Androgen insensitivity syndrome: a survey of diagnostic procedures and management in the UK

R M Viner, Y Teoh, D M Williams, M N Patterson, I A Hughes

Abstract
Objective—A two year survey of androgen insensitivity syndrome (AIS) to assess current diagnostic and management strategies.

Methods—Cases were ascertained by inclusion on the British Paediatric Surveillance Unit monthly report card for 24 months.

Results—Fifty one of 139 notifications were confirmed as AIS; 29 cases were complete AIS and 22 cases partial AIS. Seventy six per cent of complete AIS presented with an inguinal hernia, and half the complete AIS patients had an established family history of the disorder. Presentation in the partial AIS group was through ambiguous or undermasculinised genitalia; 59% of partial AIS were raised as male.

Conclusions—The importance of karyotyping girls with inguinal hernias is confirmed, and further attention should be given to genetic counselling for families of complete AIS patients. A large number of cases were misreported as partial AIS, emphasising the importance of undertaking a comprehensive diagnostic evaluation in intersex states. A large percentage of children with partial AIS were raised as boys despite severe genital undermasculinisation, indicating the current lack of validated measures that predict genital response to androgen treatment. The management of AIS is discussed and diagnostic guidelines provided to improve the diagnostic yield in AIS.

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Keywords: androgen insensitivity syndrome; inguinal hernia; intersex

A two year national survey of the androgen insensitivity syndrome (AIS) was undertaken via the British Paediatric Surveillance Unit to determine existing diagnostic procedures and management strategies. A pilot study of patients with the partial form of AIS had shown that data on gonadal histology, anatomy of the internal genitalia, and steroid hormone concentrations were incomplete. AIS defines a female or ambiguous phenotype in a 46XY male with testes and normal testosterone production and metabolism. As androgens are essential for normal male sexual development and fertility, defects in androgen action are associated with abnormal sexual differentiation and fertility. Complete AIS is a rare X linked single gene disorder that results in a normal female phenotype, and typically presents in early adult life with primary amenorrhoea, although a significant number present with inguinal hernias in infancy. The significance of the relative rarity of bilateral inguinal hernias in girls is often not appreciated; it is estimated that 1–2% of such infants have complete AIS. The diagnosis is confirmed in both forms of AIS by a male karyotype and normal testosterone production and metabolism, in the presence of normal testicular histology, and generally the absence of müllerian duct remnants.

Partial AIS is a clinically heterogeneous disorder and presents a more complicated diagnostic problem. The degree of androgen unresponsiveness is variable, so the affected infant presents at birth with undermasculinised external genitalia of varying severity. Characteristically, there is microopenis with chordee, a bifid scrotum, and a perineal urethral opening, and gonads that may or may not be palpable within the bifid scrotum. The partial AIS phenotype must be differentiated from other conditions with a 46XY karyotype, which can give rise to the same genital abnormality such as defects in testosterone biosynthesis, 5α-reductase deficiency, mixed gonadal dysgenesis, and true hermaphroditism. Accurate early diagnosis is important and has a profound bearing on the sex of rearing, genetic counselling, and subsequent management; a trial of androgen treatment in early infancy to assess the growth of penile erectile tissue may provide important information on androgen responsiveness. There is a lack of knowledge regarding the criteria used to decide the management of infants with partial AIS, particularly with respect to sex of rearing. Analysis of the cases identified through our survey suggests that guidelines for clinicians on the appropriate diagnostic and management strategies for AIS patients, particularly in the case of suspected partial AIS, would be helpful.

Methods
SURVEY PROCEDURE

Cases were ascertained by active surveillance via inclusion on the surveillance unit monthly report card for a two year period. Previous studies using multiple ascertainment methods have suggested that this reporting procedure alone provides between 60–80% case ascertainment rates. Cases were defined as an infant or child under 16 years of age with a 46XY karyotype and with either normal female external genitalia (defined as complete AIS) or abnormal external genitalia that are consistent...
with the partial AIS phenotype, that is, microphallus/citroremegaly, bifid scrotum, perinealscrotal hypospadias. Clinicians were asked to report any child under their care who satisfy-
ed the case definitions, including those newly
diagnosed in the past month, and those
children diagnosed before the start of the study
and who were still 16 years of age, or less, at the
time of the study.

Once a case was notified, the referring clinici-
ian was asked to complete a questionnaire
detailing further information about the clinical
phenotype, family history, imaging studies of
internal genitalia, gonadal histology, results of
endocrine investigations, and management
decisions on sex of rearing and hormone treat-
ment. Determination of diagnosis was made
from information provided in consultation with
referring clinicians. If a case of AIS was
confirmed as part of separate studies, referring
clinicians were asked to collect blood samples
from the index case and family members for
DNA extraction, the venesection being coordi-
nated with other investigations requiring ven-
esection, or from the determination of a karyotype
from information provided in consultation with
referring clinicians. If a case of AIS was
confirmed as part of separate studies, referring
clinicians were asked to collect blood samples
from the index case and family members for
DNA extraction, the venesection being coordi-

Table 3 shows details of gonadal position and
histology; values are number (%)

