JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:
HALDER A.MULLERIAN DUCTS REMNANTS IN 46,XY DISORDER OF SEX DEVELOPMENT.Journal of Clinical and Diagnostic Research [serial online] 2010 April [cited: 2010 April 5]; 4:2169-2174.

Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2010 &month= April &volume=4&issue=2&page=2169-2174 &id=561

ORIGINAL ARTICLE

Mullerian Ducts Remnants in the 46 XY Disorder of Sex Development

Halder A

ABSTRACT

**Objective: ** The objective of this study was to find out the prevalence of mullerian duct remnants in the 46 XY disorder of sex development due to disorders in androgen synthesis/action.

**Methods*:* ** Thirty eight cases of 46 XY disorder of sex development of disorders in androgen synthesis/action were evaluated for diagnosis and management, including mullerian duct remnants. Mullerian ducts remnants were found in nine of them (23.7%). The diagnostic evaluation consisted of pelvic ultrasonography, genitography, cystourethroscopy, genitoscopy and laparoscopy or laparotomy.

**Results: ** The common types were an abnormally large prostatic utricle communicating with the urethra and a rudimentary uterus.

**Conclusion: ** It is concluded that mullerian ducts remnants are common with the 46 XY disorder of sex development due to disorders in androgen synthesis/action. During evaluation of patients, this aspect should be kept in mind and during management, appropriate measures should be undertaken to prevent future complications like chronic urinary tract infections, stones and voiding troubles.

Key Words: 46 XY disorder of sex development; disorders in androgen synthesis/action; Mullerian duct remnants; Prostatic utricle

Key Message : Mullerian ducts remnants are common with the 46 XY disorder of sex development due to disorders in androgen synthesis/action. During management, appropriate measures of mullerian ducts remnants should be undertaken to prevent future complications.

Associate Professor, Department of Reproductive Biology, AIIMS, New Delhi, (India)
(Ex Assistant Professor, Department of Medical Genetics, SGPGIMS, Lucknow, India)
Corresponding Author:
Dr. Ashutosh Halder
Associate Professor
Department of Reproductive Biology
All India Institute of Medical Sciences
New Delhi 110029
(India)
Tele: 011-26594211
Fax: 011-26588663
Email: ashutoshhalder@gmail.com; ahalder@aiims.ac.in

Introduction

Normal male sexual differentiation is governed by two testicular hormones: testosterone (synthesized by the interstitial Leydig cells) and antimüllerian hormone (AMH; produced by Sertoli cells present in the seminiferous tubules) [1],[2]. Androgen in the form of testosterone causes differentiation of the wolffian duct into the epididymis, vas deferens and seminal vesicles, whereas androgen in the form of dihydrotestosterone (DHT; testosterone is converted to dihydrotestosterone by the enzyme 5 α reductase) is needed for the virilization of the urogenital sinus and the external genitalia [3]. The AMH produces regression of the mullerian duct i.e. uterus, tubes and upper vagina. At about 6 weeks of embryonic life, the mullerian ducts appear adjacent to the wolffian ducts. Mullerian ducts give rise to the uterus, the fallopian tubes

and the upper vagina in females. In males, most portions of the mullerian duct regress, except for the cephalad end which persists as the appendix testis and the caudal end as the prostatic utricle [4]. The prostatic utricle is a composite of the urogenital sinus and the mullerian duct. Regression of the mullerian duct in males is controlled by AMH, which is produced by the sertoli cells soon after testicular differentiation [5].

Incomplete embryonic regression of the mullerian ducts in otherwise normal males, has been attributed to an autosomal gene mutation that results in inappropriate synthesis and/or action of AMH (AMH deficiency syndrome) [6],[7]. Mullerian ducts remnants (MDR) are seen frequently also in cases of the 46 XY disorder of sex differentiation (DSD) with [8],[9],[10] and without gonadal dysgenesis [11],[12].

