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46,XY Female: SRY and AR Basis: Genotype & Phenotype Correlation

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Abstract

46,XY females are referred with different terms and The Consensus Statement on Management of Intersex Disorders (2006) presented a widely accepted system of nomenclature and proposed the umbrella term of Disorders of Sex Development (DSDs). The rationale of the present study, is to correlate the phenotype in cytogenetically confirmed 46,XY females specifically with the molecular genetic basis of SRY and AR genes and also with the karyotypes and the age at referral.

Material and Methods: Gather data from division of Human Genetics, St. John's Medical College, Bangalore. The data includes both cytogenetic and molecular genetics analysis of 46,XY females.

Results: The classified features of the probands under 12 groups were further subdivided and then, percentage occurrence of the features was calculated as per the presence or absence of SRY gene or the mutation in AR gene versus the karyotype and age at referral. Among the total features, probands for the AR gene analysis have manifested 116 (51.3%) and in them, the probands with AR- manifested 72 (62%). The absence of the uterus was the selective feature for the AR- or AR + status in 8/8 and 4/5 probands and also between AR and SRY. On the contrary, the sparse axillary hair was the feature between SRY- and SRY+ status. Probands with 46,XY karyotype have manifested 193 features (85.4%) out of which 64 were seen in AR- probands (33.3%). In AR- and with 46,XY karyotype, the absence of the uterus was noticed in the 7 probands. The features that were common in all the 4 SRY- and 5 SRY+ with 46,XY karyotype were the smooth skin, female voice, primary amenorrhea and female genitalia; but in the 4 SRY- they were the sparse axillary and pubic hair.

Discussion: In the present study, it could be interpreted that with the help of genetic counseling and appropriate management and therapy, the probands with SRY+ and AR+ could be reared as male and female individuals. It is seen that the probands have manifested age related features. It is stated that, as per the presence of the uterus and other mullerian derivatives, the phenotype of adult 46,XY females could be grouped into 3 major categories.

Conclusion: 46,XY females comprise a heterogenous group, which differ not only in their diagnostic category and anatomy but also in their journey through life to adult services. Medical and surgical care required.

Keywords: XY females; Gonadal dysgenesis; Androgen insensitivity .

Introduction

46,XY females are referred with different terms and The Consensus Statement on Management of Intersex Disorders (2006) presented a widely accepted system of nomenclature and proposed the umbrella term of Disorders of Sex Development (DSDs). In table 1 is given the new nomenclature to DSDs and in table 2 the genetic background to the conditions with DSDs. (Berra *et al* 2010)[1]

The authors also stated that as per the presence of the uterus and other Mullerian derivatives; clinically the phenotype of 46,XY females could be grouped under 3 major categories. (Table 3)

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Table 1: New nomenclature: DSDs (Source- Lee *et al* 2006)[2]

Previous	Current
Intersex XY sex reversal	DSD 46,XY gonadal dysgenesis (GD)
Male pseudohermaphroditism Undervirilised XY male	46,XY DSD
Female pseudohermaphroditism Masculinised of XX female	46,XX DSD
True pseudohermaphroditism XX male, XX sex reversal	Ovotesticular DSD 46,XX testicular DSD

Table 2: Genetic basis: DSDs (Source- Mendonca et al 2009)[3]

Groups of conditions	Clinical syndromes	Genes
Abnormalities of gonadal development	GD-Swyer's syndrome Denys-Drash syndrome Campomelic dysplasia Testicular regression syndrome	SRY,DHH,NR5A1 WT1 SOX9 -
Defects of testosterone synthesis	Leydig cell hypoplasia-LH receptor defects Steroidogenic enzyme deficiency -Lipoid adrenal hyperplasia -3 β hydrosysteroid dehydrogenase type II deficiency -17 α hydroxylase & 17,20 lyase deficiency -17 β hydrosysteroid dehydrogenase deficiency(17 β -HSD) Altered steroidogenesis due to disrupted electron transfer -P450 oxidoreductase deficiency	LHGCR -STAR,CYP11A1 -HSD3B2 -CYP17A1 -HSD17B3 PDR
Defect of testosterone processing	5 α reductase type 2 deficiency (5AR)	SRD5A2
Defects in androgen action	CAIS (Complete androgen insensitivity syndrome) PAIS (Partial androgen insensitivity syndrome)	AR AR
Ovotesticular 46, XY DSD	-	-