<table>
<thead>
<tr>
<th>Gonad position</th>
<th>Complete AIS (n=29)</th>
<th>Partial AIS</th>
<th>Reared male (n=13)</th>
<th>Reared female (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral intra-abdominal</td>
<td>6 (21)</td>
<td>2</td>
<td>1 (8)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Bilateral inguinoscrotal</td>
<td>14 (48)</td>
<td>10 (77)</td>
<td>6 (47)</td>
<td></td>
</tr>
<tr>
<td>One inguinal + one intra-abdominal</td>
<td>9 (31)</td>
<td>2 (15)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gonad position</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral normal testes</td>
<td>12 (41)</td>
<td>1 (8)</td>
<td>7 (58)</td>
<td></td>
</tr>
<tr>
<td>One normal testis*</td>
<td>8 (28)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>0</td>
<td>8 (62)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (31)</td>
<td>4 (30)</td>
<td>2 (22)</td>
<td></td>
</tr>
</tbody>
</table>

*Unilaterally normal testis—other testis not biopsied or not identified.

Results
Table 1 details notifications during the survey
period. Fifty one of the total 139 notifications
were confirmed as cases of AIS. There was
insufficient information to make a diagnosis
from 37 notifications. The diagnostic criteria
for complete AIS and partial AIS were fulfilled
in 29 and 22 cases, respectively.

Complete AIS
All complete AIS patients had normal female
genitalia and were reared as females. Presenta-
tion in complete AIS was predominantly by the
discovery of a hernia in an apparently female
infant (76%); other cases were identified on the
basis of a family history of the X linked disor-
der, or from the determination of a karyotype
for other reasons (table 2). Regardless of the
mode of presentation, inguinal hernia was
present in 28 (90%) of complete AIS patients;
nine (31%) were unilateral, 17 (59%) bilateral.

Table 3 shows details of gonadal position and
histology. One or two palpable testes were
present in approximately 80% of complete AIS
patients. Gonadal histology was consistent with
AIS in all patients in whom histological
examination of the testes was performed (table
3). Apart from the report of a 'vestigial' uterus
in one complete AIS patient, female internal
genitalia were absent in all AIS patients.

Partial AIS
Presentation in partial AIS was through
ambiguous or undermasculinised genitalia. In
59% of the partial AIS cases, the sex of rearing
was male. Factors that appeared to affect sex of
rearing in partial AIS were the degree of labio-
scrotal fusion, site of urethral opening, whether
the testes were palpable, and phallus size. All
infants with unfused labia (n=4) were raised as
female and a further five infants with fused
labia were also raised as female. All those raised
as male (n=13) had fused labioscrotal folds.

Table 4 summarises information concerning
family history. Approximately half the cases of
complete AIS had an established family history
of the disorder. There were four pairs of related
complete AIS patients, and in four cases a his-
tory suggestive of androgen insensitivity was
present. In contrast, only one quarter of partial AIS cases had a family history suggestive of AIS. Associated congenital anomalies were absent in the complete AIS group, except for one patient with red-green colour blindness. Associated anomalies were more common in the partial AIS group, with one example each of coarctation of the aorta, microphthalmos, ectodermal dysplasia, short stature with mental retardation, and chromosomal translocation 10q:16, q26.2:q21.

GONADECTOMY

Table 5 shows details of when gonadectomy was performed. This took place before puberty in half the complete AIS patients, whereas about one quarter had, or were due to have, removal of gonads after puberty. For the remainder, plans were unknown at the time of the survey. Median age for gonadectomy in complete AIS was 8 years (mean 5.5 years), with a median prepubertal gonadectomy age of 1 year (mean 1.7 years). Gonadectomy was performed in all partial AIS patients raised as females, and in none of those raised as males. Median age for gonadectomy in partial AIS patients was 21 months (mean 24.1 months).

Five complete AIS patients (17%), but no partial AIS patients, raised as female were being given oestrogen replacement therapy at the time of the survey. Three partial AIS patients raised as male were receiving androgen replacement therapy. Genital surgery other than gonadectomy was performed in all the partial AIS females (vulvovaginoplasty), and in nearly half of partial AIS males; this included hypospadias repair, orchidopexy, and release of penile chordee.

Discussion

This study provides an overview of the characteristics and management of AIS in a large group of patients in the UK. The survey did not provide incidence or prevalence figures for AIS because of many unconfirmed reported cases, the limitations of case ascertainment using a single reporting method, the incomplete lifetime ascertainment of complete AIS due to the normality of the female phenotype, and confidentiality problems associated with reporting disorders of sexual development.

