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A Rare Case of Infertility: SRY Positive 46, XX Testicular Disorder of Sexual Differentiation

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Abstract

Aim
To highlight the complexity of infertility causes by describing the rare case of a man with a testicular disorder of sexual differentiation.

Diagnosis
A 33 years old Caucasian male presented with a 3-year-old history of primary infertility. His investigations revealed a low testosterone and a raised LH and FSH levels. A sample sent for sperm analysis revealed azoospermia. Chromosomal analysis and karyotyping revealed a 46 XX SRY positive karyotype.

Treatment
The patient was initiated on testosterone replacement and on calcium/vitamin D supplements.

Conclusion
Fertility evaluation requires complex assessments and a broad knowledge of possible causes.

Introduction

Approximately 15% of couples are infertile; male factor infertility is found to be the sole factor responsible in 20-30% of infertility cases but may contribute to infertility in up to 50% of cases. In 10-20% of males presenting with azoospermia a chromosomal abnormality is identified[1].

Case Report

A 33-year-old Caucasian male presented with his wife to the fertility clinic. They had a three year history of primary infertility. His wife had no significant history and her investigations were all normal. The patient's past medical history revealed bilateral undescended testes as a child for which he underwent bilateral orchidopexy. There was no significant family history. He was a smoker, drank 2 units of alcohol per week and denied any medication or illicit drug use. He had normal erections and libido and no history of decreased frequency of shaving, changes in voice or gynecomastia. He had no history of trauma, chemotherapy or radiotherapy. His height was 1.8m with a weight of 92.4 kg (BMI 28.5 kg/m^2). Clinical examination revealed bilateral small testes, 10 ml on the right and 5 ml on the left (normal range 15-20 ml). There was normal virilization with Tanner stage 5 pubic hair.

Laboratory investigations (Table 1) revealed a testosterone of 6.7 nmol/l (10.4-41.6 nmol/L), LH of 4.4 IU/L (1.8-12 IU/L) and FSH of 43.1 IU/L (1-8 IU/L). A sample was sent for sperm analysis and revealed azoospermia. Viral screen was negative; iron studies and prolactin level were normal. Genetic analysis for cystic fibrosis was negative. A pelvic MRI was normal for a male. Chromosomal analysis and karyotyping using fluorescence in situ hybridization (FISH) technique revealed a 46 XX SRY positive karyotype through translocation of the SRY gene between the X and the Y chromosome – 46,XXdel(X)t(X;Y)(p22.3;p11.3)(SRY+).

Table 1: Biochemical investigations.

Blood Test	Value	Reference Range
Testosterone	6.7 nmol/l	10.4-41.6 nmol/L
LH	4.4 IU/L	1.8-12 IU/L
FSH	43.1 IU/L	1-8 IU/L
HbA1c	38 mmol/mol	20-40 mmol/mol
IgA anti tTTG	<1 U/ml	0-10 U/ml
PSA	0.74 ug/L	0-2.5 ug/L
Free T4	13.2 pmol/L	10.5-22.0 pmol/L
TSH	1.03 mIU/L	0.27-4.2 mIU/L
Prolactin	112 mIU/L	86-324 mIU/L

The patient was initiated on testosterone replacement therapy and on calcium and vitamin D supplements. He was referred for genetic counselling and psychology support. The couple was referred for assisted reproduction and successfully had a baby with donor sperm.

At follow-up, mood, libido, energy and erectile function are normal.

Discussion

Testicular disorders of sexual differentiation (DSD), previously known as the XX male syndrome, is a condition in which individuals with two X chromosomes in each cell have a male phenotype and has a reported incidence of 1 in 20,000 newborn males[2]. There are three clinical phenotypes: normal phenotype, males with genital ambiguities and males who are hermaphrodites.

Sex determination is due to a single gene – SRY-that is normally located on the Y chromosome. The SRY gene produces testis determining factor (TDF) which triggers undifferentiated gonadal tissue in embryos to form testes. If the SRY gene is absent or inactivated, an embryo develops into a female, even if the Y chromosome is present [3,4]. 46, XX males can be classified as SRY positive (80%) and SRY negative (20%), depending on the presence or absence of Y-specific sequences[5].

Three mechanisms are suggested for the etiology of 46, XX male DSD: (a) Translocation of Y chromosome with the SRY gene on the X or on autosomal chromosomes, (b) X-linked mutation in the genes that cause testicular differentiation or mutation in autosomal genes and (c) occult mosaicism of the Y chromosome limited to the gonadal tissue or eliminated during development[3,4].

Sox genes encode proteins related to each other and to SRY by the presence of a DNA binding motif - the HMG domain[6]. *Sox3* and *Sox9* HMG can functionally substitute for the *SRY* HMG because both SRY-*Sox3* and *SRY-Sox9* transgenes cause sex reversal in XX transgenic individuals[7]. Molecular testing includes fluorescence in situ hybridization (FISH) and/or chromosomal microarray (CMA):SRY-positive 46,XX testicular DSD is established in individuals with evidence of SRY; SRY-negative 46,XX testicular DSD is established in individuals with no evidence of SRY on CMA or FISH and evidence of copy number variants or rearrangements in or around SOX9 or SOX3.

Sensitivity is necessary when conveying information to individuals with 46, XX testicular DSD regarding the genetic cause and associated sterility of the disorder. Providers are encouraged to anticipate the need for further ongoing psychological assistance.

Declaration of Conflicts of Interest:
The authors have no conflict of interests to declare.

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