Androgen insensitivity syndrome (AIS) is a heterogeneous group of defects in the androgen receptor, resulting in varying degrees of defective masculinization in 46 XY individuals. The AIS phenotype is complicated by the presence of somatic mosaicism for the AR gene mutation [13], [14]. Cases of 46 XY DSD of AIS occasionally also exhibit mullerian ducts remnants [15],[16],[17],[18],[19]. Mullerian ducts remnants in AIS may be associated in as many as 35% cases [20]. This report presents nine cases with 46 XY DSD of disorders in androgen synthesis/action (probably AIS andunlikely to be a 5 α reductase deficiency syndrome) with MDR.

Patients and Methods

A total of 63 cases of DSD were evaluated in the department of Medical Genetics, SGPGIMS, Lucknow, India, as part of a specialized referral care. There were 41 cases of 46 XY DSD, 15 cases of 46 XX DSD (14 cases of congenital adrenal hyperplasia and one in utero androgen exposure), 04 cases of ovotestis DSD (formerly true hermaphrodite) and 03 cases of gonadal dysgenesis (including one with mixed gonadal dysgenesis). Among 41 cases of 46 XY DSD, there was 38 cases of disorders in androgen synthesis/action (AIS) and one each of AMH deficiency syndrome, testicular enzyme defect and testicular atrophy. Ambiguity of the external genitalia was the presenting complaint. There was no other abnormality. The cases were between one month and 24 years at the time of evaluation. All patients underwent cytogenetic study and hormonal evaluation (FSH, LH and testosterone; also estradiol to pubertal cases) including human chorionic gonadotropin (hCG) stimulation test in pre-pubertal cases. A minimum of 20 metaphases were examined in each case as per the routine cytogenetic practice of the laboratory. As part of the work-up to establish the diagnosis and to outline the plan of management, all cases were evaluated for internal sex organs. For this purpose, the patients were subjected to lower abdominal ultrasonography, genitogram, genitoscopy, urethro-cystoscopy and laparoscopy/laparotomy. An enlarged prostatic utricle was graded according to Ikoma [21] (Grade 0: opening located on the posterior urethra but the utricle does not extend over the verumontanum; Grade I: larger than Grade 0 but it does not reach the bladder neck; Grade II: more enlarged and its dome extends over the bladder neck. The prostatic utricle opens into the central area of the verumontanum in the prostatic urethra in Grades 0, I and II. In rare cases, the opening is situated in the bulbous urethra, just distal to the external sphincter and this is classified as Grade III).

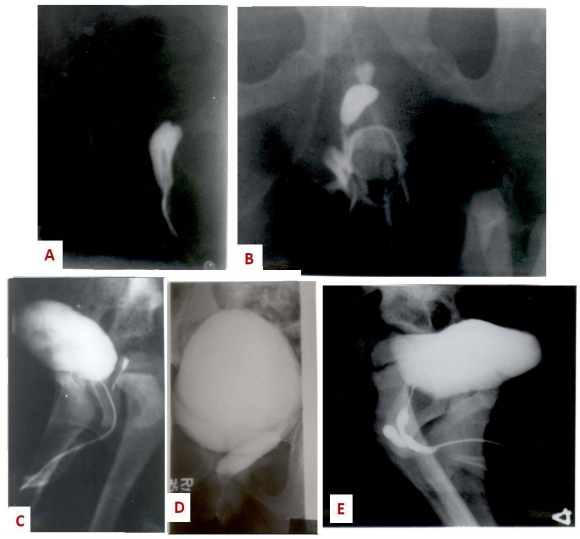
Results

Out of 38 cases of disorders in androgen synthesis/action (AIS), there were 9 cases with MDR. Nine cases with MDR were between 7 months to 18 years at the time of evaluation. [Table/Fig 1] shows the summary of major clinical findings of the 9 cases of disorders in androgen synthesis/action (AIS) with mullerian duct remnants and [Table/Fig 2] it also shows various genitogram findings of some of the cases.

