

Mini-Reviews

Complete Androgen Insensitivity Syndrome—A Review

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Abstract. This review paper highlights important diagnostic and therapeutic concerns for girls with Complete Androgen Insensitivity Syndrome (CAIS). CAIS is an androgen receptor defect disorder associated with vaginal and uterine agenesis in women with a 46,XY karyotype. The major clinical issues surrounding this syndrome include timing of gonadectomy, hormone replacement, vaginal dilation, and attention to psychological issues.

Key Words. Vaginal agenesis—Testicular feminization—Hormone therapy—Genetic disorder—Vaginal dilatation

Introduction

Complete androgen insensitivity syndrome (CAIS) is not a *nouveau* condition first described with the advent of modern diagnostic strategies. Anecdotal reports of androgen resistance date back to the 19th century and include suppositions that both Queen Anne and Joan of Arc were affected by the condition.^{1,2} In 1953, Morris described the clinical phenotype of “testicular feminization” after reviewing 82 cases. Morris’ phenotype included a female body habitus with normal breast development and minimal pubic and axillary hair. Although the external genitalia were within normal limits, the vagina was typically absent or rudimentary and the uterus absent. Gonads, found in the labia majora, inguinal ring, or intra-abdominally, were variably noted on physical exam.³ It was in this early description that the mechanism of androgen resistance, and not androgen deficiency,

was cited as the clinical culprit.³ The change in nomenclature from testicular feminization to androgen insensitivity syndrome (AIS) was prompted by the finding of normal urinary 17-ketosteroid levels, an androgen metabolite, as well as by absence of a treatment effect when 46,XY women were treated with methyltestosterone, suggesting androgen resistance rather than a deficiency.^{4,5}

Epidemiology

AIS is a genetic condition carried on the X chromosome. Although it is inherited in an X-linked, recessive fashion, up to 30% of mutations are sporadic *de novo* mutations.¹ The estimated prevalence of AIS is between 1 in 20,000 and 1 in 99,000 genetic males.^{6–8} If one examines phenotypic females with inguinal hernias, the prevalence is noted to be 0.8% to 2.4%.^{9–11} A literature search found no study documenting a difference in prevalence based on ethnicity, geography, or exposure.

Genetics

The gene responsible for creating the AIS phenotype has been localized to the proximal, long arm of the X chromosome at Xq11-12.^{12,13} There are 4 functional subsections, and 8 exons, within the 110-kDa androgen receptor (AR) protein.¹⁴ The subsections, or domains, consist of the (1) exon 1 encoding the N-terminal transactivation domain (NTD), (2) exons 2 and 3 which encode the DNA-binding domain (DBD), (3) the “hinge” region which binds the NTD and DBD and consists of residues 628-669, and (4) exons 4-8 which encode the ligand binding domain.^{1,15}

Similar to the other receptors found in the ligand-dependent nuclear receptor family, the DBD is highly conserved, containing the zinc finger region. The zinc fingers are responsible for direct DNA binding

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through the P-box and protein-protein interactions, as well as receptor dimerization, through the D-box. In short, the zinc fingers are responsible for target gene binding. Found within the NTD is a series of CAG amino acid repeats whose length seems to be inversely proportional to the AR transcription factor activity.¹ Also found within this domain is a polyglycine area. A contraction of this region has also been associated with AIS.¹⁵

Approximately 70% of AR mutations are X-linked recessive. There is an international database (The Androgen Receptor Mutations Database: <http://androgendb.mcgill.ca/>) that tracks known mutations and their associated phenotypes. Currently, there are approximately 750 known AR mutations resulting in various diseases including CAIS, partial androgen insensitivity syndrome (PAIS), mild androgen insensitivity syndrome (MAIS), and spinal and bulbar muscular atrophy (Kennedy's disease).

Testicular Function and Reproductive Tract Development

Beginning in the neonatal period, androgens are critical to human development. Male development can only occur if androgens are available to act on target tissues and complete sexual differentiation.¹ In the form of testosterone, androgens are responsible for Wolffian development and the formation of the epididymis, vas deferens, and seminal vesicles. Development of male external genitalia, including the penis and scrotum, is dependent on the presence of dihydrotestosterone (DHT). Production and secretion of testosterone, and its conversion to DHT, begins in the mid first trimester, at approximately 7–8 weeks of gestation. Placental human chorionic gonadotropin (hCG) mediates the initial production of testosterone via the Leydig cells. Sexual differentiation and development continues through 14–16 weeks of gestation.¹⁶ By the 16th week of gestation, placental hCG levels decrease and fetal LH secretion begins to control circulating androgen levels.^{1,4}