Table 3

1. 46, XY females with functioning testis producing AMH (antimullerian hormone) are born without the uterus. In early gestation, AMH secreted from Sertoli cells causes the differentiation of the mullerian duct system. Included are the females affected by AIS, 5AR and 17 β-HSD deficiencies.
2. 46,XY females without functioning testis and with GD do not produce AMH; thereby the mullerian duct system differentiates to form the uterus. Moreover, in the absence of the testosterone, the mesonephric ducts fail to develop & the undifferentiated urogenital sinus & external genitalia mature into the female structures. Included in majority are the females with 46, XY GD or Swyer' syndrome.
3. 46, XY women with ovotesticular DSD have variable testicular functions, which result in unpredictable secretion of AMH and variable uterine appearance. For example, hemi-uterus may develop if testicular tissue is predominantly unilateral.

In general, in the females referred with DSDs, along with the phenotype, the 46,XY status is confirmed with the cytogenetic analysis; but, the molecular basis is determined only in a small percentage of cases with DSDs (Achermann *et al* 2008)[4].

The rationale of the present study, is to

correlate the phenotype in cytogenetically confirmed 46,XY females specifically with the molecular genetic basis of SRY and AR genes and also with the karyotypes and the age at referral.

Material & Methods

At Division of Human Genetics, St. John's Medical College, Bangalore, during the period

Table 4: 46, XY female: SRY & AR basis versus Phenotype

Features	AR- (n8)	AR+ (n5)	AR (n13)	SRY- (n5)	SRY+ (n7)	SRY (n12)	AR & SRY (n25)
1.Short stature	-	-	-	-	1	1	1
2. Skin							
Smooth	6	4	10	5	7	12	22
Hirsuitism	1	-	1	-	-	-	1
Coarse	1	-	1	-	-	-	1
Hyperpigmentation	-	1	1	-	-	-	1
3. Voice							
Female	6	4	10	5	7	12	22
Male	2	-	2	-	-	-	2
Infantile	-	1	1	-	-	-	1
4. Barrel Chest	1	-	1	-	-	-	1
5. Breast							
Not Developed	6	2	8	1	1	2	10
Normal	1	2	3	-	2	2	5
Hypoplasia	1	1	2	4	4	8	10
6.Axillary Hair Growth							
Normal	1	-	1	-	-	-	1
Sparse	7	4	11	5	4	9	20
Absent	-	1	1	-	3	3	4
7.Pubic Hair Growth							
Normal	2	1	3	-	1	1	4
Sparse	5	3	8	5	6	11	19
Absent	1	1	2	-	-	-	2
8. Android Pelvis	2	-	2	-	-	-	2
9.Primary Amenorrhea	5	4	9	5	6	11	20
10. Genitalia							
Female	6	4	10	5	7	12	22
Ambiguous Genitalia	1	1	2	1	-	1	3
Hypogonadism	1	-	1	1	-	1	2
Total	56	34	90	37	49	86	176
11. Gonads							
Testis	4	3	7	-	-	-	7
Inguinal swelling	2	1	3	-	-	-	3
Ovary Streak	-	-	-	2	2	4	4
Ovary	-	-	-	-	1	1	1
Absent	2	1	3	3	4	7	10
12. Uterus							
Absent	8	4	12	-	1	1	13
Infantile	-	1	1	-	-	-	1
Present	-	-	-	1	-	1	1
Rudimentary	-	-	-	1	1	2	2
Hypoplasia	-	-	-	3	4	7	7
Antiverted	-	-	-	-	1	1	1
Total	16	10	26	10	14	24	50
Grand Total	72 62%	44 38%	116 51.3%	47 42.7%	63 57.3%	110 48.7%	226 -

