



British Society for Paediatric Endocrinology and Diabetes

ANDROGEN INSENSITIVITY SYNDROME (AIS)

AIS is a rare inherited condition in which the body is unable to respond to androgens, the male sex hormones. These chemical signals are secreted into the blood by the testes and are responsible for all the physical and psychological features of maleness. When the body is completely resistant to androgens, the condition is called complete androgen insensitivity syndrome (CAIS). If the body does respond a bit to androgens, the condition is called partial androgen insensitivity syndrome (PAIS) (see later).

CAIS

Inheritance.

CAIS is a genetic condition carried on the X chromosome. Males have one X and one Y chromosome and develop testes whereas females have two Xs and develop ovaries. The condition only occurs in XY persons as XX persons can compensate for the abnormal gene which is present in only one of their X chromosomes. However, a female could still be a carrier of the gene abnormality. A clinical geneticist would be able to counsel on the risks of passing on the abnormal gene.

Cause.

The gene on the X chromosome determines the structure of an androgen receptor, a protein to which androgens dock when they enter cells. This docking acts like a lock and key which opens the door for androgens to enter the nucleus, the power house of the cell. In CAIS, the androgen receptor (the lock) does not work at all so the androgens (the key) cannot open the door to allow androgens docked to its receptor to get in to the cell nucleus and do its work. Babies with CAIS have XY sex chromosomes and so develop testes which produce normal male amounts of androgens. However, the cells do not respond to these androgens because the key just not turn the lock. Since androgens are needed to develop the male genitalia before birth, the baby born with CAIS looks like a normal girl.

Diagnosis.

The diagnosis of CAIS may be made soon after birth if a baby girl develops a hernia in the groin or a swelling in the labia. This is due to the testis which is present in CAIS trying to get down to the scrotum where it should be in boys. Of course, there is no scrotum in CAIS. When the surgeon performs a hernia repair the testis may be found in the hernia and a small biopsy is taken to confirm via the microscope that it is a testis and not an ovary. The sex chromosomes would then be checked to confirm they are XY. The diagnosis of CAIS is more often made at puberty when a girl has not started her periods. This is

because there are no ovaries, but also no uterus. The forerunner of the uterus and Fallopian tubes are also present in the early developing male embryo but the testis produces a hormone (called anti-Mullerian hormone) which prevents the tubes and uterus developing in a male. This hormone, in contrast to the androgens, does work normally in CAIS and hence the absence of the uterus. The vagina does develop but may be shorter than normal. A girl with CAIS develops breasts normally at puberty because all the androgens are converted in to estrogens (the female hormone). Pubic and under arm hair is either absent or very scanty growth because the receptor (lock) also needs to work properly to grow hair in these parts of the body. A genetics test is performed to confirm the presence of a mutation in the gene on the X chromosome which determines the structure of the androgen receptor. This information can also be used if other members of the family wish to be tested to see if they are carriers of CAIS.

Treatment.

In girls with CAIS there is a very small chance that the testis may eventually form a tumour. This is very unlikely before puberty. So if the diagnosis of CAIS is made in infancy, the general view now is to leave the testes in place so that the physical changes of puberty occur naturally. A hernia may need to be repaired. However, some parents do want the testes removed early so puberty will need to be induced with estrogens. This is given in the form of a tablet in a small dose starting around the age of puberty (about 11 years of age) and the dose increased gradually over the next few years. No periods will occur since there is no uterus. If the testes are left in place, puberty occurs naturally and at the correct age. Later, the young woman with CAIS can decide about having the testes removed. The medical advice is to do so by early adulthood because of the small risk (less than 5%) of a tumour developing. Replacement treatment with estrogen is then needed and this can be given as tablets or skin patches.

At around the age of puberty an examination under anaesthetic is arranged to assess the appearance of the genitalia and size of the vagina. Surgery is rarely needed for a shortened vagina as the use of vaginal dilators is often an effective first line treatment.

Outlook.

Girls and women with CAIS are fully fit and have a normal life span. Psychological well-being is similar to other women with female identity and behavior. Disclosure about issues such as the XY chromosomes, the presence of testes, absence of a uterus, infertility and sexual function is a step-wise process that starts in late childhood and continues through to young adulthood. This is undertaken through the support of relevant professionals working as a team and involvement, if desired, with AIS patient advocacy groups.

PAIS

The inheritance and cause of this form of AIS is similar to CAIS. The main difference rest with the effects of some action of androgens in this condition. So, the key is able to turn the lock a bit and partially open the door to allow some androgens to enter the cell nucleus. How much androgen is acting will generally influence the appearance of the external genitalia at birth. Typically, the genitalia are ambiguous so that the sex of the baby is not instantaneously male or female when the baby is born. How to deal with this problem is covered in a separate leaflet on Disorder of Sex Development.

Diagnosis

There are many conditions that can give rise to the appearance of the genitalia found in PAIS. There is typically severe hypospadias (a condition where the opening of the urethra is at the tip of the penis), the scrotum is not completely fused like a sac, the penis may be small and the testes may not be completely descended. A number of tests are needed to confirm that PAIS is the cause of this appearance. They include checking the sex chromosomes (should be XY) and showing that the testes are present and make normal amounts of androgens. The precise diagnosis is made by finding a mutation in the gene on the X chromosome which determines the structure of the androgen receptor. A mutation in this gene is found in only about 20% of infants that have the signs of PAIS. In the rest, the baby may have been born small and perhaps the placenta did not work properly in early pregnancy to produce enough androgens to develop the male genitalia. As in CAIS, there is no uterus or Fallopian tubes.

Treatment

A decision needs to be taken soon about sex assignment and hence, sex of rearing. Most infants with PAIS are raised male. Surgery is needed for the hypospadias, starting early in the second year of life. More than one operation is usually needed for a severe hypospadias. An operation will be required to bring the testes down in to the scrotum. All such treatment is completed long before the boy starts school. What happens at puberty depends on how well the genitalia had responded to androgens by the time of birth. The testes will start producing androgens again at puberty but it may be necessary to give treatment with additional androgens if the progress of puberty is a bit slow. Adult males with PAIS are usually infertile but there are rare examples of fertility, particularly with the use of modern artificial reproductive techniques ("IVF"). Occasionally, a decision may be taken that it is best to assign the sex at birth female as the genitalia have responded very little to the lock and key action of the androgens. In this situation, the surgeon is able to create a vagina and change the appearance of the penis to resemble a penis. The testes need to be removed before puberty and estrogen treatment started at puberty to induce female development. Adult females with PAIS are infertile.