Mullerian inhibiting substance (MIS), or anti-Mullerian hormone, and insulin-like factor 3 are also critical in fetal reproductive development. MIS, produced by the Sertoli cells of the fetal testes, controls regression of the mullerian ducts. In the absence of MIS, the mullerian system develops into the uterus, oviducts, and upper vagina. However, in CAIS, MIS is produced normally by the testes resulting in inhibition of growth of the uterus and fallopian tubes. Insulin-like factor 3, also produced by the testes, controls the first phase of scrotal descent via outgrowth of the gubernaculum, while androgens control descent into the scrotum.^{1,4,17}

During the postnatal period, androgens are responsible for the initiation and progression of adrenarche as well as for puberty. In the developing female, adrenal and ovarian androgens play a role in the development of pubic and axillary hair. In the developing male, deepening of the voice, enlargement of the phallus, and male pattern hair development are controlled by androgens.

Presentation

In complete androgen resistance, there is no activity at the androgen receptor. This, in turn, creates a normal female birth phenotype in the setting of an XY genotype. The normal functioning testes produce physiological levels of testosterone and DHT. Due to the lack of negative feedback, it is not uncommon to find super-physiologic levels of testosterone and DHT in these patients.

The most typical presentation is that of primary amenorrhea in a phenotypic female adolescent. However, in an infant or child, the presentation may be of an inguinal hernia in a phenotypic female. Recent data shows a 1.1% incidence rate of CAIS in a child with a premenarcheal inguinal hernia, while 80–90% of girls with CAIS eventually develop an inguinal hernia.^{11,18,19}

In later presentations, a phenotypic female, with normal breast development, will present with primary amenorrhea. Exam reveals Tanner breast development consistent with age with scant to absent axillary and pubic hair. Height is typically normal to slightly advanced and the genitourinary exam reveals normal external genitalia and a rudimentary, blind ending vagina. In one Brazilian study, the average vaginal length was found to be 2.5–3.0 cm in a cohort of postpubertal CAIS patients.¹

Diagnosis

In the infant population, a full evaluation should be undertaken in the setting of an inguinal hernia. This includes a physical exam with an attempt to pass a sterile Q-tip into the vagina. In a toddler who is presenting with an inguinal hernia, an exam under anesthesia may be warranted to reduce patient anxiety and trauma. Based on the aforementioned 1–2% incidence rate of CAIS in the inguinal hernia population, a karyotype should be considered in all female children diagnosed with a hernia.^{1,18} Imaging studies, including the gold standard MRI, should be obtained in the CAIS patient to document internal anatomy (Fig. 1). If MRI is not available, transabdominal pelvic ultrasound may be useful.

In the adolescent patient, presenting with primary amenorrhea, a full physical exam should be



Fig. 1. Sagittal MRI image from a CAIS patient. Relevant anatomy, including the bladder and rectum are labeled. As expected, no uterus or vagina is seen.

performed in the office, with special attention to breast development and to pubic and axillary hair. A detailed exam of the external genitalia with documentation of hymenal anatomy should be performed. If the hymen is not easily identified, the provider should attempt to locate a patient's vagina by passing a sterile Q-tip. In addition, to rule out a lower vaginal obstruction, a rectal exam should be performed. The rectal exam, in combination with the absence of cyclical pain, helps to exclude an outflow tract obstruction.

As part of the differential diagnosis, one must consider Mayer-Rokitansky-Küster-Hausler (MRKH) syndrome or Mullerian Agenesis, a more common cause of primary amenorrhea with an incidence rate of 1 in 5000.²⁰ The MRKH patient, who will also have primary amenorrhea, normal breast development, and an underdeveloped vagina, typically has normal axillary and pubic hair.⁴ In this clinical setting, a karyotype is critical to making the diagnosis.

CAIS can be differentiated from Swyer's syndrome, XY complete gonadal dysgenesis, based on the lack of breast development and short stature typically seen with the later.¹ Imaging studies, such as ultrasound and MRI, are warranted to help delineate internal anatomy, localize testes, and rule out testicular tumors. In teenagers, the physical examination will narrow the differential diagnosis, and vaginal agenesis will most likely be due to the more common MRKH (46,XX) or CAIS (46,XY).

Hormone testing in the adolescent CAIS population will generally reveal an elevated testosterone in the setting of an abnormally high LH. Estradiol is also frequently found to be elevated.¹ Therefore, some clinicians choose to screen with a testosterone level (normal in MRKH and elevated in CAIS), and if in

the male range, obtain a follow-up karyotype. The importance of karyotype testing in this clinical scenario can not be overstated.

