Abstract:
A 16 year old phenotypic female presented with primary amenorrhea and on investigation was found to have no uterus, tubes or ovaries, instead intra-abdominal tests were found. Further investigation revealed high levels of LH and Testosterone and 46, XY karyotype, suggestive of genotypic male with Complete Androgen Insensitivity Syndrome. We present this case, taking this opportunity to discuss the presentation and pathophysiology of the condition and recommend guidelines for early diagnosis and optimal care of the individuals.

Key words: Androgen Insensitivity Syndrome (AIS), Complete Androgen Insensitivity Syndrome (CAIS), Testicular Feminization, Androgen receptor defect, Androgen resistance.

Introduction:
Complete Androgen Insensitivity Syndrome (CAIS) is a rare X-linked recessive disorder affecting between one in 20,000 to 64,000 male births [1][2]. This is the extreme of a spectrum of insensitivity of androgens due to mutations (germ line and somatic), clinically presenting as a adolescent phenotypic female who is tall and lean, with feminine features and normal breast development but with amenorrhea, deficient axillary and public hair and absent or blind ending vagina. They may also present as children with inguinal hernia, often bilateral, in about 1 – 2% of cases [3].

Not infrequently, these individuals have been found to have persistent Mullerian duct derivatives [4] like atrophic fallopian tubes (study of Rutgers and Scully quoted).

The gene coding for the Androgen receptor, the AR gene has been located in the 11 – 12 position of the long arm of the X chromosome [4]. Mutations of this gene can be either transmitted (two thirds) by the clinically normal mothers, in which case other siblings will be affected, or may arise de novo (one third).
Case report: A 16 year old phenotypic female presented with primary amenorrhea. She had a lean and tall body habitus, her breast development was Tanner Stage 4, axillary and pubic hair was Tanner Stage 2, and had a short (2.5 cm) blind ending vagina with normal appearing mucosa and candidiasis. An Ultrasound abdomen revealed absence of uterus, tubes and ovaries (a fact discovered four years ago when she had a laparoscopic appendectomy) and two ovoid structures near the internal inguinal rings resembling testes. Biochemical tests were as follows:

<table>
<thead>
<tr>
<th>TEST</th>
<th>VALUE</th>
<th>NORMAL RANGE (TANNER 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERUM ESTRADIOL</td>
<td>31.32 pg/ml</td>
<td>40-410 pg/ml, adult females</td>
</tr>
<tr>
<td>SERUM PROGESTERON</td>
<td>0.10 ng/ml</td>
<td>0.1 – 9.5 ng/ml</td>
</tr>
<tr>
<td>SERUM FSH</td>
<td>3.21 mIU/ml</td>
<td>1.0-92 mIU/ml</td>
</tr>
<tr>
<td>SERUM LH</td>
<td>25.28 mIU/ml</td>
<td>0.4-11.7 mIU/ml</td>
</tr>
<tr>
<td>SERUM PROLACTIN</td>
<td>9.57 ng/ml</td>
<td>3.2 – 20.0 ng/ml</td>
</tr>
<tr>
<td>SERUM TESTOSTERONE</td>
<td>502.69 ng/dl</td>
<td>10-40 ng/dl</td>
</tr>
<tr>
<td>SERUM T3</td>
<td>1.12 ng/ml</td>
<td>0.8-2.1 ng/ml</td>
</tr>
<tr>
<td>SERUM T4</td>
<td>9.0 ng/ml</td>
<td>5.01-12.45 ng/ml</td>
</tr>
<tr>
<td>SERUM TSH</td>
<td>3.94 mIU/ml</td>
<td>0.7-6.4 mIU/ml</td>
</tr>
</tbody>
</table>

The intra-abdominal testes were found to have rudimentary seminiferous tubules with no spermatogenesis and with interstitial fibrosis. Laparoscopy confirmed the complete absence of the uterus, cervix and tubes. There was only a long round ligament like structure arching up from the pelvis and extending between the internal rings on either side.

### Discussion:

<table>
<thead>
<tr>
<th>Grading</th>
<th>Genital appearance and clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (MAIS)</td>
<td>Normal phenotype, possibly gynecomastia or mild impairment of virilization</td>
</tr>
<tr>
<td>2 (PAIS)</td>
<td>Male phenotype, but small penis, penoscrotal hypospadia</td>
</tr>
<tr>
<td>3 (PAIS)</td>
<td>Predominantly male phenotype with micropenis, perineal hypospadia, cryptorchidism and possibly bifid scrotum</td>
</tr>
<tr>
<td>4 (PAIS)</td>
<td>Ambiguity of the external genitalia: very large clitoris, urogenital sinus with perineal opening and labio scrotal folds</td>
</tr>
<tr>
<td>5 (PAIS)</td>
<td>Predominantly female phenotype: large clitoris, separate openings of the urethra and vagina</td>
</tr>
<tr>
<td>6 (PAIS)</td>
<td>Female phenotype, androgen-induced pubic and axillary hair growth at the time of puberty. 50% inguinal hernia.</td>
</tr>
<tr>
<td>7 (CAIS)</td>
<td>Normal female phenotype. Lack of androgen induced pubic and axillary hair growth at the time of puberty. 50% inguinal hernia.</td>
</tr>
</tbody>
</table>

Table: Clinical classification of androgen insensitivity syndromes (Quigley, 2005):
* MAIS: mild androgen insensitivity syndrome;
* PAIS: Partial androgen insensitivity syndrome;
* CAIS: Complete androgen insensitivity syndrome [5].

