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True Hermaphroditism: Clinical and Cytogenetic Studies

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ABSTRACT

Clinical and cytogenetic studies of 14 patients with true hermaphroditism revealed 46, XX (5 cases); 46, XY (3 cases); 46, XX/46, XY (4 cases); 46, XX/47, XXY (1 case); 48, XXXY (1 case). Hormonal profiles of follicle stimulating hormone, luteinizing hormone and testosterone concentrations together were insignificant when compared to controls. Parental consanguinity was seen in 71.4% of the cases, supporting the role of autosomal recessive gene(s) for the cause of ambiguity in true hermaphroditism.

Key words: True hermaphroditism, ovotestes, sex determination, autosomal recessive gene

INTRODUCTION

True hermaphrodtism is defined as presence of ovarian as well as testicular tissue in either the same or opposite gonads (1,2). These patients may have a separate ovary and testis, or more often, one or more ovotestes (1,3,4). Most individuals with true hermaphroditism may have 46, XX complement (2,5), although a few individuals have 46, XY (6), 46, XX/46, XY (7), 46, XX/47, XXY (8), 46, XX/46,XY/47, XXY (9).True hermaphroditism was identified in 14 subjects out of 105 cases of sexual ambiguity attending Institute of Genetics for investigations and advice during the period January, 1993 and December, 1996. In this study, we report the clinical and cytogenetic studies conducted in these 14 patients.

METHODS

Between January 1993 and December 1996, 105 patients with ambiguous genitalia were investigated at the Institute of genetic Diseases and Hospital for Genetic Diseases, Osmania University, Begumpet, Hyderabad, India. In 14 of them, true hermaphroditism was diagnosed based on gondal histopathology. Their age, birth order, religion, maternal reproductive history, history of consanguinity and clinical

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features were recorded in a special case proforma. The external genitalia were assessed clinically according to the Prader's (10) classification. Mucosal cells obtained by buccal scrapping were stained for X-chromatin (11) and Y-chromatin (12). Chromosomal analysis was done using cultured lymphocytes from peripheral blood by arresting metaphase with colchicine according to the method of Moorhead (13) and staining for G-banding (14). Karyotypes were determined by examining 50 metaphases from each patient. Follicle stimulating hormone [FSH], luteinizing hormone [LH] and testosterone concentrations were estimated in the serum by radioimmunoassay [RIA] in patients as well as age matched control subjects.

RESULTS

The age of these patients ranged from 6 months to 18 years. The clinical manifestations encountered in these subjects included small phallus [6.7%], hypospadias [7.6%], bifid scrotum [1.9%], enlarged clitoris [4.8%]. Urethral opening was seen in 1.9% of the cases. Normal testes were found in 2.9% patients.The degree of virilization was relatively marked according to Prader's rating (10). Histopathological examination revealed: testis/ovary [21.4%], ovary/ovotestis [21.4%], testis/ovotestis [35.7%] and ovotestis/ovotestis [2.4%]. Parental consanguinity was observed in 71.4% of patients with true hermaphroditism when compared to 17.5% observed in the control group [Table 1]. The most common karyotype [Table 2] was 46, XX [5 cases] and other chromosomal constitutions were 46, XY [3 cases], chimerism 46, XX/46, XY [4 cases], 46, XX/47, XXY [1 case] and 48, XXXY [1 case].

DISCUSSION

Diagnosis of the true hermaphroditism is based mainly on the histologically verified ovarian [follicles] and testicular [seminiferous tubule] tissues and can be made irrespective of the chromosomal complement (3). The ovotestes is the most common gonadal structure observed in true

Table 1. *Parentalconsanguinity in 14 patients with true hermaphroditism and 200 controls*

Type of consanuinity	True hermaphroditism (n=14)	%	Controls (n=200)	%
First cousins	8	57.1	28	14.0
Second cousins	1	7.1	4	2.0
Uncle-niece	1	7.1	3	1.5
First cousins once removed	0	0	0	0
Uncle-niece once removed	0	0	0	0
Total	10	71.4	32	17.5
Non-consangunity	4	28.6	165	82.5

All percentage figures corrected to first decimal phase

Table 2. *Correlation between clinical, cytogenetic and hormonal findings in 14 subjects with true hermaphroditism*

Patient No.	Age	Phenotype	Karyotype	FSH	LH	Testosterone	Clinical features
1.	6 mo	Female	46, XX/47, XXY	4.20 (2.0)	7.20 (1.0)	U.D. (0.05)	Testis felt in left side labia majora, external genitalia female type, hypoplastic fallopian tube, ovotestes
2.	18 mo	Female	48, XXXY	5.80 (2.1)	4.50 (1.30)	U.D. (0.05)	Clitors enlarged, small penis, testis felt in left labial region, scrotal sacs not formed, small ovotestes in the inguinal canal, mental retardation
3.	2.5 yrs	Female	46, XX/46, XY	3.70 (3.5)	3.50 (2.20)	0.06 (0.10)	Labia majora fused, enlarged clitoris/ small penis, urethral opening at the base of the penis. Right gonad was ovary, no testicular tissue was confirmed, unicorn uterus, fallopain tube present.
4.	19 mo	Male	46, XX/46, XY	3.8 (2.1)	4.2 (1.3)	0.07 (0.05)	Simple urethral opening, no vaginal opening, clitoris enlarged or small penis, labia majora present, right testis felt in inguinal region, ovo-testes present on either side
5.	4 yrs	Male	46, XX/46, XY	4.50 (3.80)	5.20 (2.50)	0.09 (0.15)	Undescended testes on both sides, kept in scrotal sacs, dysmorphic facies, low set ears, right inguinal ovotestis, left ovary present

contd...