Table 5: SRY and AR basis: Phenotype versus Karyotype

Features	AR+ XY (n5)	AR- (XY) (n7)	AR- (X/XY) (n1)	SRY- XY (n4)	SRY- X/XY (n1)	SRY+ XY (n5)	SRY+ X/XY (n2)	Total
1.Short stature	-	-	-	-	-	-	1	1
2. Skin								
Smooth	4	5	1	4	1	5	2	22
Hirsutism	-	1	-	-	-	-	-	1
Coarse	-	1	-	-	-	-	-	1
Hyperpigmentation	1	-	-	-	-	-	-	1
3. Voice								
Female	4	5	1	4	1	5	2	22
Male	-	2	-	-	-	-	-	2
Infant	1	-	-	-	-	-	-	1
4.Barrel Chest	-	1	-	-	-	-	-	1
5. Breast								
Not developed	2	5	1	1	-	1	-	10
Normal	2	1	-	-	-	1	1	5
Hypoplasia	1	1	-	3	1	3	1	10
6.Axillary hair growth								
Normal	-	1	-	-	-	-	-	1
Sparse	4	6	1	4	1	3	1	20
Absent	1	-	-	-	-	2	1	4
7.Pubic hair growth								
Normal	1	2	-	-	-	1	-	4
Sparse	3	4	1	4	1	4	2	19
Absent	1	1	-	-	-	-	-	2
8. Android pelvis	-	2	-	-	-	-	-	2
9. Primary amenorrhea	4	5	-	4	1	5	1	20
10.Genitalia								
Female	4	5	1	4	1	5	2	22
Ambiguous genitalia	1	1	-	1	-	-	-	2
Hypoplasia	-	1	-	1	-	-	-	1
Total	34	50	6	30	7	35	14	176
11. Gonads								
Testis	3	4	-	-	-	-	-	7
Inguinal swellings	1	2	-	-	-	-	-	3
Ovary-streak	-	-	-	1	1	1	1	4
Ovary	-	-	-	-	-	1	-	1
Absent	1	1	1	3	-	3	1	10
12. Uterus								
Absent	4	7	1	-	-	1	-	13
Infantile	1	-	-	-	-	-	-	1
Present	-	-	-	1	-	-	-	1
Rudimentary	-	-	-	1	-	1	-	2
Hypoplasia	-	-	-	2	1	4	-	7
Anti verted	-	-	-	-	-	1	-	1
Total	10	14	2	8	2	12	2	50
Grand Total: 46,XY (n21) 45,X/46,XY (n4)	44(24.3%)+64(33.3%)+38(19.7%)+47(24.3%)= 193(85.4%) 8(24.2%)+9927.3%)+16(48.5%)= 33(14.6%)							
Total	44 22.7%	64 33.3%	8 24.2%	38 19.7%	9 27.3%	47 24.3%	16 48.5%	

Table 6: SRY and AR basis: Phenotype: Age at referral: Below (<) and Above (>)14 years

