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# Partial Androgen Insensitivity Syndrome
## A Case Report

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Until about 10 weeks of development in the womb, male and female embryos appear identical in external anatomy; the same structures then begin to differentiate as male under the influence of testosterone, or as female if testosterone is absent. In the presence of intermediate amounts of testosterone or partial insensitivity to the effects, the external genitalia may develop in an "in-between" way. Androgen insensitivity syndrome (AIS)-formerly known as testicular feminisation is a X-linked recessive condition resulting in a failure of normal masculinisation of the external genitalia in chromosomally male individuals.

People with AIS have a male karyotype of 46XY, but may not develop a male Phenotype. The failure of virilisation can be either complete androgen insensitivity syndrome (CAIS) or Partial androgen insensitivity syndrome (PAIS) depending on the amount of residual receptor function. The best available data internationally suggest an AIS incidence of approximately one case per 20, 400 liveborn males. CAIS appears more common than PAIS, although exact figures are unavailable.

A pilot study of patients with the partial form of AIS has shown that data on gonadal histology, anatomy of internal genitalia and steroid hormonal concentrations were incomplete (Williams et al, 1990) AIS defines a female or ambiguous phenotype in a 46XY male with testes and normal testosterone production and metabolism (Patterson et al,1994).There are two general categories for the 'complete' and 'incomplete' versions of AIS. Complete Androgen Insensitivity Syndrome (AIS) is the most pronounced form of the condition where the person's body is almost completely uninfluenced by androgen, also sometimes called Testicular Feminisation. In CAIS there will be no ovaries, fallopian tubes or uterus and the vagina will be blind ending and possibly short or absent. Female pubertal development occurs but there will be no menstruation and no possibility of conceiving / bearing children. The undescended tests may result in an inguinal hernia in infancy. This is when AIS may be diagnosed in an apparently female child (approximately 50% of cases).

PAIS is a less pronounced from of the condition where the person's body is immune to androgen influence to varying degrees. Affected individuals have normal testes with normal production of testosterone and normal conversion to dihydrotestosterone (DHT)Which differentiates this condition from 5 alpha-reductase deficiency. Because the testes produce normal amounts of mullerian inhibiting substance (MIF) affected individual do not have fallopian tubes, or uterus ,or proximal (upper) vagina. In PAIS, the external genitalia may be ambiguous, that is intermediate in structure between male and female. The phenotype of individuals with PAIS may range from mildly virilized female external genitalia (clitorimegaly without other external anomalies) to mildly undervirilized male external genitalia (hypospadiac and/or diminished penile size). PAIS is also known as "Reifenstein syndrome".

### Case Report

I describe a patient in whom incomplete AIS was diagnosed on the basis of phenotype, laboratory investigations a and ultrasound findings.The patient presented at age 18 years with primary amenorrhea. She had been raised as a female. She reported that her voice had changed and become at the age of 13 years. On general examination she was relatively tall at 1.55 metres. The breasts were not developed and axillary's and public hair was scanty. Genitalia tract examination revealed a small phallus. (See Fig.1) The patient had no cervix and the vagina was short (6 cm in length) and ended in a blind pouch. There were bilateral masses in the labia majora, which were testes and were later resected.Her two older sisters were not affected.

A pelvic sonogram confirmed that the uterus was absent. Unfortunately a vaginogram was not done. The chromosomal karyotype was 46XY. The patient

was given the diagnosis of Partial Androgen Insensitivity Syndrome.

The parents were informed and counselled about the definitive treatment option which was surgical. Preoperatively, patient's serum testosterone concentration was 614ng per decilitre (21.3 nmol per litre). This was within the normal range for men. Unfortunately the facility for estimating the serum 5 alpha dihydrotestosterone concentrations was not available.Bilateral orchidectomy was performed concurrently with a reduction phalloplasty leaving a small vestige to serve as a clitoris. Histological examination of the testes revealed small numbers of immature sertoli cells and germ cells and a moderate number of Leydig cells. Later a vaginal lengthening procedure was performed using bilateral Gracilis myocutaneous flaps.She was advised to present later for breast augmentation mammoplasty.

## DISCUSSION

Complete AIS typically presents in early adult life with primary amenorrhea, although a significant number present with inguinal hernias in infancy (Viner et al,1997). the presentation of three quarters of complete AIS patients through inguinal hernials, nearly half of which were unilateral in a previous report (Viner et al,1997) emphasis's the importance of considering AIS in any female infant with hernias. Estimates of the incidence of AIS in such infants have ranged from 1-12% (Jagiello and Atwell, 1962; Pergament et al, 1973) The syndrome of the relative rarity of bilateral hernias in girls is often not appreciated ;it is diagnosis of complete AIS is straightforward with few other conditions producing a similar phenotype. However Leydig 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 (Kremer et al, 1985) 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 Mullerian duct remnants. Partial AIS is a clinically heterogeneous disorder and presents a more complicated diagnostic problem (Patterson et al, 1994; Quigley et al, 1995) .The diagnosis and management of partial AIS is surrounded by inaccuracy and confusion 3.Pelvic ultrasound ,as was done in this case ,to identify the presence or absence of mullerian structures; is particularly important as it can be done quickly, in contrast to some biochemical tests where the results may not be easily available and can be delayed. For example, in this patient ,the 5 alpha-dihydrotestosterone concentration was not estimated to confirm it was normal male range and thus help in making a diagnosis. Also, a vaginogram was not done. However the absence of breast development pointed to the diagnosis of Partial rather than Complete Androgen Insensitivity Syndrome. In the latter type the breasts are typically well developed. PAIS 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, 5 alpha-reductase deficiency, mixed gonadal dysgenesis and true hermaphroditism (Conte and Grumback, 1996 ;Berkovitz,1992). Other conditions that have been misreported as partial AIS have included examples of abnormal genitalia forming a component of known syndromes such as Denys-Drash 10 , Smith-Lemli-Opitz (Mueller, 1994; McGaughran et al, 1994) , and Wilm's tumour ,aniridia, genital anomalies, and mental retardation (WAGR) (Clarkson et al, 1993)