Patient No.	Age	Phenotype	Karyotype	FSH	LH	Testosterone	Clinical features
6.	9 mo	Female	46, XX/46, XY	3.20 (2.00)	3.90 (1.00)	0.11 (0.05)	Clitoris enlarged, labia majora and minora well developoed, palpable gonads, vagina well developed, inguinal ovotestis, left ovary present
7.	7 yrs	Male	46, XX	2.50 (4.20)	3.15 (3.50)	0.28 (0.20)	Penoscrotal hypospadias, right testis in the scrotal sac, left testis not palpable, uterus not visible but ovotestis present on left side
8.	7 mo	Male	46, XX	3.20 (2.00)	3.50 (1.00)	U.D. (0.05)	Short stature, absence of external genital organs, short penis, hypospadias, no testicular sacs, rudimentary uterus with vaginal canal, both ovary and testis present on either side
9.	12 yrs	Male	46, XX	2.10 (6.00)	3.00 (3.50)	U.D. (3.00)	Micropenis, hypospadias/chordee, testes not palpable, both ovary and testis present
10.	18 yrs	Male	46, XX	3.20 (9.10)	3.50 (12.50)	U.D. (3.00)	Penis short, urethral opening at penoscrotal junction, testes not descended both sides, rudimentary uterus present, ovotestis and testis present on both sides

contd...

Patient No.	Age	Phenotype	Karyotype	FSH	LH	Testosterone	Clinical features
11.	16 yrs	Male	46, XX	5.25 (8.90)	5.20 (12.00)	0.17 (3.00)	Thin built, breast development present, glans penis/enlarged clitoris, no scrotal sacs, labia majora present, no testis, urethral opening present below the penis, ovotestes present
12.	21 mo	Male	46,XY	2.50 (2.10)	3.15 (1.30)	U.D. (0.15)	Scrotal sacs present, vaginal opening present, small penis, both testes palpable and descended, both ovary and testis present
13.	14 yrs	Female	46, XY	7.42	12.5	1.15	Mascuine features, public hair positive, penis absent, scrotal sacs well developed, hypoplastic uterus, ovotestis was present on left side and testis present on right side
14.	14 yrs	Female	46, XY	9.25	6.35	1.23	Penis has hordee and perineal hypospadias, a blind tract about one inch long present in the location of vagina, no uterus or cervix, no breast development, scrotum developed with descended testes both sides, ovotestes present

Numbers in paranthesis are control values

Yrs = years; mo = months; U.D. = undetectable

FSH = Follicle stimulating hormone; LH = luteinizing hormone

hermaphroditism. The proportion of ovotestes observed in the present study [78.5%] is higher than that reported in earlier reports (5). Most of the cases in the present study had the chromosomal complement of 46, XX. Similar findings have been reported in other studies. Moreover, it seems likely that all the cases do not result from the same aetiology, and some could result from chimerism i.e., the presence of both XX and XY cells in a single individual (46, XX/46, XY). The aetiology of true hermaphroditism is heterogenous and varies according to chromosomal complement, mutant sex determining genes, translocation of testicular determinants from Y-chromosome to X-chromosome or an autosome. Possible explanation for the presence of testes in individuals with XX chromosomal constitution includes translocation of SRY gene from Y to X; translocation of testicular determinants from Y to an autosome; undetected mosaicism or chimerism; and sex revarsal gene(s). Presently, the key role of Y chromosome in gonadal dysgenesis is not clear (15,17). Testicular differentiation may depend not only on the absence of SRY gene but also controlled by other genes working independently of the SRY gene (18). The genetic factors, probably autosomal factors also play a role in the pathogenisis of true hermaphroditism as suggested by several familial aggregates (19,20). Perhaps different genetic factors are responsible for the occurrence of 46, XX males and true hermaphrodites in the same kindred (22,23). Eicher and Washburn (24) have suggested that autosomal genes may cause sex reversal in mice. A condition similar to that may prevail in humans. It is possible that perturbation of an ordinary autosomal gene may prelude in appropriate sex reversal in man as well. Pedigrees of these subjects with 71.4% consanguinity supports the view of autosomal recessive gene(s) responsible for the cause of ambiguity in individuals with true hermaphroditism.

The choice of sex assessment for raising the patients with true hermaphroditism depends on various age factors such as age, degree of virilization of the external genitalia, capacity of testicular tissue, presence or absence of uterus among others. The rearing of the child with sexual ambiguity may not necessarily agree with the genetic sex (25) because one must not consider not only the disorder itself but the status of the external genitalia. This decision best be made by a team consisting of pediatrician, urologist, gynecologist and geneticist.

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