Treatment

In the female infant or toddler, no immediate therapy is needed or warranted. These patients have normal female hormonal levels, and have, in fact, never been exposed to elevated androgen levels, so they will develop into phenotypically normal females with scant axillary and pubic hair. Since the vast majority do not have even a rudimentary uterus, menstrual suppression is not an issue. These girls typically undergo puberty at the same time as their 46,XX counterparts and reach normal, if not slightly tall, final heights. Literature shows an average age of thelarche of 11.1 years with peak height velocity at 12.3 years. These time courses are consistent with average female values.²¹

Women with CAIS have been shown to have decreased bone density.²² However, adult bone density is similarly decreased regardless of the time of gonadectomy.¹ Adequate estrogen replacement during late adolescence and in the twenties will help build bone, but these patients need to be maintained on calcium and vitamin D as well as to institute regular weight bearing exercise. DEXA scanning should be instituted early with the addition of bisphosphonate therapy when indicated.

Though rates of dysgerminoma and gonadoblastoma in XY gonadal dysgenesis and 45,XO, 46,XY mixed gonadal dysgenesis can rise as high as 15–30%, the background rate in the CAIS population is lower.²³ Because the testes are normal (save the location) and not dysgenetic, tumors prior to puberty are rare. Recent studies reveal an 0.8% incidence in CAIS and a 5.5% incidence in AIS overall.²⁴ Approximately 5% of all dysgerminomas are associated with CAIS, XY gonadal dysgenesis, and 45,XO, 46,XY mixed gonadal dysgenesis.²⁵ Due to these incidence rates, the current recommendation is for removal of gonads after puberty. If there are concerns for carcinoma in situ or malignancy prior to puberty, the testicles can be removed and puberty induced with exogenous hormones, though this does not provide for the same natural progression into and through puberty.²⁶

Once final height and breast development have been obtained, the gonads can be removed laparoscopically. If there is concern for malignancy based on physical exam or imaging, one may need to consider the utility of a laparotomy. Because the gonads are frequently located along the pelvic sidewall, the surgery closely resembles a bilateral oophorectomy (Fig. 2). At times, the gonads will have descended into the inguinal canal necessitating a deeper

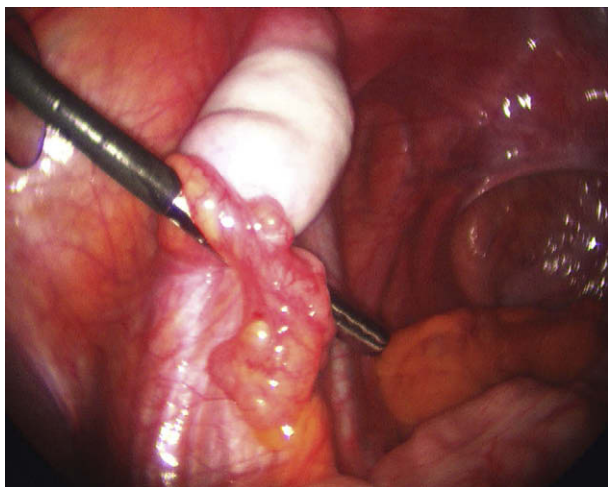


Fig. 2. Surgical photograph obtained at the time of laparoscopic gonadectomy. Within the image, one can identify the left gonad, as well as note the absence of the uterus.

dissection which may be unfamiliar to gynecologists. A general surgery or urology consult is indicated in these situations. Hormonal supplementation, most easily supplied through oral or transdermal estrogen, should be instituted after gonadectomy.

The issue of vaginal creation must also be addressed. The most important determinant of this process is the patient, who needs to be prepared to address this issue. As there is no medical urgency to vaginal creation, this process is frequently delayed until the patient voices a desire to proceed. This desire may be at the time of diagnosis, in late adolescence, or when sexual activity is desired. Extensive counseling regarding the process is an absolute before proceeding with vaginal creation.

Options for vaginal creation include dilation or surgical creation. The current expert consensus is to proceed with vaginal dilation when the patient and family are ready. The process of vaginal dilation can be uncomfortable, both physically and emotionally, for young girls. The process utilizes dilators of increasing size, and attempts to create length are made before attempts to create width are started. Once a CAIS patient has initiated regular, vaginal intercourse, dilation may be foregone. Should the patient no longer be engaged in regular intercourse, regardless of age, regular dilation should be resumed.

Should nonsurgical dilation be unsuccessful or undesired, then surgery is the other option for vaginal creation. It should be emphasized that surgical creation should not be considered a first-line therapy, but only attempted if dilator therapy has failed or the mature patient elects surgery after an extensive discussion regarding the risks and benefits.²⁷ There are various surgical techniques for vaginal creation, including the McIndoe vaginoplasty, the Williams

vulvovaginoplasty, vaginal creation using bowel, and the Vecchietti procedure, though the intricacies of these are beyond the scope of this article. For a review of surgical vaginal creation, please see Chapter 10, Structural Abnormalities of the Female Reproductive Tract, in *Pediatric & Adolescent Gynecology, 5th Edition*.²⁷ Complications of surgical vaginal creation include the standard complications of bleeding and infection, but specific risks, including stricture and scarring, must also be addressed. Vaginal dilation is necessary and critical following surgery to prevent vaginal stricture and scarring. Patients need to be extensively counseled to this particular aspect of their post-surgical management and must be willing to participate actively in their own care before surgery is undertaken.

