Androgen Insensitivity Syndrome – Diagnostic and Management Issues: A Case Report

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Abstract:

In a genetically male (XY) foetus, active intervention by administration of male hormones is needed for development of a complete male reproductive system and male phenotype. When there is target organ resistance to androgens, virilisation is prevented and Androgen Insensitivity Syndrome occurs. It is an X linked recessive disorder where genotypic males are phenotypically females. However, they lack the female reproductive system. Sensitive handling of such cases is required, as the individual and "her" parents undergo immense pychological trauma inorder to come to terms with the gender identity issue.

Key Words: *Androgen insensitivity syndrome; Testicular feminising syndrome*

Background

Androgen Insensitivity Syndrome (AIS) is an X linked disorder characterized by variable defects in virilisation of genotypical 46 XY individuals.[1] This syndrome, also known as Testicular Feminizing Syndrome was first described by John Morris in 1953 at Yale.[1] It presents as a form of male pseudohermaphroditism where a phenotypic female has male gonads. These individuals have 46 XY chromosomes as their genotype, thereby causing tremendous psychological trauma to both the individual and "her" parents. In utero, androgen insensitivity causes an interruption of foetal development of the reproductive system. The embryonic testicles develop inside the body and produce androgens which are ineffective due to unresponsiveness of foetal body tissues to their actions.

Case report

A 20 year old married woman of Indian origin, presented to the gynaecological outpatient of a rural medical college of central India, with history of not having attained menses, bilateral inguinal swellings and marital disharmony due to coital difficulties. She was the elder of two sisters. Her younger sister (16 years old), had attained menarche at the age of 14 years. She was married for the last 1 year, but was separated from her husband. In the early days of marriage, sexual intercourse was attempted once or twice but was abandoned due to difficulty in penetration of vagina and dyspareunia. The woman was sent back to her parental home by her husband, citing non consummation of marriage. On examination, "she" had normal feminine outlook, was above average height (170 cm) and thin built (weight 40 kg). Axillary and pubic hairs were absent; however she had very well developed breasts. Her face was clean with no signs of acne and her sense of smell and vision were normal. Examination of external genitalia showed well developed normal looking labia majora, minora and clitoris. However, there were two, 3x3 cm, oblong swellings in each inguinal region, probably inguinal testicles. Per vaginum examination revealed a 5 cm long vagina which ended in a blind pouch. No cervix was observed and on bimanual examination no uterus was palpable. Ultrasonography confirmed the absence of a uterus, cervix and both ovaries. Inguinal ultrasound confirmed presence of bilateral inguinal testicles. Hormone studies showed serum luteinising hormone, follicle stimulating hormone and testosterone all of which were within normal levels for males. Serum oestradiol was 60.22pg/ml, adequate for phenotypic female development. Karyotype was determined to be 46 XY.

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Having made a diagnosis of Androgen Insensitivity Syndrome, the woman and her parents were counselled about her condition. Special attention was paid to her being phenotypically female with normal breasts and well developed vagina. They were also counselled regarding need for removal of the male gonads. With due consent gonadectomy was performed, the histopathology report of which showed bilateral atrophic testes. She was prescribed oestrogen replacement therapy postoperatively. In her next follow up visit the woman came with her husband. With the help of a social worker, psychologist and counsellor, the nature of the condition was explain to the couple. Her husband was assured that the size of the vagina was adequate for normal sexual relationship. The couple is now able to have intercourse and are planning adoption of child for which our centre is supporting them.

Discussion

Intersex is a condition where a person has contradictory phenotype and genotype. AIS is one such disorder where a phenotypic female has testes as gonads. Since its first report by Morris, investigators have tried to elucidate the underlying mechanism of occurrence. In 1970, Lyon and Hawkes reported a X linked gene for testicular feminization.[2] In 1989 the exact location of the human androgen receptor gene (AR gene) was defined on Xq 11-12, and in the same year the proof that AIS was caused by mutation in the AR gene was published by Brown et al.[2]

Androgen Insensitivity Syndrome is an archetype of hormone resistance. Androgens are secreted by these individuals in normal or increased amounts, but due to defective androgen receptor function there is loss of target organ response to the male hormone and therefore its effects are reduced or absent.[1,3,4] The basic aetiology of loss of function is a mutation on the androgen receptor gene in the form of complete or partial deletions, point mutations or small insertions. These can cause a variety of functional defects ranging from a complete loss of receptors on the cell surface (because of incomplete protein synthesis) to alteration in substrate binding affinity. Loss of AR function means that despite normal levels of androgen synthesis, the post receptor events that mediate the effects of the hormone do not occur. This results in prenatal under virilisation of external genitalia, the absence of pubic and axillary hair and no voice changes at puberty in an individual with XY karyotype. Although the external genitalia are female, the development of the female internal organs is suppressed by Mullerian inhibiting factor from the foetal testes. A mother who carries the defective gene has a 1:2 chance of any XY genotype child having AIS manifestation and 1:2 chance of any chid with XX karyotype being a carrier of this anomaly.[5]

AIS has traditionally been classified into 3 groups: depending on genital phenotype.