Features	AR- (n2) >14	AR- (n6) <14	AR+ (n1) >14	AR+ (n4) <14	SRY- (n5) >14	SRY- (n3) >14	SRY+ (n4) <14
1.Short stature	-	-	-	-	-	1	-
2. Skin							
Smooth	1	5	1	3	5	3	4
Hirsuitism	-	1	-	-	-	-	-
Coarse	1	-	-	-	-	-	-
Hyper pigmentation	-	-	-	1	-	-	-
3. Voice							
Female	1	5	-	4	5	3	4
Male	1	1	-	-	-	-	-
Infant	-	-	1	-	-	-	-
4.Barrel chest	1	-	-	-	-	-	-
5. Breast							
Not developed	2	4	1	1	1	-	1
Normal	-	2	-	2	-	1	1
Hypoplasia	-	1	-	1	4	2	2
6.Axillary hair growth							
Normal	-	1	-	-	-	-	-
Sparse	2	5	1	3	5	1	3
Absent	-	-	-	1	-	-	3
7.Pubic hair growth							
Normal	-	2	1	-	-	-	1
Sparse	2	3	-	3	5	3	3
Absent	-	1	-	1	-	-	-
8. Android pelvis	1	1	-	-	-	-	-
9. Primary amenorrhea	-	5	-	4	5	2	4
9.Genitalia							
Female	1	5	-	4	5	3	4
Ambiguous genitalia	-	1	1	-	-	-	-
Hypogonadism	1	-	-	-	-	-	-
Total	14	43	7	28	35	19	30=176
10. Gonads							
Testis	2	2	-	3	-	-	-
Inguinal swelling	-	2	1	-	-	-	-
Ovarian streak	-	-	-	-	2	1	1
Ovary	-	-	-	-	-	-	1
Absent	-	2	-	1	3	2	2
11. Uterus							
Absent	2	6	1	3	-	1	-
Infantile	-	-	-	1	-	-	-
Present	-	-	-	-	1	-	-
Rudimentary	-	-	-	-	1	1	-
Hypoplasia	-	-	-	-	3	1	3
Antiverted	-	-	-	-	-	-	1
Total	4	12	2	8	10	6	8=50
Grand total	18	55	9	36	45	25	38=226
<14 years	55(42.6%)+36(28%)+38(29.4%)=129(57%)						
<14 years	18(18.5%)+9(9.3%)+45(46.4%)+2525.8%)=97(94.3%)						

of 35 years, from 1976 to 2010, 108 female probands were cytogenetically confirmed to have XY status. The gathered information was duly filled in the proforma. Among the 108 cases, the details were complete in 90 for the primary and secondary sexual features; out of which 12 cases with GD and 13 with AIS and the family with due consent volunteered for the genetic analysis on SRY and AR genes. Their age ranged from 4 to 39 years. The steps involved in the molecular genetic analysis were: DNA isolation, DNA quantification, PCR amplification, gel electrophoresis, sequencing PCR, direct DNA sequencing and DNA analysis and CAG repeat analysis with gene scan. (Thangaraj *et al* 2002b, 2003b, Singh *et al* 2006)[5,6,7]

Results

The classified features of the probands under 12 groups were further subdivided and then, percentage occurrence of the features were calculated as per the presence or absence of SRY gene or the mutation in AR gene (Table 4) versus the karyotype (Table 5) and age at referral (Table 6).

Among the total of 226 features, probands for the AR gene analysis have manifested 116 (51.3%) and in them, the probands with AR- manifested 72 (62%). The absence of the uterus was the selective feature for the AR- or AR + status in 8/8 and 4/5 probands and also between AR and SRY. On the contrary, the sparse axillary hair was the feature between SRY- and SRY+ status.

Probands with 46, XY karyotype have manifested 193 features (85.4%) out of which 64 were seen in AR- probands (33.3%). In AR- and with 46, XY karyotype, the absence of the uterus was noticed in the 7 probands. The features that were common in all the 4 SRY- and 5 SRY+ with 46, XY karyotype were the smooth skin, female voice, primary amenorrhea and female genitalia; but in the 4 SRY- they were the sparse axillary and pubic hair.

Observed features

Below 14 years, in AR- (n6), it was absence of uterus; in AR+ (n4) primary amenorrhea, female voice and genitalia and in SRY+ (n4) primary amenorrhea, smooth skin, female voice and genitalia. Above 14 years, in AR- (2) non-developed breast, sparse axillary and pubic hair growth, presence of testis and absence of uterus; in AR+ (n1) smooth skin, sparse axillary hair, normal pubic hair, ambiguous genitalia and inguinal swelling and in SRY- (n5) primary amenorrhea, smooth skin, female voice, sparse axillary and pubic hair, female genitalia.

