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Original Article

Physiological, Psychological and Genetic Expressions of XY Female Reporting at Tertiary Care Infertility Clinic of Kingdom of Saudi Arabia

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Abstract

Background: Disorder in sex development (DSD) refers to a variety of diagnoses in which the development of chromosomal make-up, gonadal development, or anatomical development is abnormal. The most prevalent XY, DSD diagnosis is Complete Androgen Insensitivity Syndrome (CAIS), in which an individual has XY chromosomes but is phenotypically feminine.
Objective: To analyze the clinical features, management along with findings of diagnostic procedures like Ultra sounds and genetic testing of XY female reporting at tertiary care infertility clinic of KSA.
Study type, settings & duration: This retrospective study of 6 months duration was conducted on the basis of a five year data i.e. (2013-2018) of the female presented with amenorrhea at A Tertiary Care Infertility Clinic of KSA.
Methodology: Data of 110 female fulfilling the inclusion criteria was retrieved from institutional data base on a predesigned questionnaire. Data was collected regarding patient's demographics characteristics, clinical presentation and management, along with findings of ultrasound and genetic testing.
Results: Total 110 patients of primary amenorrhea reported to the Reproductive Endocrinology and Infertility Medicine Department (REIMD) from 2013–2018. Among them 40 had uterine/cervical/vaginal abnormalities, 30 had Mayer-Rokitansky-Küster-Hauser(MRKH)/ Obstructed Hemi-vagina and Ipsilateral Renal Anomaly (OHIRA) syndrome, 35 had primary Premature Ovarian Insufficiency (POI) and 5 patients with Disorder of Sex Development (DSD) XY females were identified. Median age of patients was 18 years (interquartile range (IQR) 15-22) with a median BMI of 25.6 (IQR 20.5, 37.2). In three (60%) patients there was complete androgen insensitivity, while two (40%) had partial androgen insensitivity. All of them presented with positive family history. Examination revealed blind ending vagina (80%), clitoromegaly (20%) with tall stature (100%). The genetic study carried out for four patients showed SRD5A2 gene mutation. Treatment was with hormonal replacement therapy after laparoscopic gonadectomy and cystoscopy with multidisciplinary team in four cases (80%).
Conclusion: The diagnosis of XY females can be challenging, and awareness of this condition is needed, particularly as the mental health issues are increasing. There appears to be a clear association between number of family members affected and XY females. Though consistent management strategy was evident in our series, mental health issues were challenging. Moreover, genetic analysis results necessitate the need for Whole Genome Sequencing (WES) to find out the exact mutational variability in the population.
Key words: XY females, expressions, genetic, physiological, psychological.

Introduction

Androgen insensitivity syndrome (AIS) is a form of the sexual disorder that affects 2 to 5 per 100,000 people.[1] The genetic constitution of a male is with one X chromosome and one Y chromosome in every cell.[2] On the seventh week of a human fetus, the testes develop that secrete testosterone and antimullerian hormone (AMH).[3] The mullerian ducts, uterus, fallopian tubes and upper vagina are regressed by AMH, while testosterone helps to separate the wolffian ducts into the epididymis, vasa

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Authors Contribution

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deferentia and seminal vesicles. [2,3] In cases where there is disruption of this sexual differentiation, the result will be atypical development of the gonads, or the phenotypic sex, thus leading to disorders of sexual development (DSD).[1-3] DSD are classified into two types; 46, XX DSD and 46, XY DSD.[1,4] The patients with DSD are diagnosed when they present with either amenorrhea or delayed puberty.[4,5]

