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Androgen insensitivity syndrome

Numerous clinical syndromes are now recognised to be associated with resistance to the action of hormones in target tissues.¹ There is no clearer clinical example of this phenomenon than the development of an external female phenotype in a genetic male, in whom there is total resistance to the action of androgens, the so called androgen insensitivity syndrome.² Approximately two thirds of cases of androgen insensitivity are familial with an X linked pattern of inheritance.

Clinical phenotypes

Two phenotypic forms of the androgen insensitivity syndrome are recognised. The complete form (CAIS), previously known as the testicular feminisation syndrome,³ is associated with normal female external genitalia. The condition may present in infancy or childhood with labial swellings or inguinal hernias that are found to contain testes. More typically, CAIS presents in late adolescence with primary amenorrhoea. There is absence of female internal genitalia on ultrasound scan or laparoscopy and testicular histology shows spermatogenesis to be incomplete or absent, although Leydig cells are abundant. Plasma testosterone concentrations are within the age appropriate male range or in some instances even higher as a result of the increased stimulation by luteinising hormone.

The partial form of the androgen insensitivity syndrome (PAIS) is associated with a wide range of genital abnormalities, and typically presents at birth with genital ambiguity. Severe hypospadias and associated abnormalities such as a micropenis, bifid scrotum, and bilateral cryptorchidism are common. Alternatively, the external genital phenotype may be predominantly female with partial labial fusion and clitoromegaly. Clinically milder forms of PAIS may also include isolated familial hypospadias and some cases of infertility in otherwise phenotypically normal males.² The diagnosis of PAIS depends on demonstrating a normal testosterone response to human chorionic gonadotrophin

(HCG) stimulation. Measurement of steroid precursors in plasma and their metabolites in urine after HCG stimulation should exclude other testosterone biosynthetic defects.⁴ Pelvic ultrasound generally shows absence of female internal genitalia, although vaginal remnants may persist. As male pseudohermaphroditism due to a number of different causes may present with a clinical phenotype similar to PAIS,⁴ careful evaluation is clearly important to optimise management.

Investigation

The following approach is suggested for the investigation of patients with male pseudohermaphroditism. Examination of the internal genitalia by ultrasound scan or by laparoscopy is needed to look for evidence of müllerian structures such as a uterus. An opportunity should be taken at the time of any reconstructive surgery to examine, if possible, gonadal histology in case of dysplasia or true hermaphroditism. An HCG stimulation test (1500 units daily for three days) with normal testosterone production is a prerequisite if a diagnosis of PAIS is to be considered. Testosterone biosynthetic defects can be excluded by measurement of precursor steroids such as 17 hydroxyprogesterone, androstenedione, dehydroepiandrosterone and its sulphate.⁵ The autosomal recessive disorder, 5 α -reductase deficiency, can be excluded by measurement of testosterone and dihydrotestosterone in plasma together with 5 α - and 5 β -reduced androgen metabolites in urine after HCG stimulation.⁶ Further information about possible androgen insensitivity can be obtained from androgen binding studies and molecular analysis of the androgen receptor gene.

Androgen binding studies

The evidence that androgen insensitivity occurs because of some abnormality in the androgen receptor was first obtained

from assays of androgen binding activity in genital skin fibroblasts.⁷ A range of androgen binding abnormalities have been defined, but a general classification describes binding as negative, deficient, or positive. The majority of patients with CAIS have negative or deficient binding, whereas PAIS is usually associated with positive binding. Qualitative defects in androgen binding are found in approximately 10% of patients with PAIS.⁸

Androgen receptor gene studies

An added impetus was given to the understanding of androgen insensitivity syndrome when the gene for the androgen receptor was cloned.⁹⁻¹⁰ The gene is located on the long arm of the X chromosome, Xq11-12,¹¹ and is comprised of eight exons encoding three clearly defined functional domains.² The C terminal domain is encoded by five exons and is responsible for receptor binding to androgen; a central domain encoded by two exons is involved in the binding of receptor to chromosomal DNA; the N terminal domain is encoded by one large exon. This domain is the least well characterised and is involved in the receptor's role in gene regulation.

