IS THE COMBINATION OF MALE-TO-FEMALE TRANSSEXUALISM WITH A 46,XYY CHROMOSOMAL PATTERN MORE THAN ACCIDENTAL?

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Running head: transsexualism and 46,XYY

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ABSTRACT

Development of gender can be conceived as part of the sexual differentiation process of the human. Transsexualism is the condition in which a person with apparently normal somatic sexual differentiation has the conviction that s/he is actually a member of the other sex. Knowledge about the dynamics of development of gender identity is limited. The classical paradigm of human sexual development is that genetic factor(s) determine the fate of the gonad. Further sexual differentiation is thought to be determined by gonadal hormones. There is a renewed interest in genetic factors co-determining sexual differentiation. We report a case of male-to-female transsexualism with a 46,XYY chromosomal pattern, the seventh in the literature. While the prevalence of subjects with a 46,XXY pattern is higher, there are fewer cases of transsexualism reported with 46,XXY than with 46,XYY, posing the question whether the association is only accidental.

Transsexualism is the condition in which a person with apparently normal somatic sexual differentiation has the unshakeable conviction that he or she is actually a member of the other sex. This conviction is accompanied by the irresistible urge to live in the gender experienced as self. There is very limited knowledge about the dynamics of gender development in the human species and there is as yet no plausible explanation why the vast majority of people develop a gender identity in agreement with their identifiable criteria of sexual differentiation (chromosomes, gonads, genitalia, levels of sex hormones) and why, by contrast, a minority will experience gender transpositions, partial or complete, in their lives.

Sexual differentiation begins with the sex difference of the chromosomes established at conception, and ends with the sexual differentiation of the brain expressing itself in gender identity, sexual orientation, sexual and non-sexual gender-related behavior. In humans, it has been assumed that the combination of chromosomes present in all cells of the body (normal: XY, XX, or abnormal: XXY, XYY, XO etcetera) has no direct effect on gender identity or sexual orientation. Rather, the influence has been thought to be indirect and derivative through determination of the nature of the embryonic gonadal anlagen and their hormonal products [1] [2-6]. The extent to which hormones contribute to sexual differentiation of the brain in humans remains to be determined[7]. In humans this information has been obtained from "experiments of nature": genetic and endocrine disorders that spontaneously occur in the fetus [2-5]. Overall, clinical observations support the hypothesis that in human prenatal development, effects of androgens on sexual brain differentiation can be recognized, but these are not of the hormonal-robot type found in subprimate mammals, in which sex steroids in the set of behaviors studied typically exert on-off activational effects and straight forward organizational effects [2-5]. The organizational effects of prenatal androgens are more noticeable in gender role behavior than in gender identity [8].

There are certainly other, unidentified factors that modulate or override androgen effects on the central nervous system. For instance, male and female cells differ because of differential effects of sex chromosome genes expressed within the cells themselves [9] and some genes on the X chromosome escape inactivation potentially resulting in sex differences in gene dosing [10, 11]. Therefore, it is probably worthwhile to report chromosomal errors in persons who present with cross-sex gender identification. We present here a case of MTF with a chromosomal pattern of 47,XYY.

Case Presentation

S., a 30-year old male of Chinese ethnicity and Central American nationality presented to our private psychotherapy practice in order to obtain a psychological evaluation and a subsequent recommendation letter for the initiation of estrogen therapy due to gender dysphoria. Evaluation of presenting complaints met the DSM-IV-TR for transsexualism. Patient reported intermittent self-dosing of various oral contraceptives and Estradiol 4mg/q.d. for three years, and subsequent IM self-administration of Estradiol Valerate USP 40 mg/q.14.d. for one year at the time of diagnosis. Height (180 cm) and weight (80 kg) were above average for Chinese males. Patient is the younger of two brothers in an intact nuclear family constellation. During multiple interviews, patient stated a desire for cross-gender female identification since early childhood. He was very confused as a child when he was told that his breasts would not grow, since he always thought he would bear children and breastfeed. Prepubertal gynecomastia was clinically diagnosed but no therapeutic corrections were instituted. Patient reported emotional sensitivity in early childhood and an inability to socialize with male peer groups. Frequent crying episodes due to bullying in primary school accompanied patient's social isolation from both male and female children. Patient reported having been highly passive, quiet and introverted during his middle and high school education, with academic performance consistently below average, particularly in arithmetic and