Discussion

A vast literature is available on 46,XY females, AIS and SRY gene mutations. TFS includes males who may manifest female phenotype in the presence of intact SRY. In TFS, the target cells of the testosterone have deletion in the AR gene resulting in the absence of the male sexual differentiation and phenotypically female. In pure gonadal dysgenesis, the associated features are the absence of the testicular and male differentiation; testosterone and secondary sexual development. (Gardner *et al* 2008)[8]

The genesis of the 46,XY females are because of the cross over error between X and Y resulting in the transmission of SRY gene to X, in males, during the meiotic gametogenesis. Hence, the individuals with Y but without the SRY gene would become XY females with gonadal streaks rather than ovaries and poorly developed secondary sexual characters (Jorde *et al* 2010).[9]

Individuals with AIS have female external genitalia; undergo breast development during puberty; primary amenorrhea; inguinal testis; scanty secondary sexual hair; absent uterus and fallopian tube and blind vagina. It may be noted that inguinal hernia which is uncommon in girls is present, especially

bilaterally then AIS should be considered. Individuals with incomplete or partial androgen insensitivity undergo variable virilisation. Affected individuals are sterile and may have female sexual orientation. They also need the removal of the testis because of the increased risk of developing testicular malignancy and should placed on oestrogen therapy for the development of the secondary sexual characters as well as for the prevention of the osteoporosis in the longer term. (Turnpenny and Ellard 2012)[10]

From the available vast literature, the present study is discussed with the relevant publications. In the present study, from tables

Table 7

Categories	Berra et al 2010	Present study 2011
1	Without uterus: 46,XY females with functioning testis and antimullerian hormone (AMH) & without differentiated mullerian duct system. Examples: Androgen Insensitivity Syndrome (AIS) 5α- reductase deficiency (5αR) 17β-hydroxysteroid dehydrogenase deficiency (17-HSD)	Without uterus: 13/25 (52%) 13= AR-8;AR+5;SRY-5;SRY+7 Karyotypes & AR & SRY genes: 46,XY & AR- =7 45,X/46,XY & AR- =1 46,XY & AR+ = 5 46,XY & SRY- =4 45,X/46,XY & SRY- =1 46,XY & SRY+= 5 45,X/46,XY& SRY+ = 2 - -
2	With uterus: 46,XY females without functioning testis and AMH; with differentiated mullerian duct system; undifferentiated urogenital sinus and female external genitalia. Examples: 46,XY gonadal dysgenesis (GD) or Swyer's syndrome	With uterus: 12/25 (48%) 12=AR+1;SRY-5;SRY+6 Infantile uterus 1=AR+ Uterus 1+SRY- Rudimentary uterus 2= SRY-1; SRY+1 Hypoplasia uterus 7=SRY-3;SRY+4 Antiverted uterus 1=SRY+ Karyotypes & AR & SRY genes: 46,XY & AR+ = 1 (infantile) 46,XY & SRY- = 1 (present) 46,XY & SRY- = 1 (rudimentary) 46,XY & SRY+ = 1 (rudimentary) 46,XY & SRY- = 1 (hypoplasia) 45,X/46,XY & SRY- = 1 (hypoplasia) 46,XY & SRY+ = 3 (hypoplasia) 45,X/46,XY & SRY + = 1 (hypoplasia) 46,XY & SRY+ = 1 (antiverted) Female external genitalia: 22/25 AR-6;AR+4;SRY-5;SRY+7 Karyotypes & AR & SRY genes: 46,XY & AR- = 5 45,X/46,XY & AR- = 1 46,XY & AR+ = 4 46,XY & SRY- = 4 45,X/46,XY & SRY- = 1 46,XY & SRY+ = 5 45,X/46,XY & SRY- = 2
3	46, XY females with ovotesticular DSD and with variable testicular tissue, AMH function and uterus.	-

1 and 2, it could be interpreted that with the help of genetic counseling and appropriate management and therapy, the probands with SRY+ and AR+ could be reared as male and female individuals. From table 3, it is seen that the probands have manifested age related features.