(1)Complete (CAIS)

(2)Partial (PAIS)

(3) Mild or minimal (MAIS).[2]

The incidence of CAIS is 1:20000-64000 /male births.[3,6] These subjects are born unambiguously female with normal female external genitalia and are reared as females. At puberty, breast development occurs but axillary and pubic hair is absent and there is no onset of menses (as in our case). They present with either primary amenorrhea or inguinal hernia, in an apparently female infant. Regardless of presentation, inguinal hernia is present in 90 % of AIS patients (31% unilateral and 59% bilateral).[7] Generally, the Mullerian part of the vagina (upper 1/3rd), is missing in these individuals, but in some cases the vagina may be no more than one or two centimetres in length. Other Mullerian structures such as the uterus and fallopian tubes are conspicuously absent. Even the Wolffian duct derived epididymis, vas deferens and seminal vesicles and prostate are absent.

Partial AIS comprises a vast spectrum of clinical phenotypes depending on the severity of under virilisation. Subjects may present as predominantly female with mild clitoromegaly and some fusion of labia at one end of the spectrum while at the other there is predominantly male appearance of external genitalia with micropenis, perineal hypospadias, cryptorchidism and gynaecomastia. The testes have reduced number of germ cells with azoospermia.[2]

In mild AIS the genitalia may be under developed in males or there may be simple coronal hypospadias or prominent midline raphe in the scrotum. They present with impaired fertility and reduced spermatogenesis.[2]

The endocrinological profile of both CAIS and PAIS is the same, with elevated serum testosterone and luteinizing hormone (LH) levels. The high levels of increased testosterone form a substrate for aromatize activity which gives rise to substantial amounts of oestrogen. This results in adequate breast development at puberty in CAIS subjects. In PAIS, human chorionic gonadotropin testing

is necessary to demonstrate normal testosterone and dihydrotestosterone production in order to exclude defects in testosterone biosynthesis and 5 alpha reductase deficiency. High levels of leutinizing hormone results from reduced sensitivity of hypothalamus and pituitary to negative feedback by sex steroids. The increase in LH results in increased production of testosterone. Ultrasonography of the inguinal region, CT scan of abdomen and pelvis and sometimes MRI are useful in locating the presence of testicular tissue.[8] Karyotyping of the individual is mandatory for diagnosis. A sophisticated family history and genetic studies may be undertaken to detect carriers in the family.

Management starts with the assignment of sex at birth. In general, the sex of rearing is assigned on the basis of genital phenotype, hormonal data, clinical response to testosterone treatment trial, feasibility of reconstructive surgery and molecular basis of the AR gene. This is a complicated decision in children with ambiguous genitalia. However in CAIS infants there is no such dilemma and the sex of rearing is always female. Experienced psychiatric support is extremely important in the management of these women. Some clinicians and parents, in a misguided attempt to spare the individual psychological trauma, withhold the genetic and gonadal information. However, most professional caregivers recommend that the truth be known to the patient and adequate psychological support be provided. The parent's emotional needs should also be addressed, preferably by trained staff, so that they can support their child. Counseling was the mainstay of treatment in our case, and the woman later acknowledged its importance to us. The sense of stigma, once removed, allow individuals to accept their biological status in order to have a normal female gender identity.[2,9] Another important consideration is the treatment of vaginal hypoplasia, which should not be overlooked because it may be discovered very early by self examination. These patients may then live in fear and isolation with this secret for many years. Vaginal penetration difficulties and dyspareunia may be associated with this presentation and as a consequence, failed attempts at intercourse may lead to alienation, as in our case. A small hypoplastic vagina can be treated with nonsurgical methods such as pressure dilatation performed by the patients in the privacy of their homes. Plastic surgical methods of lengthening the vagina should be resorted to judiciously and only after a trial of non-invasive techniques. Vaginoplasty in childhood has poor results as regular dilation with dilators or regular intercourse is necessary to avoid stenosis.[2, 3, 9]

The removal of contradictory gonads in CAIS is a common practice and should be considered once natural puberty is achieved, since feminization is achieved by conversion of androgen to oestrogen. Gonadectomy prevents the risk of malignancy (5-10 %) in undescended testis. Once the gonads are removed, there is risk of reduced bone mineral density and osteoporosis, hence adequate oestrogen supplementation should be provided. Pre-pubertal gonadectomy is indicated only if inguinal testes are physically or aesthetically uncomfortable and if inguinal herniorhaphy is necessary. Oestrogen therapy is required to maintain feminization and to avoid osteoporosis.[8]

Conclusion

Androgen Insensitivity Syndrome is one of the examples of male pseudo hermaphroditism and requires sensitive handling. Our case emphasizes addressing the psychological issues and providing a holistic approach to management. Talking with patients and her relatives is therapeutic and permits the release of pent up feelings. Important issues such as marital relationships can be confronted and resolved. Active discussion and allaying of fears help in strengthening gender identity. Reproductive failure being the norm, providing additional support such as child adoption also improves the quality of life and gives a feeling of completeness as a woman. We were able to achieve this in our case. This case is unique because the individual presented to us at the age of 20 years with primary amenorrhea. Parents had made no efforts to get her investigated prior to that and had married her off without paying adequate attention to the very important issue of not having attained menarche. Gynaecological consultation was sought when marital disharmony occurred and the daughter of the house returned to her parental home. The psychological trauma the individual underwent, due to delay in seeking professional help was tremendous. We are satisfied that a reasonable solution could be found for our case.

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