Rare disease

Is 46XX karyotype always a female?

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Summary

A 19-year-old man, from a middle east country was referred by his physician to the endocrine department for bilateral gynaecomastia, low libido and sparse facial hair. There was no history of any chronic illness, mumps or traumatic injury to testis. He had clinical features suggestive of gonadotropin deficiency which was confirmed on biochemical testing. On karyotype and fluorescent in situ hybridisation analysis, he was found to have 46XX(SRY+) karyotype.

BACKGROUND

The 46XX testicular disorder of sex development is characterised by the presence of a 46XX karyotype, male external genitalia ranging from normal to ambiguous, two testicles, azoospermia and absence of Müllerian structures. Majority of individuals with 46XX testicular disorder of sexual differentiation (DSD) present after puberty with normal pubic hair and normal penile size, but small testes, gynaecomastia and sterility resulting from azoospermia. A smaller percentage present with ambiguous genitalia at birth, when it might be recognised at an early stage. Gender role and gender identity are reported as male. If undetected and left untreated, men with 46XX testicular DSD experience the consequences of testosterone deficiency.

CASE PRESENTATION

A 19-year-old man from a middle east country was referred by his physician to the endocrine department for bilateral gynaecomastia and sparse facial hair (figure 1). He was third of the six siblings, of consanguineous marriage and had male external genitalia. He had a normal ante-natal history and his developmental milestones were normal. There was no history suggestive of any illicit drug intake, chronic illness, mumps or traumatic injury to testis. On further questioning, he complained of low libido and decreased frequency of shaving. The patient's height was 165 cm and had normal axillary hair and pubic hair. His voice was normal. His IQ was 100. The stretched penile length was 7 cm but both testes were soft, small and atrophic (figure 2). The skin was normal, no palpable nerves or myotonia was demonstrable. There was no clinical evidence of thyrotoxicosis, liver or renal disease or nutritional deficiencies.

INVESTIGATIONS

The gonadotrophin levels were markedly elevated: follicle-stimulating hormone (FSH)—15 mIU/ml and leutinising hormone (LH)—20 mIU/ml (normal: FSH 1.2–5 mIU/ml; LH 2–9.8 mIU/ml). Serum testosterone was low, but prolactin levels and thyroid profile were within normal limits. MRI pelvis did not show the presence of

Müllerian structures or any abnormality of the urinary system. Ultrasonogram showed the right testis as 21×15×10 mm and left testis as 23×17×12 mm in volume. Semen analysis revealed azoospermia, semen volume was 3 ml and was fructose positive. Dual-energy x-ray absorptiometry scan revealed osteopaenia. Vitamin D levels were 16 ng/ml (suggestive of deficiency). Chromosomal analysis performed on peripheral blood using 72 h. Stimulated culture-GTG (pretreatment with trypsin then Giemsa stain) (pretreatment with trypsin then Giemsa stain) banding which showed 46XX chromosomal complement (figure 3). Fluorescent in situ hybridisation (FISH) analysis was done using centromeric probes for chromosomes X and Y (Vysis CEPX/CEPY) to rule out low-level mosaicism and probe specific for the sex-determining region (SRY) (Vysis CEPX/LSI SRY) to identify any cryptic rearrangement resulting in translocation of SRY region onto the chromosome other than Y or to analyse the presence of the SRY region even in the absence of Y chromosome. All the 500 cells and 20 metaphases revealed two 'green' signal for 'X' chromosome and one 'orange' signal indicating the presence of SRY region on one of the 'X' chromosome consistent with the diagnosis of 46XX (SRY+) (figure 4).

DIFFERENTIAL DIAGNOSIS

Klinefelter syndrome (47XXY) and its variants (48XXXY, 49XXXXXY and 46XY/47XXY mosaicism) are suspected in men with hypogonadism, small testes and gynaecomastia.

46XX/46XY—may present as true hermaphrodites depending upon the relative ratio of XX and XY cells: phenotype may vary from normal man to normal woman.

45X/46XY—affected individuals present often as men and may have short stature depending on the percentage of 45X cells.

Syndromic XX testicular disorder of sexual differentiation (DSD)—these are characterised by palmoplantar keratosis and predisposition to squamous cell carcinoma of the skin. These have been shown to involve mutation of R-Spondin 1 (RSPO1).

46XX testicular DSD may be associated with microphthalmia and linear skin defects when X/Y abnormal interchange involves microdeletion of Xp.

Figure 1 Patient showing Gynaecomastia.

46XX ovotesticular DSD—these are true hermaphrodites (have both testicular and ovarian tissue either as an ovotestes or as an ovary and a testes), whereas individuals with 46XX testicular DSD have only testicular tissue. Possible bias of sampling of a gonadal biopsy may miss the ovarian portion of gonads. A uterus or a hemiuterus can be radiologically demonstrated and endocrine evaluation may reveal oestrogen production.