It is stated that, as per the presence of the uterus and other mullerian derivatives, the phenotype of adult 46,XY females could be grouped into 3 major categories (Berra *et al* 2010).[1] In table 7 is shown the features of the 46,XY female under the 3 categories of the present study with that of the observations from the literature.

It is seen, that in the present study, based on the presence or the absence of the uterus along with the female external genitalia, 13 probands could be included into the category of AIS without uterus and 12 as GD with uterus and female external genitalia. The grouping is in accordance to the classification by Berra *et al* (2010).[1] Among the 13 AIS, 12 are under the subcategory of the study on AR gene and among the 12 GD cases, 11 are under the study of SRY gene category. From the classified presence of uterus, it is seen, that the hypoplasia and rudimentary uterus are associated to the SRY- and SRY+. The association to the karyotype and the AR gene showed the absence of the uterus in 46, XY with AR- in 7 and AR+ in 4.

The age of the presentation has led to 6 groupings:

i. Diagnosis in utero;
ii. AG at birth;
iii. Cloacal exstrophy;
iv. Inguinal hernia;
v. Virilisation at puberty;
vi. PA. (Berra *et al* 2010)[1]

In the present study, the probands fitting into the 1st and the 3rd groups have not been observed.

AG at birth

AG is considered to be the common presentation inn the pediatric age group. The presence of the Y may initiate a degree of virilisation at birth; thereby implicates the presence of the functioning testes and AMH and the likelihood of the absence of the uterus.

In the present study, the observed AG in 2 cases are associated to the absence of the uterus; 46,XY karyotype and one each with AR- and AR+ gene. One case has been referred below 14 (AR-) years and the other one above 14 (AR+).

Inguinal hernia

From literature, it is seen that the descent of the testes are androgen dependent; hence their presence indicates CAIS. (8) In a study on 93 females with CAIS 32 (34%) had inguinal hernia and their age ranged from one month to 11 years. It is also estimated that 0.8 to 2.4% of the premenstrual girls with inguinal hernia have CAIS. (9) In the present study, 3 cases of the AIS (3/13, 23% or 3/25, 12%) had bilateral inguinal hernia along with the absence of uterus and 46,XY karyotype and AR- (2) and AR+ (1) genes. 2 with AR- gene are above 14 and one with AR+ is below 14 years.

Virilisation at puberty

The features include failure in the development of the female secondary sexual characters, enlarged clitoris, deepening of the voice and excessive body hair in a male pattern. The origin of the androgens is likely to be testicular with concomitant AMH secretion and absent uterus. The diagnosis could be 5AR or 17β–HSD deficiency. In the present study, 2 with AR- and below and above 14 years and one with AR+ above 14 years manifested virilisation (coarse/ hairy/ hyperpigmented skin).

Primary amenorrhea

46,XY females presenting with PA vary in the age of their first assessment. They may not have androgen as in 46,XY GD or completely resistant to the effect of the androgen as in

CAIS. The former group is also oestrogen deficient and therefore present with pubertal delay. Women with CAIS usually have normal breast development and the presentation may be a little later than those with GD. The assessment of the uterus in women with oestrogen deficiency presenting with PA is particularly difficult with the ultrasound often reporting an absent uterus. From the experience it is suggested that it is better to delay making any conclusion regarding uterine development until at least 6 months of oestrogen priming have taken place. In the present study, PA as the chief complaint was present in 20 (AR-5/ AR+4/ SRY-5/ SRY+6). The 11 PA with SRY- and SRY+ genes are exactly matched the 11 with uterus (SRY-5/ SRY-6); the 9 PA cases with AR- and AR+ genes are associated to the 12 without uterus (AR-8/AR+4). As informed in the literature it is these cases which need the follow up for the presence of the uterus.