The Androgen insensitivity syndrome (AIS) is of two types, complete androgen insensitivity syndrome (CAIS) can either present in infancy as inguinal swellings or in adolescence as primary amenorrhea.[6] The female adolescent breast and pubertal growth is in accordance to age due to excess aromatization of androgens but menstrual cycle does not start.[6] Individuals of this sort of disorder have feminine external sex features, but have no uterus, meaning they do not menstruate and are infertile.[5,6] Typically they are raised as females and have feminine gender traits, but they have male internal sex organs, the testes, which are undescended.[7] These testes are abnormally positioned in the abdomen or pelvis that are at risk of cancerous changes most commonly gonadobalastomas.[2] It is the abnormal location of testes which necessitates their surgical removal. [7]
Partial androgen insensitivity (PAIS) is less common in comparison to complete androgen insensitivity. Partial and moderate manifestations of androgen insensitivity syndrome arise from the partial response of the body's tissues to androgen effects.[8] Individuals with partial androgen insensitivity (also known as Reifenstein syndrome) can have female genitals and some may have ambiguous genitals.[8,9] Raising of these individuals vary as some may be grown up as males while others as females. Therefore, the gender identity may be a male or a female. Patients of moderate androgen insensitivity are born with male sex features, but they are frequently infertile and appear to undergo breast enlargement at puberty.[9]

The diagnosis of AIS is further confirmed with blood tests, karyotyping, and ultrasound.[5] The SRY gene provides instructions for the development of a protein called the androgen receptor. SRY gene provides directions for making a protein called an androgen receptor.[6,9] Androgen receptors allow cells to react to androgens that guide the sexual growth of men. In both males and females, androgens and androgen receptors also have other important functions, such as regulating hair development and sex drive. SRY gene mutations inhibit androgen receptors from controlling the expression in the target tissues of androgen-responsive genes.[4]

Depending on the androgen insensitivity stage, the sex characteristics of an infected individual will diversify from mostly female to mostly male.[3] This condition's succession pattern is X-linked recessive. On the X chromosome, the mutant gene that produces the condition is determined. There is only one X chromosome in males that is genetically present. Two X chromosomes are genetically found in females, so a mutation in both copies of the gene must be found to contribute to AIS.[10] Mothers with a mutated copy of the SRY gene on one of their two X chromosomes lead to two-thirds of cases of androgen insensitivity syndrome, while the majority of the cases are caused by a new mutation that arises naturally during fertilization or early fetal development.[4,10]

Methodology

There were 110 patients of primary amenorrhea that presented to the Reproductive Endocrine and Infertility Medicine Department (REIMD) at King Fahad Medical city from 2016-2018.

Clinical data were collected including menstruation, marital status, family history, psychological problem, diagnosis, cause, breast examination, secondary sexual characteristics, vaginal presence and external genitalia. The laboratory investigation revealed thyroid-stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), 17-hydroxyprogesterone (OHP), dehydroepiandrosterone (DHEAS), total testosterone, prolactin, ultrasound and MRI (magnetic resonance imaging) were recorded. The genetic makeup including karyotyping, cytogenetic analysis, fluorescence in situ hybridization (FISH) and molecular genetics were carried out to find involved genes. Cytogenetics interpretation was based on FISH analysis result and chromosome analysis findings. The FISH was carried out using the Yp11.3 (SRY) critical region DNA probe with the X centromere (DXZ1) control locus, to identify the copy number of the X chromosome and the presence of the SRY region. Multidisciplinary team management was key in our study; surgery with age at gonadectomy, histopathology of the gonads and hormonal replacement therapy were discussed. Moreover, psychological manifestation as anxiety or depression ‘what they are raised as and what they want to be’ were discussed in consultations and social worker counseling, were included.

The Ethical approval was obtained from Institutional Review Board of King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia.

Results

Out of 110 patients presenting with primary amenorrhea 40 presented with uterine/ cervical/ vaginal abnormalities, 30 presented with Mayer Rokitansky Küster Hauser(MRKH)/ Obstructed Hemi-vagina and Ipsilateral Renal Anomaly syndromes(OHAIRA), 35 presented with primary premature ovarian failure and 5 patients with disorders of the sex development (DSD) XY females were identified (Figure-1).