(Table/Fig 1) Shows Summary of Major Clinical Finding of 9 Cases of Disorders in Androgen Synthesis/Action (AIS) With Mullerian Duct Remnants

SN	Age	External Genitalia(before TRT)					MDR			Investigations					hCG ST	TRT
		Phallus	Scrotum	Urethra	Introitus	Gonads	Uterus	Vagina	PU	T	LH	FSH	Others			
1	18 yrs	5 cm	LL PF	FL	+	pal., ing., UL	well dev	9 cm	normal	11.3	08	05	180 (E2)		nd	nd
2	4 yrs	2 cm	bifid	FL	+	pal., ing., BL	rudim.	+	not visual.	UD	<1	<1	HP: normal for age		as T was adult range positive	equivocal
3	18 yrs	3 cm	hypoplas.	CUGS	CUGS	pal., scrot., BL	rudim.	+	not visual.	12.4	12	6.5	234 E2		nd	nd
4	5 yrs	2 cm	LL	FL	blind	pal., labial, BL	absent	+	grade 3	0.4	UD	UD			as T was adult range positive	nd
5	7 mo	1.5 cm	hypoplas.	FL	+	pal., ing., UL	absent	small	grade 2	8.2	1	80	4; 17OHP HP: normal for age		positive	no respon
6	11 yrs	4 cm	hypoplas.	PH	blind	pal., scrot., BL	absent	small	grade 2	4.2	5	4			positive	nd
7	13 yrs	2.5 cm	LL	FL	+	pal, labial, BL	absent	blind	grade 2	10.9	67	>100	HP: testis Leydig cell hyperplasia, no spermatogenesis		nd	nd
8	9 mo	1 cm	PF	CUGS	CUGS	pal, scrot. BL	absent	+	grade 2	0.34	5	5			as T was adult range equivocal	nd
9	6 yrs	2 CM	hypoplas	PH	CUGS	rt. isternal ring lt. inguinal canal	absent	+	grade 2	4.5	10	5	HP: prepubertal testis		as T was adult range equivocal	no respon

MDR = mullerian ducts remnants derived from ultrasound, genitogram, cystourethrography, genitoscopy, laparoscopy & laparotomy
hCG ST. = human chorionic gonadotropin stimulation test
TRT = testosterone response test;
PU = prostatic utricle
T = testosterone (normal adult value 10-38 nmol/l); LH = hutanizing hormone; FSH = follicle stimulating hormone
Rudm. = rudimentary; + present; hypoplas. = hypoplastic; pal. = palpable; ing. = inguinal; scrot. = scrotal; yrs. years; mon. = months;
LL PF = labia like, posterior fusion only; UL = unilateral; BL = bilateral; nd = not done; FL = female like; PF = posterior fusion
CUGS = common urogenital sinus
E2 = estradiol (pmol/l: normal male 40-190 pmol/l); 17OHP = 17 hydroxy progesterone
PH = perineal hypospadius; UD = undetectable; well dev = well developed



(Table/Fig 2)
(A)Genitogram Plates Showing Well Developed Vagina With Cervical Indentation.
(B)Prostatic Utricle With Rudimentary Uterus.
(C)Grade 2 Prostatic Utricle.
(D) Grade 1 Prostatic Utricle.
(E)Grade 0 Prostatic Utricle.

Phenotype

The appearance of the genitalia of 9 cases with MDR ranged from near normal female to male with perineoscrotal hypospadias and micropenis. However, the genitalia were ambiguous in most of the patients. Among the three pubertal patients (reared as females), two sought attention because of virilization and suboptimal breast development,whereas the third one presented with virilization and asymmetric breast development.

Karyotype

All nine patients with MDR were found to have 46, XY chromosomes in peripheral blood lymphocytes.