Disclosure and Psychosocial Considerations

The issue and timing of diagnosis disclosure has been controversial. In 1953, John Morris compiled 82 cases from the medical literature and argued that the genotype of the CAIS patient should be hidden and that the patient need only be informed that “childbearing is impossible.”³ This set the tone for the mid-20th century with most clinicians advocating against disclosure. At times, the argument was even made that parents should not be informed of the true genotype. The idea of a physician’s “therapeutic privilege” was cited as the principle on which non-disclosure was based.²⁸

The practice of non-disclosure held a footing in our society through the 1990s. In 1988, the argument was made that the diagnosis could, or should, be withheld if it was thought that the patient, or family, would not be able to deal with the ramifications.²⁹ Four years later, this idea was upheld when Shah stated, “The disclosure of genotype is irrelevant to care and may be confusing to patient and family.”³⁰

Based on the principles of beneficence, non-maleficence, autonomy, and justice, it is now established practice to disclose the genotype at the time of diagnosis.²⁷ If the diagnosis is made in infancy or soon after, the parents, often in conjunction with a psychotherapist, will make the decision when to disclose. If the diagnosis is made in adolescence, the patient and family are generally told immediately.

The method of disclosure, and who should be involved in the conversation, will be dependent on the child’s age and cognitive function. Informing the parents first, so that they can participate in informing their child, may be beneficial in some settings.³¹ One of the most critical parts in explaining the diagnosis is that the patient should understand that she is a healthy, albeit an infertile, girl.³² The role, and attitude, of the clinician can not be overstated. When

later questioned, a majority of patients say they remember the interaction and dynamic between themselves and the diagnosing physician and that it plays a large role in how they see themselves and their condition.³³

A diagnosis of CAIS often leads to psychological distress in the teen and her family and counseling should be strongly encouraged. A psychologist, with experience in Disorders of Sexual Development (DSD) counseling, should be made part of the treatment plan as soon as possible.¹ Genetic counseling for the family is also recommended.^{1,32}

Although many parents have questions regarding gender identity and sexual preference, there is no documented increased rate of gender identity disorder, bisexuality, or homosexuality in CAIS patients.³⁴ As these girls have never been exposed to male androgen levels, their brain development, along with their physical development, is completely female.

Partial Androgen Insensitivity Syndrome and Mild Androgen Insensitivity Syndrome

PAIS, a heterogeneous form of CAIS, presents as varying degrees of female virilization or male feminization due to differing degrees of androgen receptor activity. PAIS is only one etiology of DSD, defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is a typical.³⁵ The clinical spectrum of PAIS ranges from isolated hypospadias, in milder cases, to simple clitoromegaly, in more severe forms. The testes may or may not be undescended. Perineoscrotal hypospadias, micropenis, and a bifid scrotum are other common findings.

The differential diagnosis consists of partial gonadal dysgenesis, 17 β -hydroxysteroid dehydrogenase deficiency, 5 α -reductase deficiency, and mixed gonadal dysgenesis in association with a mosaic Turner syndrome (45,XO/46,XY).¹

As the PAIS patient is exposed to varying levels of androgen receptor activity, and sometimes conflicting societal and familial pressures and expectations, rates of bisexuality, homosexuality, and gender identity disorder may be higher than incidence rates within the general population, as also seen in conditions such as congenital virilizing hyperplasia and 5- α reductase deficiency.^{34,36}

The condition of MAIS was more recently described as the result of male infertility evaluations.^{37,38} These phenotypic and genotypic men were found to have evidence of androgen action defects clinically manifested as oligospermia with normal testosterone and inappropriately elevated serum LH levels. Other physical manifestations include

gynecomastia in young men and minor hypospadias, typically diagnosed in infancy.¹

Summary

CAIS is characterized by a lack of androgen receptor activity. Most cases are transmitted in an X-linked recessive pattern, though up to 30% of mutations are de novo. The disorder should be suspected in a premenarcheal female with an inguinal hernia or in an adolescent with primary amenorrhea greater than two years after the development of breast growth. Physical exam and karyotype testing are critical to making the correct diagnosis. In CAIS, gonadectomy should be performed after puberty unless there is concern for malignancy or virilization prior to that time. The presentation of PAIS and MAIS is varied and the treatment based on clinical presentation.

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