Normally, Testosterone directly affects the bone, muscle and spermatogenesis, while its derivative Dihydrotestosterone has effects on the prostate, external genitalia and the genital skin.

Like in normal males, the production of the Mullerian Inhibitory Substance by the Sertoli cells in the testes inhibits development of any structures of Mullerian origin like the tubes, uterus, cervix and the upper third of the vagina.

Since individuals with CAIS have no functioning androgen receptors that the cellular level, there is absent development of any of the structures of Wolffian duct origin, like the epididymis, vas deferens and seminal vesicles [4]. The penis or scrotum also do not develop and the gubernaculaus is either insufficient or absent, so the testes remain crypt orchid. In newborns with complete androgen insensitivity syndrome (CAIS), the most frequent initial finding is unilateral or bilateral masses in the inguinal canals that are found to be testes during surgery [6], with a higher incidence of congenital inguinal hernia, often bilateral presenting in childhood [3].
Complete androgen insensitivity syndrome appears to be more common than partial androgen insensitivity syndrome, although exact figures are unavailable [7].

These individuals have large amounts of circulating androgens due to the absence of the negative feedback to the hypothalamus which is a result produces high levels of Luteinizing Hormone [8] which in turn stimulates the testes to overproduce androgens, and though these are ineffective in masculinization, are converted peripherally to estrogens, along with a small amount of estrogens normally produced by the testes. This, added to the finding that these individuals are ten times more sensitive to the effect of estrogens than are normal females, allows for the development of the female phenotype, with normal breast development, and development of the normal female external genitalia and a small blind lower two thirds of the vagina [4]. The increased height in these individuals seems to be related to the presence of the Y chromosome [9], also said to be related to the increased size of permanent tooth crowns [10] as compared with those of normal females. “Bone mineral density is directly related to the presence and amount of androgen activity, and thus these patients are likely to have less BMD as measured by the densitometer, in the hip and spine regions” [9]. “Women with complete androgen insensitivity syndrome often have reduced mean clitoral length compared with controls but are just as satisfied with sexual function as controls/healthy females” [11,12].

Approximately two thirds of cases inherit their faulty AR gene from their carrier mothers, who have a 50% chance of passing it on to their children, male or female. The other third develop the disease via new mutations.

In the experience of the primary investigator (who is also a practicing gynecologist) there have been three other similar cases (anecdotal information only) treated by him over the last five years.

- 25 year old phenotypic female, with amenorrhea and absent uterus and tubes had problems after marriage as coitus was not possible.
- 24 year old female phenotypic female, with amenorrhea and absent uterus and tubes was married after the husband was informed about the inability to have children, and had vaginal dilations.
- 18 year old phenotypic female, with amenorrhea and absent uterus and tubes committed suicide due to problems after marriage without informing the husband about the condition.

**Conclusion:**

1. CAIS is more difficult to diagnose than partial forms of the disease since extremely all features appear normal (except for a high incidence of inguinal hernia) till affected individuals fail to attain menarche.
2. Although classified as a Disorder of Sexual Differentiation (DSD), these individuals do not have any gender identity crisis, (at least till the diagnosis is made known to them) and are brought up as normal females.
3. Given its vast population, it is expected that there are between 10,000 and 30,000 individuals with CAIS living in India, and as such there needs to be better surveillance and detection for early and optimal management.
4. It is advisable to further investigate all female infants with inguinal masses, children with inguinal hernia, (especially bilateral) and adolescents with delayed menarche with ultrasound evaluation of the abdomen to look for agenesis of Mullerian structures, and confirm with karyotyping.
5. It is possible to lead a reasonably normal life after removal of the testes, with lifelong estrogen replacement and vaginal dilation or reconstruction, as long as there are no expectations towards conception and child bearing.
6. The affected individual, the parents, and also the prospective marital with their families should be educated and counseled regarding the condition, its treatment options and outcomes to avoid later problems.

**Summary:**

Complete Androgen Insensitivity Syndrome is at least as common (and more difficult to clinically suspect) than all the other variants of AIS put together. Simple tests are recommended during infancy, childhood and later on to diagnose and confirm. Early diagnosis enables optimal planning for long term management.

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**References:**