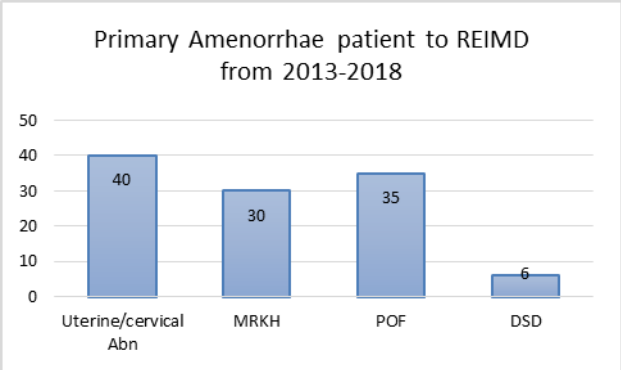

Figure 1: Frequency distribution of primary amenorrhea cases in different clinical categories. (n=110)

Five cases of the XY females were identified from 2016-2018. The median age of the patients was 18 years (interquartile range (IQR) 15, 22) with a median BMI of 25.6 (IQR 20.5, 37.2). Four of five patients were unmarried. Primary amenorrhea was the most common presenting symptom (5 cases) (100%). All of them had positive family history of females with similar presentation. All females reported psychological issues in the form of depression or anxiety, interpersonal sensitivity, aggression and psychoticism. Our study concluded that due to markedly increased mental distress, treatment should concentrate, in addition to physical factors, more on psychological well-being. Only professional therapeutic aid was available to all patients which is not adequate for severely compromised psychological outcomes. Physical examination revealed blind-ending vagina (80%), clitoromegaly (20%) with tall stature (100%). The development of secondary sexual characteristics in 40% was delayed, however, breast development in 60% was Tanner stage 3-4. The median FSH level was 3.7 IU/ml, LH 21.6 IU/ml, TSH 3.7, 17OH progesterone 2.8, Dehydroepiandrosterone Sulphate (DHEAS) 4.3 pg/ml and prolactin of 250. In three patients (60%), there was complete androgen insensitivity, while two (40%) had partial androgen insensitivity. The diagnosis was made by ultrasound showing absent uterus and ovaries with bilateral testes in the inguinal region and rudimentary vagina with a normal renal system (100%). The diagnosis of complete androgen insensitivity (CAIS) was made in 67% cases compared to 33% with partial androgen insensitivity (PAIS) cases (Figue-2). Moreover, the karyotyping revealed XY females in 100% of cases. The result revealed the presence of one X chromosome centromeres and one SRY gene signals which was consistent with a male genotype. Karyotype showed (DXZ1, SRY) x1. Genetic study was carried out for patients which showed SRD5A2 gene mutation. Moreover, this result was confirmed with chromosomes karyotype analysis, which is reported separately by repeat peripheral blood sample to the cytogenetic lab for confirmatory karyotype analysis. It showed that the number of metaphases chromosome analyzed were 20 and 2 were karyotyped with no extra counts of chromosome. The diploid number of chromosomes per cell were 46 and the sex chromosome constitution was XY. There were no numerical or structural chromosome aberrations and the banding resolution was 525 with final a karyotype of 46 XY. Analysis of chromosomes showed 46 XY, a typical male karyotype, with no significant anomalies in numbers or structures (Figure-3).

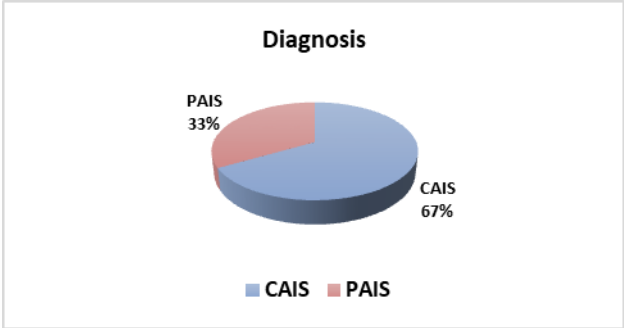

Figure 2: Distribution of findings of genetic analysis of XY female.

Treatment was with hormonal replacement therapy after laparoscopic gonadectomy and cystoscopy with a multidisciplinary team in four cases (80%). Although all the subjects were raised as females, psychological consultation revealed that 40% of them had a strong desire to be male.