A number of mutations of the androgen receptor gene have now been reported in both CAIS and PAIS.^{2,12} The vast majority are point mutations involving a single nucleotide change, which may result in the substitution of one amino acid for another in the protein sequence or may substitute a stop codon for an amino acid codon so producing a truncated receptor protein. As expected, when androgen binding is altered, mutations are generally found in the C terminal androgen binding domain. An androgen receptor gene mutation affecting the androgen binding domain has recently been identified in a pair of brothers with severe perineal hypospadias. This was the only manifestation of undervirilisation in these patients and suggests that isolated familial hypospadias represents a variant of PAIS.¹³ Mutations have also been identified in the two exons encoding the DNA binding domain of the androgen receptor.¹⁴ In a CAIS family containing two affected siblings, one of the two exons encoding the DNA binding domain was completely deleted in the affected individuals.¹⁵ Androgen binding is normal in such instances and the phenotype is the result of impaired binding of the androgen-receptor complex to chromosomal DNA.

The evidence to date indicates that a mutation of the androgen receptor gene is responsible for most if not all cases of CAIS. In contrast, many patients with PAIS demonstrate no defect in androgen binding and no androgen receptor gene mutation can be identified.¹² In such cases, it must be assumed that partial androgen insensitivity is the result of defects in other genes which must have a role in sexual development. Mutational analysis of the androgen receptor gene has greatly enhanced our understanding of the molecular basis of androgen insensitivity and the normal mode of action of the androgen receptor. It has also improved the possibilities for genetic counselling for affected families and has allowed prenatal diagnosis to be offered.

Management

Management of CAIS is relatively straightforward as the sex of rearing is always female. However, appropriate counselling of parents in which clear and accurate information is given about longer term issues of hormone replacement and fertility must be carried out by an experienced endocrinologist. Reconstructive surgery to the external genitalia is not required but the gonads need to be removed because of the risk of malignancy.^{16,17} The timing of this varies, but there is now a tendency to proceed with gonadectomy early, rather than to wait until after puberty.

Management of PAIS is more complicated. The critical problem is the current lack of a reliable indicator of whether an infant reared as male will virilise at puberty. Trying to establish a precise diagnosis is clearly important, but often takes a considerable time. The paediatric surgeon must be involved at an early stage when assessing the anatomy of the external genitalia. Occasionally, a trial of androgen treatment with, for example, a course of monthly injections of testosterone enanthate (25 mg) for two to three months may be required, before finally deciding whether a severely undervirilised infant can be reared as a male. It is important to delay birth registration until a decision has been made. Although the term PAIS implies that virilisation will not occur in the long term, this may not be the case, even when there is a mutation of the androgen receptor gene.¹⁸ PAIS patients reared as females require appropriate genital surgery and gonadectomy performed early and oestrogen replacement at the time of puberty. In PAIS males, repairing a severe hypospadias and bringing the testes down into a normal scrotal sac is a task most surgeons choose to perform at about 3 years of age. Preoperative androgen treatment may produce phallic growth and facilitate surgical reconstruction.

The androgen insensitivity syndrome is currently one of the subjects of study undertaken through the auspices of the British Paediatric Surveillance Unit. The survey should provide details on precise diagnosis as well as some indication of the incidence and prevalence of the condition. It is only when such information becomes available that it is possible that recent knowledge of the molecular biology of androgen action may be used to predict the longer term outcome of androgen insensitive patients reared as males.

DENISE M WILLIAMS
MARK N PATTERSON
IEUAN A HUGHES

Department of Paediatrics,
University of Cambridge,
Addenbrooke's Hospital,
Hills Road, Cambridge CB2 2QQ

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