Androgen Insensitivity Syndrome [1]

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Androgen Insensitivity Syndrome (AIS) is a human disorder in which an individual's genetic sex (genotype) differs from that individual's observable secondary sex characteristics (phenotypes). A fetus [4] with AIS is genetically male with a 46,XY genotype. The term 46,XY refers to the chromosomes found in most cells of the fetus [4]. Most cells have a total of 46 autosomes, or non-sex chromosomes, and a pair sex chromosomes, XX for genetic females, or XY for genetic males. Due to a defect on the androgen receptor gene (AR) located on the X chromosome, a fetus [4] with AIS cannot process male sex hormones [5] or androgens [6]. The effect on the fetus [4] is that, compared to genetically male fetuses without AIS, it doesn't develop normal male phenotypes. The resistance to androgens [6] affects all of the fetus [4]'s organs during embryonic development and during puberty. Although genetically male, persons with AIS can be socially raised as either female or male (sex-of-rearing) yet identify with a gender discordant with their sex-of-rearing. AIS and other states of intersexuality challenge physicians, scientists, and society to evaluate definitions of sex.

Although physicians and scientists studied intersexuality, or hermaphroditism, before the early 1900s, physicians used only an individual's gonads to determine an individual's sex. The individual was male if he had testes [7] and female if she had ovaries. Frank Rattray Lillie's studied freemartin [8] cattle in 1916 at the University of Chicago [9] in Chicago, Illinois, and he suggested that regardless of genetic sex, hormones [10] influence the development of sex characteristics, a process called sex differentiation [11]. Such characteristics include penises and prostates in males, and breasts and vaginas in females, but also include differences in hair, bones, and muscles between males and females. As scientists learned more about genetics, they determined sex according to an individual's chromosomes, gonads such as testes [7] in males or ovaries in females, and secondary sex characteristics such as breasts and hips and females, and facial hair and broader shoulders in males. Thus, any variation from the expected match between an individual's genetic sex, gonads, and secondary sex characteristics was termed hermaphroditism.

In 1876, Theodor Albrecht Edwin Klebs in Europe introduced a classification system that divided hermaphrodites into true hermaphrodites and pseudo-hermaphrodites based on their gonads. Hermaphroditism was classified into three categories: true hermaphrodite, male pseudo-hermaphrodite, or female pseudo-hermaphrodite. A true hermaphrodite was an individual who had one or more gonads which contained testicular and ovarian attributes, or an ovotestis. A female pseudo-hermaphrodite was genetically female and had ovaries, but exhibited male secondary sex characteristics. A male pseudo-hermaphrodite was genetically male and had testes [7], but exhibited female secondary sex characteristics.

AIS was grouped with other variations of sexual development as male pseudo-hermaphroditism until 1953. That year John McLean Morris a professor at the Yale University [12] School of Medicine and a doctor at the Yale-New Haven Medical Center in New Haven, Connecticut, published a paper in which he described eighty-two humans [13] with common features of a sex disorder, and he called the syndrome testicular feminization. Morris questioned whether the secondary sex manifestations of AIS patients resulted from hormones [10] or from the ability of organs in the body to respond to hormone [10] stimulation. In 1957 Lawson Wilkins, a professor at Johns Hopkins University [15] in Baltimore, Maryland, published the results of his study, in which human male pseudo-hermaphrodites did not exhibit male secondary sex characteristics after androgen injections. Mary F. Lyon and Susan G. Hawkes at the Medical Research Council [16] Radiology Unit at Harwell, UK linked testicular feminization to the X chromosome in 1970 when they determined that a gene on the X chromosome caused complete androgen insensitivity in mice, the males of which could also have testicular feminization and thus served as a model for the human syndrome, and on which researchers could experiment.

In 2006 a group of fifty international experts introduced new nomenclature and classification for humans [13] states of intersexuality or hermaphroditism as disorders of sexual development. As scientists learned more about androgen resistance, they renamed the syndrome Androgen Insensitivity Syndrome. By the early decades of the twenty-first century, researchers located greater than 600 mutations of the AR (androgen receptor) gene on the human X chromosome.

Normal sex differentiation [11] requires interplay between the sex chromosomes and hormones [10]. The egg [17] and the sperm [18] each carry twenty-three chromosomes; the egg [17] provides only the X chromosome and asperm [18] can have either an X or a Y chromosome. At fertilization [19], the union of the egg [17] and the sperm [18] determines the genetic sex of the embryo as either female (46,XX) or male (46,XY). A few days after gestation [20], the gonadal ridge, precursor to testes [7] or ovaries, develops on an embryo. During the second month of gestation [20], all fetuses have both male (Wolffian) and female (Mullerian) internal sex ducts and their external genitalia appear female. In XY embryo, a gene on the Y chromosome called the sex-determining region (SRY) produces a protein that causes the bipotential gonads, formed from the gonadal ridge, to develop into testes [7]. Without the SRY gene, the bipotential gonads become ovaries. As the testes [7] develop, they secrete two hormones [10], Mullerian
Inhibiting Substance (MIS) and androgens \[^6\]. MIS inhibits the Mullerian ducts in an embryo from developing into uterus \[^21\], a cervix \[^22\], and fallopian tubes \[^23\]. Androgens released by the testes \[^7\] increase the growth of the Wolffian ducts, which then develop into the vas deferens, prostate gland, and seminal vesicles. Normally, in a genetic female, the absence of MIS and androgens \[^6\] permits the Mullerian ducts to develop into fallopian tubes \[^23\], a cervix \[^22\], and a uterus \[^21\]. Additionally, without androgens \[^6\] in a genetic female, the Wolffian ducts regress. As the testes \[^7\] continue to develop in an XY fetus \[^4\], testosterone released by the testes \[^7\] is converted to dihydrotestosterone (DHT), a hormone \[^14\] that masculinizes the external genitalia to become the penis and the scrotum.

