

46 XX Male: A Case of Sex Reversal Syndrome

Pages with reference to book, From 19 To 20

Tasnim Ahsan, Mariam Saleem, Asif Ahmed, Merium Muzaffar (Department of Medicine, Jinnah Postgraduate Medical Centre, Karachi.)

Introduction

Sex reversal syndromes pose a serious clinical problem particularly when questions regarding sex re-assignment are raised in grown up patients. The expression of various degrees of phenotypic male gender in the absence of Y chromosome was truly perplexing until the identification of various testes determining genes and new ones continue to be identified. The presence of this male genetic material on the X chromosome is the basis of this syndrome. One such case is being described.

Case Report

A 24 year old educated, unmarried man presented to the Endocrine Clinic, JPMC, complaining of gynaecomastia. He was shaving twice weekly and claimed to have morning erections regularly and a normal libido. He was the youngest of 4 male siblings. Another older brother was reported to have similar problems and had married twice without any children. Two other brothers were mated with children and both had normal male attributes. He was short statured with a height of 165 cms. He had scanty facial hair and his skin was relatively fine. His voice remained unbroken and high pitched. Pubic and axillary hair showed normal distribution but were sparse, as was the body hair. Body contours were masculine. Penis and scrotum were well developed and normal in size. Testicles were small and soft bilaterally. He had bilateral moderate gynaecomastia. The rest of the physical examination was normal. His gender identity was definitely male. Investigations showed a low testosterone at 1.8 ng/ml (normal 2.0 - 8.1 ng/ml), FSH and LH were elevated at 35 mIU/ml and 21 mIU/ml (normal 1.0 - 12.0 mIU/ml and 2.0 - 12.0 mIU/ml respectively), suggesting primary hypogonadism, Thyroid function tests and serum prolactin level were normal. An ultrasound of the pelvis showed no evidence of uterus or ovaries but showed a normal sized prostate. Chromosomal analysis showed a female karyotype with 46 XX chromosomes. In view of the well developed external genitalia chromosomal analysis was repeated which again showed 46 XX chromosomes. Semen analysis showed complete azoospermia. Testicular biopsy was not carried out. He was commenced on testosterone replacement therapy.

Discussion

46 XX males have been well described in literature with over 150 cases reported since 1964¹. These patients are similar phenotypically and endocrinologically to patients with classic Klinefelter's syndrome except for slight differences, i.e., 47 XXY karyotype males, tend to be tall (mainly due to disproportionate leg length, which is present prepubertally but exacerbated after puberty), whereas patients with 46 XX karyotype tend to be short (mean height 168 cms), with normal skeletal proportions^{1,2}. They also have a lower frequency of intellectual and psychosocial problems^{1,2}. Unlike 47 XXY patients maternal age is not increased. Postpubertally they have varying degrees of hypogonadism as in Klinefelter's syndrome with small testes and azoospermia¹⁻³. The testicular histology is similar to that of 47, XXY males; decreased size and number of seminiferous tubules, absent germinal cells and peritubular and interstitial fibrosis. Leydig cells appear hyperplastic. In some cases the morphology is similar to germinal cell aplasia or intermediate with this disorder and

seminiferous tubule dysgenesis¹. The Y chromosome carries a gene(s) adjacent to the pseudoautosomal boundary encoding the testis determining factor. Once the testis develops in utero under the influence of testis determining gene (s), it produces the necessary hormones required for male phenotypic expression⁴. Complete male differentiation of the external genitalia and urogenital sinus occurs only if the androgenic stimulus is received during the critical period of development early in foetal life (8-12 weeks)⁵. The human testis determining gene(s) (SRY) has been isolated from a 35 kb region on the human Y chromosome. 46 XX males with genital abnormalities tend to lack evidence for Y chromosome DNA and exhibit a greater prevalence and degree of gynaecomastia than their 46 XX male counterparts in whom a y to x translocation is present⁶. The presence of Y chromosome material on the paternally derived X chromosome is usually due to an abnormal X-Y interchange during the obligatory X-Y crossing over that occurs during male meiosis⁷. The theories put forward to explain sex reversal in 46 XX male patients include (1) loss of a Y chromosome early in embryogenesis, (2) cryptic sex chromosome mosaicism with an undetected and/or circumscribed cell line containing a Y chromosome⁸, (3) translocation between a y and an x chromosome or autosome resulting in the presence of the testis determining gene (s) on an X chromosome or autosome, or (4) a mutation involving either an autosomal or X linked gene. Various studies have indicated that 80-90% of 46 XX males result from a Y to X translocation during meiosis^{5,7}. 46 XX males who showed no evidence of Y specific DNA (including SRY and ZFY probes), have been reported⁹. This suggests that testicular development in these males occurred in the absence of SRY gene (s). Phenotypic variation in 2 siblings with paternally derived SRY bearing chromosome has been described by N. Abbas et al¹⁰. One brother was a true hermaphrodite and the other was a phenotypic male. This phenotypic variability can be explained by selective inactivation of one of the SRY bearing X chromosomes¹⁰. In view of the non availability of cytogenetic studies, it was not possible to determine the origin and the presence/absence of SRY gene (s) in the proband or the affected brother (who by all accounts seemed to be another similar case) or the parents of this case of genetic misadventure.

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