Discussion

The term “disorder of sex development” covers any congenital anomaly in which the genitalia in contrast to the genes, gonads or

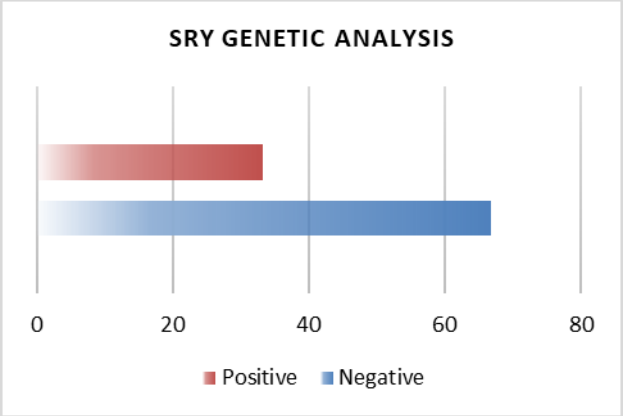

Figure 3: Distribution of findings of SRY genetic analysis of XY female.

anatomical sex is atypical. 1 In order to describe the category of DSD, now known as XY DSD or XX DSD, karyotype is used as a prefix. In our study, we selected patients based on the DSD generic definition, all with XY DSD. Among physical characteristic some pubic hair, breast development to tanner stage 3-4, and vestigial wolffian duct derivatives with inadequate length of vagina are found in patients with symptoms of functional defective androgen receptor (AR) gene mutation. [4,6] In our study, we found 60% of patients with Tanner 3-4 breast and 80% of them had a blind vagina, while 40% of the patients had ambiguous external genitalia. The median gonadectomy age was 5.5 years (5.5; IQR 1-13) and two cases of in situ carcinoma have been reported in post-pubertal patients.[7] In our sample, on the other hand, this median age of patients was 16.5 years and the histopathology of all patients was normal, nonmalignant testicular tissue.

In families with CAIS, phenotypic variance was absent, but distinct phenotypic variation was found to be moderately common in families with partial androgen insensitivity.[4,8] In our study, all patients had positive family members with the same phenotypical variation. The elevated psychological morbidity in CAIS women highlights the need for therapeutic understanding of these patients' psychiatric vulnerability.[7,8] Our study confirms this finding, as all patients experience a major psychological impact on diagnosis. Moreover, their family members also manifest symptoms of depression/anxiety due to the diagnosis, sex assignment and coping up further.

Minto CL, 2003, found that 90 % of women with CAIS had sexual problems relative to the general female population, such as sexual infrequency and trouble with vaginal penetration.[11] However, in our study, 80% had not developed sexual relationship yet. The male sex determination is directed by Y chromosome and the specific locus is termed as SRY (sex-determining region Y). In patients with 46 XY testicular dysgenesis, mutation analysis of the SRY gene strongly shows that the HMG box region with its DNA binding and bending capacity is central to this gene's role as the "switch" that initiates the testis-determining pathway.[12] A new component in testis production has been identified by the recent isolation of the SOX9 gene. Mutation study in campomelic dysplasia and sex reversal patients revealed that both the HMG box and the SOX9 transactivation domain are essential for the proper functioning of both skeletal and testis growth.[13] Our study result revealed the presence of one X chromosome centromeres and one SRY gene signals which was consistent with a male genotype. Karyotype showed (DXZ1, SRY) x1 and the genetic study confirmed SRD5A2 gene mutation.

In summary, the formation of internal and external genitalia is aided by a complex pathway governed by genes and hormones that leads to gonadal differentiation into testis or ovary.[14] After nongenetic factors have been ruled out, chromosomal analysis should be considered for a more accurate diagnosis and development of more effective management for females with amenorrhea.[15] The importance of the multidisciplinary team's participation is emphasized, as well as the need for investment in psychological and nursing care for girls with CAIS and their families.[16]

XY disorders of sex development (including complete and partial androgen insensitivity syndromes) are challenging condition but with advances in this area and multidisciplinary approach, the diagnosis is quick and treatment is promising. However, psychological aspect need more attention and long term follow up.

RM conceived the framework of manuscript, wrote the introduction, the section, method, results and discussion part; and coordinated the final report. JD contributed the infertility section, and helped in final proof reading and scientific edition.

Conflict of interest: None declared.

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