Accurate diagnosis is important and has a profound bearing on the sex of rearing, genetic counselling, and subsequent management. Sex assignment in partial AIS is, not, affected by the size of the phallus and the presence of palpable testes. However ,a surprisingly high percentage of partial AIS cases (59%) were raised as male in a recent UK study 3 even though there was severe under masculinisation of the external genitalia. In the management of this case, orchidectomy was performed as soon as possible. The risk of malignant transformation of the gonads in adult life is well-documented (Verp and Simpson, 1987) but in cases where early diagnosis is made medical opinion is divided about whether the testes should remain in place until feminization has occurred at puberty (Patterson et al,1994).

Bilateral Gracilis myocutaneoous flaps were employed for vaginal lengthening. This was preferred by the plastic surgeon to the Mclndoe procedure. Augmentation mammoplasty was planned to complete the surgical management.

In conclusion, 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 management of infants, children and adolescents with intersex conditions. In our practice even with often-limited elaborate diagnostic facilities, diagnosis and

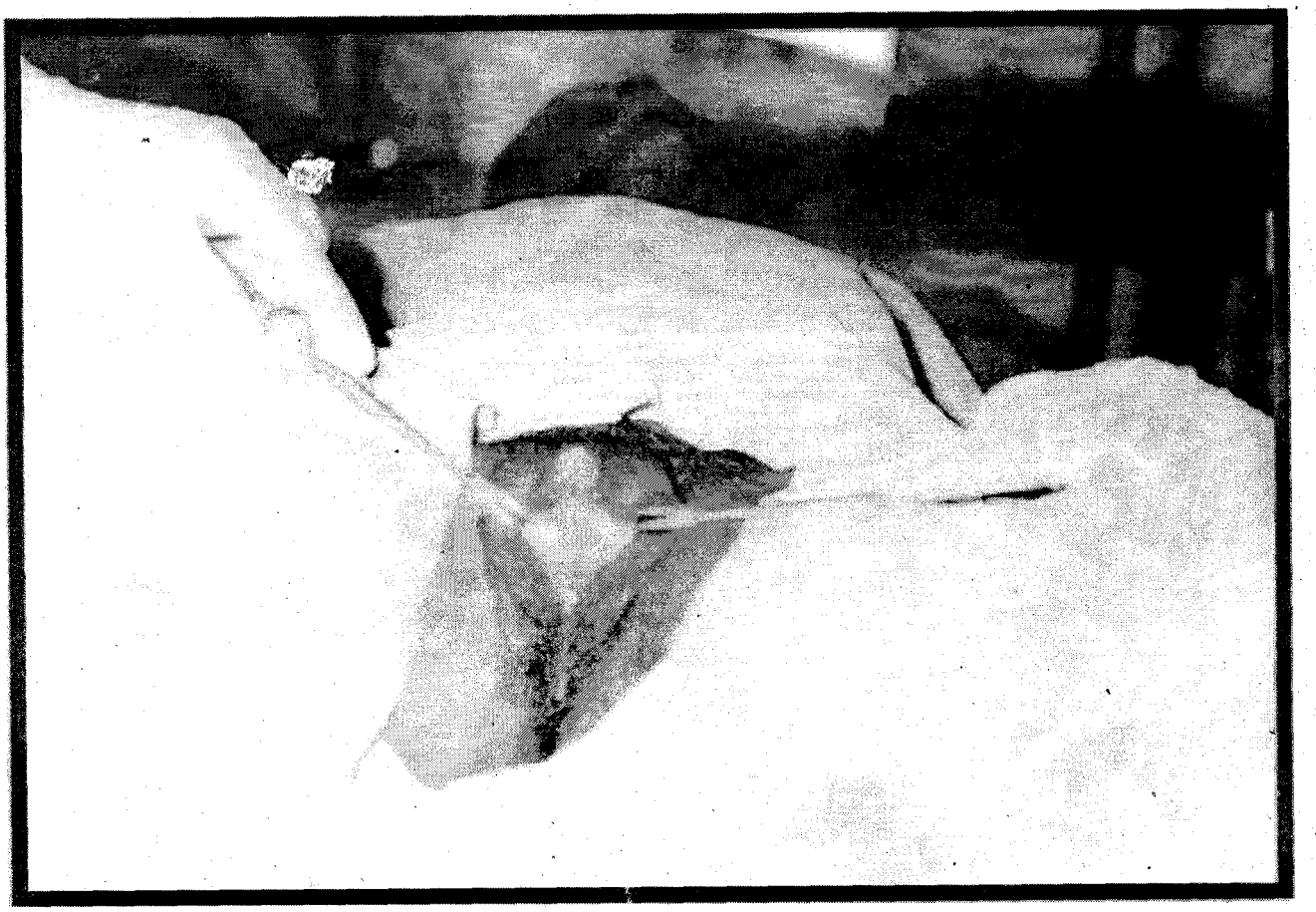

***Fig. 1: Genital picture of a patient with AIS revealing short vagina (extensively dilated with forceps) and small phallus.***

treatment of these conditions is possible. The creation of awareness of our people to the possibility of successful treatment as demonstrated by this case will eradicate some of the cultural taboos often associated with such conditions.

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