arm of chromosome Y to chromosome X. Detection and amplification of hybridization signals were done using an immunocytochemical reaction. Hybridization signals were analyzed using a fluorescence microscope.

normal mice and did not produce sperm [3]. In about 80% of cases, the SRY gene is part of the translocated fragment which is of variable length.

A feature of the 46, XX male syndrome is the large spectrum of clinical signs. A genotype-phenotype correlation has been described, with intersex and gynecomastia seen in 46, XX males that lack evidence of the SRY gene [4, 5]. On the other hand, few cases of SRY-negative 46, XX males with normal genitalia, complete masculinization and infertility were reported [6, 7]. In SRY-positive individuals, in general, the greater amount of Y material present, the more virilized the phenotype.

In our case, Y-to-X translocation was associated with small, firm testes and under-masculinized external genitalia in childhood. Testes of reduced size represent a major feature of testicular dysgenesis, especially when associated with cryptorchidism. However, in some XX (SRY+) cases, normal sized testes or atrophic, soft testes [8] may be encountered. In adult life, low-normal testosterone levels were measured in our patient, despite clinical signs of testicular insufficiency such as bilateral gynecomastia, pubic hair with a female pattern and female distribution of fat mass. However, serum LH levels were increased above 10 mU/l and the patient had low bone mass, thus, testosterone replacement therapy was initiated. In conclusion, phenotypic variability of 46, XX males cannot be totally explained only by the presence or absence of SRY. Other mechanisms have been proposed such as disruption of normal SRY expression by position effect [9], X inactivation [10], or mutations of other genes that may play a role in the definition of the phenotype.

In summary, infertility was the presenting symptom in this new first Romanian case of 46, XX male syndrome. A careful investigation of underdeveloped genitalia during childhood would have led to earlier diagnosis of this anomaly.

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