Ultrasonography, Genitogram, Genitoscopy, Cystourethroscopy and Laparoscopy

Common urogenital sinus was seen in three cases; well-developed vagina although blunt, was seen in four cases and rudimentary uterus as fibrous nodule was demonstrated in three. An enlarged prostatic utricle was demonstrated in six cases. There were five cases of grade 2 and one case of grade 3 prostatic utricle in this series.

Endocrine Status

All patients underwent evaluation for FSH, LH and Testosterone (also Oestradiol to pubertal cases) initially. The hCG stimulation test was carried out in six pre-pubertal cases. Four were positive and two were equivocal for the hCG stimulation test. Basal testosterone of adult level was seen in three pubertal cases. One pre-pubertal case had near normal adult value of testosterone and thus had equivocal hCG stimulation.

Gonads

Gonadal biopsy was carried out in four cases. Three were from the pre-pubertal age group. The findings were either normal testes, prepubertal testes or testes with Leydig cell hyperplasia without any evidence of spermatogenesis, as well as with no evidence of hyalinization and atrophy of the seminiferous tubules.

Management

Sex assignment was carried out in all cases. It was according to the sex of rearing in all, except one, whose sex was changed from female to male following a request from the patient. Bilateral orchidectomy was carried out in two patients who presented with virilization and were reared as females. Genital reconstruction was carried out in seven patients.

Discussion

These cases represent disorders in androgen synthesis/action likely to be AIS although the possibility of 5- ARDS was not excluded, as there

was no facility of the DHT assay during the study period. These were cases with chromosomal sex as 46, XY; gonads as testes; normal/near normal function of testes; no in utero exposure of oestrogen/progesterone. There were three families with multiple affected sibs with variable presentation and sex of rearing (first family with three affected and reared all as males, second family with three affected and reared two as males and one as female and third family with two affected and reared as males). The post pubertal cases also had variable presentation, including asymmetric breast development, thus indicating AIS rather than 5 ARDS clinically.

The unexpected association of MDR in persons with disorders in androgen synthesis/action (AIS) raised the question as to whether this is a random coincidence or whether these were inherited abnormalities. This association appears in literature both as sporadic case reports [15],[16],[17], [22], as well as case series [20],[23]. In one case series [20], this association was as high as 35%; in our series, this association was observed in 23.7% of the patients. The large number of patients with AIS in whom MDR has been noticed, suggests the role of androgens in the complete regression of the mullerian duct. Early testicular descent, leading to the removal of the mullerian structures from exposure to the effective range of AMH, has been suggested as an explanation for the persistence of mullerian duct remnants [16]. Oestrogen also plays an important role in the modulation of the growth and development of the internal genital ducts [24]. High oestrogen levels preserve the mullerian duct in males. The oestrogen induced inhibition of AMH action may be countered by androgen, indicating that the androgen/oestrogen ratio is essential for an adequate regression of the mullerian duct in males. This is also supported by an association between the prenatal administration of diethyl stillbesterol (DES) and the frequent occurrence of enlarged prostatic utricles (mullerian duct derivative) [25]. Similarly, the injection of DES in pregnant mice with the AIS mutation gene inhibits the regression of the mullerian duct in normal as well as mutant male offspring (much less regression in mutant mice) [26]. Human embryos with complete AIS is refractory to androgen action and thus, has an exaggerated oestrogenic response, which by interfering with AMH action, results in incomplete mullerian duct regression. Initially, it was thought that AMH does not require the action of androgen to exert its effect [27]. However, since in postnatal testis, the sertoli cells are under androgenic control, it is possible that in the presence of abnormal or deficient androgen receptors, the secretion and/or action of AMH could be impaired, resulting in the incomplete regression of the mullerian duct [28]. Probably maternal oestrogen and progesterone in the foetal circulation may also alter the ratio of androgens to antiandrogens (oestrogen), which may contribute to the incomplete regression of the mullerian duct in genetically susceptible AIS.