physical sciences. Patient states a facility for languages and developed his tri-lingual competence of speaking and writing fluent Spanish, Cantonese and English both in the home and through education. The pattern of social isolation continued until patient began his college education in the United States and commenced self-administration of estrogenic hormones. Patient has been living as a female for four years and is now pursuing a graduate degree in psychology at a private learning institution in the United States. Patient appearance in clothing and general presentation is female in both public and private contexts. Patient's first name has been changed to female in current educational records, although an official complete name change will not be possible until patient's receipt of a psychotherapist-issued recommendation letter for hormonal reassignment.

Patient reported that he began masturbating at the age of 12 while developing an attraction to females. Sexual history revealed adolescent coitus with females with feelings of subsequent dissatisfaction due to the patient's gender status being perceived as male. Patient engaged briefly in non-coital sexual activities with homosexual males during late adolescence, but experienced no arousal or emotional satisfaction. Patient reported attraction and arousal to both phenotypic females and transsexual males in the process of gender reassignment toward female. Patient plans to obtain immediate bilateral orchidectomy as an acceptable low-cost alternative to the desired procedure of SRS (sex reassignment surgery) in the future.

Chromosomal analysis: Peripheral blood was used for chromosomal analysis. The banding method used was GTG with a banding resolution of 400-550. A 47,XYY pattern was observed in all metaphases.

Discussion

We present here a case of MTF transsexualism with a chromosomal error: 47, XYY. To the best of our knowledge, this is the 7th case reported in the literature. Earlier reports are [12-17]. Most genetic studies find that the prevalence of 47,XYY is lower than of Klinefelter's syndrome

(47,XXY) (15-66% of Klinefelter's syndrome) [18, 19]. The prevalence of Klinefelter' syndrome has been estimated to be 1.09 to 1.72 per 1000 male births [20]. Transsexualism has been reported in two cases of Klinefelter's syndrome [21, 22]. Rather than would be expected by chance, the association transsexualism with chromosomal pattern of 47,XYY is more prevalent than with 47,XXY.

It is difficult to conceive how a chromosomal error would translate into a complex human faculty such as gender identity and role. Mouaffak et al have reported a case with a gender identity disorder and bipolar disorder associated with the ring Y chromosome [23]. Physical examination did not reveal any abnormality: genitalia were normal and no gynecomastia. The hormonal profile showed an elevated follicle stimulating hormone and normal testosterone level. The karyotype showed a mosaicism (45, X[2]/ 46, X, r(Y)[23]), with one cell line presenting the ring Y chromosome. The ring Y chromosome is usually associated with deletions in telomeric regions. The SRY gene (Yp11.3), which is involved in the determination of sex, is located close to the telomeric region. Its accessibility and regulation could be disturbed by the ring conformation. The SYBL1 and NLGN4Y genes both map to the Yq pseudoautosomal region and encode proteins that are essential for functional synapses.

Traditionally, a 47,XYY karyotype has been linked to violent aggressive behavior. For review and a cautionary note [24]. The association is largely based on case reports. The most common indication for a 47,XYY male to be karyotyped is developmental delay and/or behavior problems. One study concluded that many men with a chromosomal pattern of 47,XYY go undiagnosed and do not have physical signs or behave in a manner which prompts testing for a chromosome abnormality [18]. So, aggressive behavior is certainly not a general feature of subjects with 47,XYY karyotype.

In conclusion: most transsexuals have an unremarkable karyotype but of cases with an abnormal chromosomal pattern, 46,XYY is the most common reported in the literature, more common than, for instance, 46,XXY which has higher prevalence. If the association of

transsexualism would be accidental, more cases with 46,XXY than with a 46,XYY pattern would be expected.

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