Specific molecular diagnosis has been made only in a small percentage of DSD cases. Instead, most diagnoses are made on clinical grounds. Among the 46,XY females, only 47.8% have had accurate diagnosis. Ideally the diagnosis should be made at birth to assure the correct multi disciplinary assessment throughout childhood. The delayed recognition could lead to greater difficulties in accepting the diagnosis. (Berra *et al* 2010)[1] For correct diagnosis, several aspects need to be considered and one of them is the hormonal assay when gonads are in situ; because after gonadectomy, it becomes difficult to make the accurate diagnosis. Genetic diagnosis should be made as early as possible. In the present study, from the clinically and the cytogenetically confirmed 108 46,XY cases, 25 volunteered for the molecular investigation.

Based on the mullerian derivatives, the 25 were referred for molecular confirmation of AR in 13 and SRY in 12. The AR mutation was determined in 5/13 (38.5%) or 5/25 (20%) and absence of SRY in 5/12 (41.7%) or 5/25 (20%) and the total is around 40% (10/25).

The age of presentation vary according to the diagnostic category and are described under 3 groups. For females with CAIS, the younger age groups comprise those who were found in utero and those presented with inguinal hernias. The second diagnostic group presents later with PA. It is interesting that women with GD are presented years after the manifestation of the delayed puberty which should be evident by age 16. In general, between the 3 groups as per the age at referral, female with AG under the label of PAIS are presented the earliest of the 3 groups. (Berra *et al* 2010) In the present study, 3 cases with AG belonged to the 1st group. PA cases were 20; out of which belonged to the 2nd and the rest to the 3rd group.

3 with AG are in the younger age group; 2 with AR- gene above 14 and one with AR+ below 14 years. Among the 20 with PA, 2 2 with SRY+ below 14 and the rest 18 above 14 years; AR- and AR+ above 14 are 5 and 4; SRY- and SRY+ above 14 are 5 and 4.

Conclusion

46,XY females comprise a heterogenous group, which differ not only in their diagnostic category and anatomy but also in their journey through life to adult services. Medical and surgical care required. A multi disciplinary team for the care and liaison with support groups.

References

1. Berra M, Lih-Mei Liao LM, Creightona SM, Conwaya GS. Review- Long-term health issues of women with XY karyotype. *Maturitas.* 2010; 65: 172 -178.
2. Lee PA, Houk CP, Ahmed SF, Hughes IA. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinilogy. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006; 118: 488-500.
3. Mendonca BB, Domenice S, Arnhold IJ, Costa

EM. 46, XY disorders of sex development (DSD). *Clinical Endocrinol (Oxf).* 2009; 70: 173-187.

4. Achermann JC, Hughes IA. Disorders of sex development. In: Kronenberg HM, Melmed S, Polonsky KS, Reed Larsen P, editors. Williams Textbook of Endocrinology. 11th ed. Philadelphia: Elsevier; 2008.
5. Thangaraj K, Joshi MB, Reddy AG, Gupta NJ, Chakravarty B, Singh L. CAG repeat expansion in the androgen receptor gene is not associated with male infertility in Indian populations. *J Androl. 2002b;* 23(6): 815-818.
6. Thangaraj K, Singh L, Reddy AG, Rao VR, Underhill PA, Pierson M, Frame IG, Hagelbe RE. Genetic affinities of the Andaman Islanders, a vanishing human population. *Curr Biol.* 2003b; 13: 86-93.
7. Singh R, Vutukuri R, Nalini JG, Baidyanath C, Lalji S, Thangaraj, K. SRY-negative 46, XX male with normal genitals, complete masculinization and infertility. *Mol Hum Rep.* 2006; 12;5: 341-346.
8. Gardner AT, Howell RT, Davies T. Human Genetics. New Delhi: Viva Books Private Ltd; 2008.
9. Jorde LB, Carey JC, Bamshad MJ. Medical Genetics. 4th edition. Philadelphia, USA: Mosby, Elsevier; 2010.
10. Turnpenny P, Ellard S. Emery's Elements of Medical Genetics. 2012. 14th edition. Philadelphia, USA: Churchill Livingstone Elsevier.