In this series, one sib pair (cases 8 and 9) showed some discordant phenotype which is commonly possible with AIS, as often (one third cases) associated with somatic mosaicism [29],[30],[31]. Another case had high oestradiol level at puberty along with asymmetric breast development (indicates somatic mosaicism), which favours the diagnosis of AIS. The different phenotypes with similar mutation can also be explained through factors that modify AR action [32]. Individual differences in androgen levels and the timing of its production during the critical period of genital organogenesis are among the factors which are likely to be involved. In another case (case 7), gonadotropins were like gonadal failure (primary) with normal testosterone (for age) and partially virilized. Testicular histology also did not co-relate with gonadal failure of that severity, although the possibility of gonadoblastoma, gonadal dysgenesis and Klinefelter syndrome (see Table 1) were excluded. The reason for high FSH despite normal testosterone was unexplainable.

These findings suggest that incomplete regression of the mullerian duct in the 46 XY DSD of disorders in androgen synthesis/action (AIS) is a reality and that it is not uncommon (as high as 23.7%). It is suggested that every case of 46 XY DSD with disorders in androgen synthesis/action (mainly AIS) should be evaluated for mullerian ducts and care should be taken during reconstructive surgery to prevent future complications associated with this derivative.

Acknowledgement

The author thanks the Departments of Medical Genetics, Medical Endocrinology, Surgical Endocrinology, Urology, Pathology and Radiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow for assisting in the workup and management of the cases with ambiguous genitalia.

Consent

Consent was taken as per routine practice before taking clinical photograph from cases/parents of cases.

Competing Interest

Financial and non financial competing interests:None

Author's Contribution

AH carried out all evaluation workup including the initial clinical evaluation, formulated the activity plan, checked results, interpretated results and prepared the manuscript. AH will be the guarantor of the manuscript.