Peripheral karyotype

<table>
<thead>
<tr>
<th>Blood for: DNA extraction Serum AMH</th>
<th>LHRH test: Luteinising hormone, FSH, testosterone</th>
<th>HCG stimulation test</th>
<th>Surgical samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term: 1500 U daily for 3 days</td>
<td>Genital skin: Fibroblast culture Androgen binding 5α-reductase assay DNA, RNA extraction</td>
<td>Long term: 1500 U twice weekly for 3 weeks</td>
<td>Androgen metabolites</td>
</tr>
<tr>
<td>Plasma samples before/after HCG: 17-OHP Androstenedione DHA Testosterone DHT SHBG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hour urine: Androgen metabolites</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1  An investigation protocol for a patient with a partial AIS phenotype. A similar protocol can be used for complete AIS, although a human chorionic gonadotrophin test may not be necessary. AMH=antimüllerian hormone; DHA=dehydroepiandrosterone; DHT=dihydrotestosterone; SHBG=sex hormone binding globulin.
The presentation of three quarters of complete AIS patients through inguinal hernias, nearly half of which were unilateral, emphasises the importance of considering AIS in any female infants with hernias. Estimates of the incidence of AIS in such infants have ranged from 1–12%, suggesting that any girl with an inguinal hernia should have a karyotype performed.

Nearly half the patients had a proved family history of complete AIS, yet this was the mode of presentation in only 14% of cases, suggesting that more attention be given to genetic counselling for the families of complete AIS patients. There were a number of examples when an affected sibling had previously undergone a herniorrhaphy but the underlying diagnosis had not been recognised. Karyotyping female infants with first or second degree relatives with complete AIS should be considered by clinicians. Information about the management of complete AIS is mainly limited to cases presenting before puberty as the survey was restricted to age 16 years and below. The results indicate a trend towards prepubertal gonadectomy in complete AIS, the majority of cases having surgery in infancy (median age 12 months). However, oestrogen replacement therapy had not been started in late childhood or early adolescence in several cases, raising concerns about an increased risk of osteoporosis in later life. The risk of malignant transformation of the gonads in adult life is well documented, but medical opinion remains divided about whether the testes should remain in place until after feminisation has occurred at puberty.

Cases of partial AIS presented as expected because of abnormal genitalia at birth. Conditions misreported initially as partial AIS included testicular dysgenesis and examples of abnormal genitalia forming a component of known syndromes such as Denys-Drash, Smith-Lemli-Opitz, and Wilms’ tumour, aniridia, genital anomalies, and mental retardation (WAGR). Other cases were associated with specific defects in androgen production. These findings emphasise that the differentiation of partial AIS from other causes of undermasculinisation requires the demonstration of normal testicular histology, adequate testosterone production after human chorionic gonadotrophin stimulation, and normal androgen metabolism. Sex assignment in partial AIS was, not surprisingly, affected by the size of the phallus and the presence of palpable testes. However, a surprisingly high percentage of partial AIS cases were raised as male even though there was severe undermasculinisation of the external genitalia. The sex hormone binding globulin response to androgens has been advocated as a simple in vivo marker of a functional defect in the androgen receptor in partial AIS patients. Such a marker if validated in relation to functional androgen receptor assays and clinical outcome, would be useful to guide sex of rearing decisions. The phenotypic expression of partial AIS can be so variable within affected families that the severity of undermasculinisation may be unpredictable.

### Key messages
- A karyotype is essential in females with suspected hernias
- Further attention to genetic counselling is needed for complete AIS patients to improve case ascertainment in subsequent generations
- Management of suspected partial AIS should involve a specific sequence of clinical, radiological, biochemical, and molecular investigations (fig 1)

Establishing a diagnosis of complete AIS is straightforward with few other conditions producing a similar phenotype. However, Leydig's cell hypoplasia can be mistaken for complete AIS and may also present with ambiguous genitalia or only isolated micropenis. Loss of function mutations in the luteinising hormone receptor gene have recently been reported to cause this syndrome. Thus, in the absence of an increased basal testosterone, a human chorionic gonadotrophin stimulation test is indicated to verify normal androgen production in complete AIS.

The diagnosis and management of partial AIS is surrounded by inaccuracy and confusion. Many cases are interpreted as resulting from dysgenetic testes despite the lack of information on gonadal histology. Since the partial AIS phenotype may also be the expression of several other disorders, it is important to investigate cases as thoroughly as possible. Pelvic ultrasound assessment, to identify the presence or absence of müllerian structures, is particularly important as it can be done quickly, in contrast with some biochemical tests where the results may be delayed. Figure 1 illustrates a suggested flowchart for the investigation of partial AIS phenotype.

Some form of androgen insensitivity can reasonably be assumed when an XY male has normal testes as based directly on histological examination and indirectly on the absence of female internal genitalia (normal antimüllerian hormone and receptor), and evidence of adequate Leydig cell function based on the androgen response to human chorionic gonadotrophin stimulation. In these circumstances, it is reasonable to assume that the partial AIS phenotype may be associated with a dysfunctional androgen receptor. Even so, in many isolated cases of the partial AIS phenotype, androgen binding studies and mutational analysis of the androgen receptor gene are normal.

Further androgen related genetic mechanisms involved in male sex differentiation and development remain to be defined. Detailed studies of intersex conditions can play a fundamental part in identifying genes involved in sex determination and differentiation. The clinical investigation of intersex patients such as those with AIS, the development of a national database of AIS patients, and continuing research into the molecular genetics of these disorders is necessary for progress in the man-
agement of infants and children with intersex conditions.

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