CASE REPORT

XX males without SRY gene and with infertility

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The case of a 28 year old male with normal male phenotype, in whom repeated seminal analysis showed complete azoospermia, is presented. Peripheral blood culture for chromosome studies revealed 46 chromosomes with XX constitution. Polymerase chain reaction (PCR) analysis of genomic DNA failed to detect the presence of the sex-determining region of the Y chromosome (SRY). A literature review of all SRY-negative XX males with normal male phenotype showed that this case is the sixth reported case but the first to be diagnosed during the investigations of infertility. The frequency, aetiology and diagnosis of this rare syndrome are also reviewed.

Key words: azoospermia/sex-determining region Y/XX male syndrome

Introduction

XX male syndrome is a rare cause of male infertility and literature dealing with it is scanty. In mammals, the sex-determining region of the Y chromosome (SRY) gene is the testes determining factor. The clinical features of male sex reversal syndrome patients are azoospermia combined with one or more of abnormal external genitalia, gynaecomastia, short stature and pelvic cyst. There have been three reports (Zenteno et al., 1997; Kolon et al., 1998; Vernole et al., 2000) describing a total of five male sex reversal syndrome patients with normal male phenotype without SRY gene. Four of these cases were siblings while the fifth was in a 42 year old male affected by palmoplantar keratoderma. In this article, we report a case of a man with a normal male phenotype, who presented for evaluation of infertility and who was found to be a 46,XX male but with no SRY gene to the X chromosome.

Through reporting this rare case and reviewing the current literature, the aim of this report is to highlight the value of karyotyping all males with congenital azoospermia or severe oligozoospermia who present for evaluation of infertility, since the phenotype does not always correlate with the presence or absence of Y sequences in the genome.

Case report

Case history and investigations

A 28 year old married man was referred to our centre with a 3 year history of male factor infertility. His height was 171 cm with arm span equal to height. No gynaecomastia was noted and his facial, axillary and pubic hair were all of normal density and distribution. The penis and scrotum were also normal and his testicular volumes were 9 ml each. Rectal examination revealed a normal-sized prostate gland. Semen analysis showed azoospermia. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were estimated at 15.6 and 50.7 mIU/ml respectively (normal ranges are 2.5–14.0 mIU/ml and 1.5–12.0 mIU/ml respectively). The serum testosterone concentration was normal at 11 nmol/l (normal ranges are 8–32 nmol/l), as was the serum prolactin concentration at 141 IU/l (normal ranges are 55–680 IU/l).

Peripheral blood cultures from this phenotypically normal male showed a normal female chromosome complement and banding pattern. Repeat polymerase chain reaction (PCR) analysis, using Y-specific sequence tagged sites analysing about 100 metaphases of genomic DNA, confirmed the absence of the Y chromosome, including any detectable SRY gene.

Discussion

Human males with a 46,XX karyotype are sterile males with normal female chromosomes. The reported incidence varies from 1 in 9000 (de la Chapelle, 1972) to 1 in 20 000 (Nielsen and Sillesen, 1975) in newborn males. Most cases are sporadic, that is, they are without familial clustering (de la Chapelle, 1981). The majority of cases are due to interchange of a fragment of the short arm of the Y chromosome containing the region that encodes the testes determining factor (TDF) with the X chromosome (Muller et al., 1986; Page et al., 1987; Ferguson-Smith et al., 1990; Sinclair, 1998). Other less likely causes include mutation in an autosomal or X chromosomal gene, which permits testicular determination in the absence of TDF, and undetected mosaicism with a Y-bearing cell line. It is now possible to identify two forms of this syndrome: Y DNA positive and Y DNA negative. The Y DNA positive males result from a X;Y translocation with a low recurrence risk; the Y DNA negative males are due to a mutation with a high recurrence risk (Van Dyke et al., 1991).