References

[1] Jost A. Embryonic sexual differentiation. In Hermaphroditism. Genital anomalies and related endocrine disorders. 2nd Edition. Editd by HW Jones Jr, WW. Scott. Baltimore, Willaims and Wilkins Co. 1971 p. 62.
[2] Rey RA, Belville C, Nihoul-FeKeTe C, et al. Evaluation of Gonadal Function in 107 Intersex Patients by Means of Serum Antimullerian Hormone Measurement. J Clin Endocrinol Metab 1999;84:627–31.
[3] Wilson JD. Testosterone uptake by urogential tract of the rabbit embryo. Endocrinology 1973;92:1192-99.
[4] Glenister TW. The development of utricle and of the so called middle or median lobe of human prostate. J Anat 1962;96:443-55.
[5] Josso N, Picard JY, Tran D. The antimullerian hormone. Birth Defects 1977;13:59-84.
[6] Sloan WR, Patrick CW. Familial persistent mullerian duct syndrome J Urol 1976;115:459-61.
[7] Belville C, Josso N, Picard JY. Persistence of Mullerian derivatives in males. Am J Med Genet. 1999;89:218-23.
[8] Rohatgi M, Gupta DK, Menon PS, et al. Mixed gonadal dysgenesis and dysgenetic male pseudohermaphroditism—a critical analysis. Indian J Pediatr 1992;59:487–500.
[9] Borer JG, Nitti VW, Glassberg KI. Mixed gonadal dysgenesis and dysgenetic male pseudohermaphroditism. J Urol 1995;153:1267–73.
[10] Scolfaro MR, Cardinalli IA, Stuchi-Perez EG, et al. Morphometry and histology of gonads from 13 children with dysgenetic male pseudohermaphroditism. Arch Pathol Lab Med 2001;125:652–56.
[11] Krstic ZD, Smoljanic Z, Micovic Z, et al. Surgical treatment of the Mullerian duct remnants. J Pediatr Surg 2001;36:870-76.
[12] Ilias I, Kallipolitis GK, Sotiropoulou M, et al. An XY female with Mullerian duct development and persistent Wolffian duct structures. Clin Exp Obstet Gynecol 2002;29:103-4.
[13] Holterhus PM, Bruggenwirth HT, Hiort O, et al. Mosaicism due to a somatic mutation of the androgen receptor gene determines phenotype in androgen insensitivity syndrome. J Clin Endocrinol Metab 1997;82:3584–89
[14] Hiort O, Sinnecker GH, Holterhus PM, et al. Inherited and de novo androgen receptor gene mutations: investigation of single-case families. J Pediatr 1998;132:939–43.
[15] Oka M, Katabuchi H, Munemura M, et al. An unusual case of male pseudohermaphroditism, complete testicular feminization associated with incomplete differentiation of mullerian duct. Fertil. Steril. 1984;41:154-56.
[16] Dodge ST, Finkelston MS, Miyazawa K. Testicular faminization with incomplete mullerian regression. Fertil Steril. 1985;43:937-38.
[17] Ulloa-Aquirre A, Mendez JP, Angeles A, et al. The presence of mullerian remnants in complete androgen insensitivity syndrome: a steroid hormone mediated defect? Fertil. Steril. 1986;45:302-305.
[18] Damiani D, Mascolli MA, Almeida MJ, et al. Persistence of Mullerian remnants in complete androgen insensitivity syndrome. J Pediatr Endocrinol Metab 2002;15:1553-56.
[19] Van YH, Lin JL, Huang SF, et al. Novel point mutations in complete androgen insensitivity syndrome with incomplete mullerian regression: two Taiwanese patients. Eur J Pediatr 2003;162:781-784.
[20] Rutger JL, Scully RE. Pathology of testis in intersex syndromes. Semin. Diagn. Pathol. 1987;4:275-91.
[21] Ikoma F, Shima H, Yabumoto H. Classification of enlarged prostatic utricle in patient with hypospadius. Br J Urol 1985;57:334-37.
[22] Morris JM. The syndrome of testicular feminiza tion in male pseudohermaphrodite. Am J Obstet Gynecol 1953;65:1192-11.
[23] Ritchey ML, Benson RC, Kramer SA, et al. Management of mullerian duct remnants in the male patient. J Urol 1988;140:795-99.
[24] Maclaughlin DT, Hutson JM, Donahoe PK. Specific estradiol binding in embryonic mullerian ducts: a potential modulator of regression in the male and female chick. Endocrinology 1983;113:141.
[25] Driscoll SG, Taylor SH. Effects of prenatal maternal estrogen on male urogenital system. Obstet. Gynecol. 1980:56:537-42.
[26] Kobayashi B. Induction of mullerian duct derivatives in testicular feminized mice by prenatal

exposure to diethylstilbestrol. Anat Embryol (Berl) 1984;169:35-39.
[27] Griffin JE, Wilson JD. The syndrome of androgen resistance. N Engl J Med 1980;302:198-207.
[28] Scully RE, Mark EJ, McNeely WF, et al. Case 13-1990 (weekly clinicopathological exercise). N Engl J Med 1990;322:917-925.
[29] Kohler B, Lumbroso S, Leger J, et al. Androgen Insensitivity Syndrome: Somatic Mosaicism of the Androgen Receptor in Seven Families and Consequences for Sex Assignment and Genetic Counseling. J Clin Endocrinol Metab 2005;90:106–111.
[30] Gottlieb B, Beitel LK, Trifiro MA. Somatic mosaicism and variable expressivity. Trends Genet 2001;17:79–82.
[31] Holterhus PM, Bruggenwirth HT, Hiort O, et al. Mosaicism due to a somatic mutation of the androgen receptor gene determines phenotype in androgen insensitivity syndrome. J Clin Endocrinol Metab 1997;82:3584–89.
[32] Quigley CA, De Bellis A, Marschke KB, et al. Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 1995;16:271–321.