Normal penile length
Reduced testicular volume

Figure 2 Normal penile length and reduced testicular volume as demonstrated by orchidometer.

TREATMENT

He was initiated on low-dose testosterone replacement therapy initially followed by full replacement. Oral calcium and vitamin D replacement were also done. As he was more concerned with gynecomastia, he was counselled regarding reduction mammoplasty if there was no improvement on testosterone replacement therapy.

Counselling was provided by the treating endocrine team and the psychologist to the patient and his parents (with his consent). They were explained in detail about the diagnosis and that it is unlikely that he can father child/children. The options of assisted reproduction were discussed, and it was left to them to decide as per their socio-cultural, religious and personal preference.

OUTCOME AND FOLLOW-UP

As the patient was not from our country, a detailed summary was presented to him with the option of ongoing consultation at his native place. It was explained that clinical examination, bone densitometry, prostate size and prostate-specific antigen, liver function tests are to be done on periodic basis. If possible, it was suggested that he come back for review in 6 months.

Figure 3 Chromosomal analysis on peripheral blood using 72 h. Stimulated culture-GTG banding which showing 46XX chromosomal complement.

Method : Fluorescence in situ hybridization (FISH) - Vysis LAI SRY (Yp11.3) Spectrum orange / X Spectrum Green probe.

RESULTS

	Green	Orange	No. of cells	Interpretation
Chromosome	X	Y		
Signals per cell	Two	One	500	All 500 cells and 20 metaphases revealed 2 green for 'X' chromosome and one orange signal indicating presence of SRY region on one of the 'X' chromosome

Figure 4 FISH demonstrating two 'green' signal for 'X' chromosome and one 'orange' signal indicating the presence of SRY region on one of the 'X' chromosome consistent with the diagnosis of 46XX (SRY+).

DISCUSSION

The XX male syndrome was first described by de la Chapelle *et al*¹ in 1964, occurs in about 1 in 20 000 newborn males. Phenotypically there are three groups of sex-reversed 46XX individuals. The first classical group includes phenotypically normal XX men, the second group consists of men with genital ambiguities and the third group describes true hermaphrodites.²

In 1966, Ferguson-Smith³ and his colleagues proposed that this condition results from translocation of Y material including SRY on Y chromosome to the X chromosome. McElreavey *et al*⁴ proposed that SRY has been postulated to repress an inhibitor of male testicular development. SRY negatively regulates an autosomal locus, Z, which switches off male-determining genes. In normal men SRY situated on the short arm of Y chromosome just proximal to the pseudoautosomal region I negatively regulates Z locus. 46XX men lack the long arm of the Y chromosome (Yq) which contains the azoospermia factor loci and has gene complex critical for germ cell development and differentiation. FSH and LH levels were elevated in the present case as seen in cases with severe testiculopathy and complete spermatogenic arrest leading to testicular failure. Individuals with 46XX (SRY+) rarely present with atypical genitalia and are less likely than individuals with 46XX (SRY-) to have gynaecomastia.⁵

Thus, for the complete workup of XX men, it is important that conventional cytogenetic analysis be followed by FISH analysis to determine the presence of SRY gene. These investigations indicate that the amount of Y-specific material contributes to the phenotype heterogeneity.

Learning points

- ▶ A detailed history encompassing all the details is essential in cases where phenotype does not conform to the physical appearance.
- ▶ Attending residents without the experience in dealing with such cases should not feel overwhelmed when presented with such encounters.
- ▶ After the diagnosis is confirmed, a detailed psycho-social counselling must involve the patient as well as the parents/guardians in a sensitive manner and all the medical terms must be explained explicitly.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. de la Chapelle A, Hortling H, Niemi M, *et al*. XX sex chromosomes in a human male. First case. *Acta Med Scand* 1964;**175**(Suppl 412):25–8.
2. Boucekine C, Toublanc JE, Abbas N, *et al*. Clinical and anatomical spectrum in XX sex reversed patients. Relationship to the presence of Y specific DNA-sequences. *Clin Endocrinol (Oxf)* 1994;**40**:733–42.
3. Ferguson-Smith MA. X-Y chromosomal interchange in the aetiology of true hermaphroditism and of XX Klinefelter's syndrome. *Lancet* 1966;**2**:475–6.
4. McElreavey K, Rappaport R, Vilain E, *et al*. A minority of 46, XX true hermaphrodites are positive for the Y-DNA sequence including SRY. *Hum Genet* 1992;**90**:121–5.
5. Ergun-Longmire B, Vinci G, Alonso L, *et al*. Clinical, hormonal and cytogenetic evaluation of 46,XX males and review of the literature. *J Pediatr Endocrinol Metab* 2005;**18**:739–48.

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