All males with discordant phenotype/sex chromosomal pattern are azoospermic due to absence of the long arm of the Y chromosome containing the azoospermia factor (AZF) gene,
which is necessary for normal spermatogenesis (Tiepolo and Zuffardi, 1976; Grumbach and Conte, 1992; Vogt et al., 1996). The majority of cases have normal external genitalia, but 10–15% of XX males shows various degrees of hypospadias (Lopez et al., 1995). Molecular studies have detected Y chromosome material in 75% of XX males (Muller et al., 1987), which explains their testicular development. On the other hand, many theories have been put forward to explain how patients who are Y-negative, as in this case, can have testes, despite complete absence of the Y chromosome. Researchers (Ferguson-Smith et al., 1990; Vilain et al., 1994) suggested the presence of other mutations (autosomal or X-linked) which could be responsible for testicular determination in the absence of Y sequences. The presence of hidden mosaicism with a Y-bearing cell line was proposed (Fechner et al., 1990). More recently, the reporting of a Mexican family in which two siblings without genital ambiguities were SRY negative (Zenteno et al., 1997), suggested that an inherited loss of function mutation in a gene participating in the sex-determining cascade could induce normal male sexual differentiation in the absence of SRY gene. This would strengthen what has been reported (Boucckine et al., 1994), that although the absence of Y-specific DNA generally results in incomplete masculinization, exceptions do occur. Another possibility for the aetiology of maleness in these cases is a downstream gene on the X chromosome in which expression is influenced by X inactivation (Kolon et al., 1998). Lastly, it has been postulated that the sex reversal in this patient is due to a defect on a yet unidentified autosomal or X-linked sex-determining gene (Vernole et al., 2000).

A total of 60% of true hermaphrodites have a 46,XX karyotype (Van Nickerk et al., 1981). Although the majority of 46,XX true hermaphrodites are negative for the Y-DNA sequence, including SRY gene (Ranie et al., 1989; Pereira et al., 1991; Sadi et al., 1996), a minority could be positive (McElreavey et al., 1992; Abbas et al., 1993; Copelli et al., 1996; Ramos et al., 1997; Kojima et al., 1998). Nevertheless, this diagnosis was unlikely in this patient because of the Ranie J., Robertson M.E., Malcolm, S. et al. (1992) that the sex reversal in these patients is due to a defect on an unknown X chromosome in 46,XX true hermaphrodites. "The Y syndrome, together with its rarity, make it very easy to miss this syndrome in the differential diagnosis of phenotypic males with congenital azoospermia. Without karyotyping, these patients would be subjected to invasive procedures and the financial and psychological implications of these. Once the problem has been recognized, these individuals require gentle management (including regular follow-up for possible long-term androgen deficiency) and counselling through a cooperative interdisciplinary approach.

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Kolon, T.F., Ferrer, F.A., McKenna, P.H. et al. (1992) Absence of Y sequences. The presence of hidden mosaicism with a Y-bearing cell line was proposed (Fechner et al., 1990). More recently, the reporting of a Mexican family in which two siblings without genital ambiguities were SRY negative (Zenteno et al., 1997), suggested that an inherited loss of function mutation in a gene participating in the sex-determining cascade could induce normal male sexual differentiation in the absence of SRY gene. This would strengthen what has been reported (Boucckine et al., 1994), that although the absence of Y-specific DNA generally results in incomplete masculinization, exceptions do occur. Another possibility for the aetiology of maleness in these cases is a downstream gene on the X chromosome in which expression is influenced by X inactivation (Kolon et al., 1998). Lastly, it has been postulated that the sex reversal in this patient is due to a defect on a yet unidentified autosomal or X-linked sex-determining gene (Vernole et al., 2000).

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We conclude that the heterogeneous features of 46,XX male syndrome, together with its rarity, make it very easy to miss this syndrome in the differential diagnosis of phenotypic males with congenital azoospermia. Without karyotyping, these patients would be subjected to invasive procedures and the financial and psychological implications of these. Once the problem has been recognized, these individuals require gentle management (including regular follow-up for possible long-term androgen deficiency) and counselling through a cooperative interdisciplinary approach.

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