Because the defect in the AR gene is linked to the X chromosome, all 46,XY embryos that have an X chromosome with a defective AR gene and a normal Y chromosome exhibit varying degrees of sex differentiation \[^11\]. Although most cases of AIS are in individuals with families that have had other individuals with AIS, scientists estimate that thirty percent of AIS cases result from spontaneous, or de novo, mutations to AR genes \[^24\]. AIS is classified into three categories based on the degree of altered sex differentiation \[^11\]: complete AIS (CAIS), partial AIS (PAIS), and mild AIS (MAIS).

In the early twenty-first century, doctors lacked precise figures for the number of infants born with CAIS, although 2012 estimates ranged from one in 20,400 to one in 99,100 per year. During development, an 46,XY embryo with CAIS cannot process the androgens \[^6\] produced by the testes \[^7\], but it responds to other hormones \[^10\]. As a result, the testes \[^7\] form and function during embryonic development. The testes \[^7\] secrete MIS, which causes the Mullerian ducts to regress, so the uterus \[^21\], fallopian tubes \[^23\], and the cervix \[^22\] do not develop. The Wolffian ducts don't respond to the androgens \[^6\] released by the testes \[^7\], and the ducts either regress or remain in a rudimentary form, but they do not develop into a prostate gland, vas deferens, or seminal vesicles. Unresponsive to the androgens \[^6\] testosterone and DHT, the external genitalia develop as they would in a normal 46,XX fetus. At birth, a 46,XY neonate has testes \[^7\] located in the abdomen, groin, or in the labia. The external genitalia are female. The uterus \[^21\], fallopian tubes \[^23\], and cervix \[^22\] are absent. The vagina \[^25\] is a closed-end tube, and is most often shorter than those of normal female neonates. Blood levels of testosterone and DHT may be above normal due to the lack of the negative feedback loop between the anterior pituitary gland \[^26\] and the blood level of androgens \[^6\], a feedback loop that normally keeps the level of androgens \[^6\] released by the testes \[^7\] in balance. Carl Richard Moore and Dorothy Price identified this negative feedback loop in 1932 when they were researchers at the University of Chicago \[^9\] in Chicago, Illinois.

Generally parents of a CAIS child rear the child as female. Nothing may indicate that the child has the syndrome until either a testis is found due to a hernia in the groin (inguinal hernia), or at puberty when the adolescent does not menstruate. Prior to puberty, approximately one percent of children have an inguinal hernia; however, eighty to ninety percent of persons with CAIS will develop an inguinal hernia in their lifetime if their testes \[^7\] at puberty, approximately one percent of children have an inguinal hernia; however, eighty to ninety percent of persons with CAIS will develop an inguinal hernia in their lifetime if their testes \[^7\] did not menstruate at puberty. Surgeons then removed the testes \[^7\] and may have told the child that they removed her ovaries. Surgeons also removed the testes \[^7\] of children with either partial or mild AIS, but frequently performed other surgeries based on the child's exhibited secondary sex characteristics. In many cases, surgeons altered the genitalia to resemble female secondary sex characteristics.
As adults, many of the children who were born with AIS in the years since Money’s recommendation reported in support groups such as the Intersex Society of North America (ISNA) headquartered in California or the Androgen Insensitivity Syndrome Support Group, which has twenty-five national locations, that the secrecy surrounding the diagnosis made them feel abnormal. Without surgery, many also faced social stigma because of their anatomy. Many adults with AIS also declared that surgical corrections to their genitalia were inappropriate and unnecessary. For some, the sex characteristics created for them do not match the gender that they identify with. For some children born with AIS, treatments didn’t include anatomical surgeries other than the removal of the testes to prevent testicular cancer. While ISNA states that the testes should be removed, they recommend that the surgery be delayed until puberty has begun. Another medical treatment for CAIS individuals is estrogen therapy. In a family with history of AIS, DNA testing has detected fetuses with AIS. Doctors can identify fetuses whose external genitalia does not match their genetic sex. To do so, doctors use ultrasound to view the fetus in the womb. They use either sampling of the placental tissue (chorionic villi sampling) or sampling of amniotic fluid (amniocentesis) to obtain cells that will reveal the genetic sex of the fetus.

Sources


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