Original Article

Access this article online
Website: www.afrjpaedsurg.org
DOI: 10.4103/0189-6725.86061
PMID: 22005364
Quick Response Code:

Androgen insensitivity syndrome: Risk of malignancy and timing of surgery in a paediatric and adolescent population

Dragan Kravarusic, Emmanuelle Seguier-Lipszyc, Elad Feigin, Revital Nimri[1], Nessia Nagelberg[2], Enrique Freud

ABSTRACT

Background: Management of female phenotype XY disorders poses a series of problems for the treating clinician. Even after a series of investigations and imaging modalities, there are lingering doubts about the exact nature of the disease and the correct management option. Optimal timing and necessity for removal of their testes have been a debated issue by physicians. There is a generally accepted opinion among physicians that the risk of malignancy in androgen insensitivity syndrome (AIS) is considerably lower than with other intersex disorders and occurs at a later age. **Objective:** The highlight of this presentation is to reinforce the value of laparoscopic gonadectomy in management of AIS in correlation with data suggesting higher risk of malignancy. **Patients and Methods:** A retrospective review of 11 phenotypic females with XY karyotype was carried out. The patients were evaluated by a diagnostic protocol which included clinical, hormonal, sonographic and cytogenetic examinations. Patients/parents were counselled by the team concerning the different treatment modalities and contrary to the assigned gender, laparoscopy was offered to them. Uneventful bilateral gonadectomy was performed in all the patients and gonads submitted for histopathological examination. **Results:** A total of 11 patients (mean age, 10.4 ± 4.1 years), including six with complete AIS and five with partial AIS (PAIS) were reviewed. In two patients with PAIS (18.1%), histopathology revealed malignancy (bilateral seminoma and gonadoblastoma) and in an additional patient, a benign hamartoma was found. Literature evidence suggests that AIS female phenotype patients retaining their testes through puberty have a 5% chance for developing malignant tumours. Reviewing our results in correlation with literature, we found that PAIS patients may harbour a higher risk of malignancy. **Conclusions:** In complementation to hormonal tests and cytogenetic techniques, laparoscopic gonadectomy is required to complete the diagnostic work up for AIS as it also adds a final therapeutic approach with low risk and huge benefit. Since laparoscopy is now a well-tolerated and widely accepted gold standard, it should be included in routine management for patients with AIS. Risk of malignancy in PAIS should be investigated in larger cohort of these patients.

Key words: Androgen insensitivity syndrome, risk of malignancy, timing of surgery

INTRODUCTION

Androgen insensitivity syndrome (AIS), formerly known as testicular feminisation, is the most common form of male under virilisation. Affected individuals are phenotypically female, yet have male karyotype (XY). This is an X-linked recessive genetic disorder and depending on the amount of residual receptor function, androgen insensitivity can be either complete AIS (CAIS) or partial AIS (PAIS). The prevalence of the syndrome is estimated to be about 1 in 20,000.[1]

There is a generally accepted opinion among physicians that the risk of malignancy is considerably lower than with other intersex disorders and occurs at a later age. Current recommendations for AIS patients are to retain the cryptorchid gonads through puberty to receive benefit from their hormone production; enhance bone maturation; and to allow the completion of secondary sexual development.[2] Even in post-pubertal patients, gonadectomy issue is controversial despite the risk of malignancy in such gonads increasing with age, with estimated cumulative risk of 3.6% at 25 years, and 33% at 50 years of age.[3] Uncommonness of AIS and the lack of studies in individuals who have not had testes removed make the risk of malignancy difficult to quantify. We are presenting data suggesting that patients

Department of Pediatric Surgery, [1]Institute for Endocrinology, [2]Social Services, Schneider Children's Medical Center of Israel, Sackler Medical School, University of Tel Aviv, Israel

Address for correspondence:
Dr. Dragan Kravarusic, Department of Pediatric Surgery, Schneider Children's Medical Center of Israel, 14 Kaplan St., Petah-Tikva 49202, Israel. E-mail: dkravarusic@yahoo.com

with AIS may have an increased risk of developing a malignancy.

PATIENTS AND METHODS

We performed a retrospective chart review of all AIS cases seen at the Schneider Children's Medical Center of Israel between January 2000 and June 2005 [Table 1].

A total of 11 phenotypic females, ranging in age from 3 to 18 years, were evaluated by a diagnostic protocol which included clinical, hormonal, cytogenetic and sonographic examinations. Primary amenorrhea was the presenting complaint in four patients. In three of our patients, gonads were discovered during the repair of inguinal hernia, biopsy was done and once the work up was completed, final surgery was performed. The remaining four patients were evaluated for enlarged clitoris and suspected ambiguous genitalia. All patients were diagnosed and followed up by the endocrinology clinic in our institution and details of their clinical presentation were noted. A complete physical examination with special attention to the external genitalia, development of secondary sexual characteristics and virilising features was done. Chromosomal analysis was performed on lymphocyte cultures from peripheral blood. Ultrasonography was done to confirm the presence or absence of the uterus and to locate the gonads. Serum testosterone, follicle stimulating hormone and luteinizing hormone levels were performed with radioimmunoassay in all patients. After a diagnosis of AIS in phenotypic females with XY karyotype was confirmed, each patient was counselled by a multidisciplinary team concerning the different treatment modalities and laparoscopic surgery was offered to them. An informed written consent was taken prior to the procedure. Uneventful prophylactic laparoscopic gonadectomy was performed in all the patients and gonads were submitted for histopathological examination.

Surgical technique

Standard preoperative preparation was done and Foley catheter was inserted. Under general anaesthesia, Veres needle was inserted and pneumoperitoneum established. Operative laparoscopy was performed using a 5-mm camera inserted through an infraumbilical incision. Two additional ports (10 and 5 mm) were inserted under direct vision about 2 to 3 cm below the umbilicus, lateral to the lateral border of the rectus muscle. The pelvis and abdomen were explored and details of the internal genitalia were noted [Figure 1].

Prior to dissection, the course of the ureter was identified bilaterally and the gonads were resected with a harmonic scalpel from surrounding peritoneal attachments. The dissection of the gonads was started from the medial aspect and continued laterally until the entire gonad was freed. Lateral vascular attachments were double clipped and divided with laparoscopic scissors. Extra caution was exercised at the lateral ends to prevent injury to the ureter or iliac vessels. When

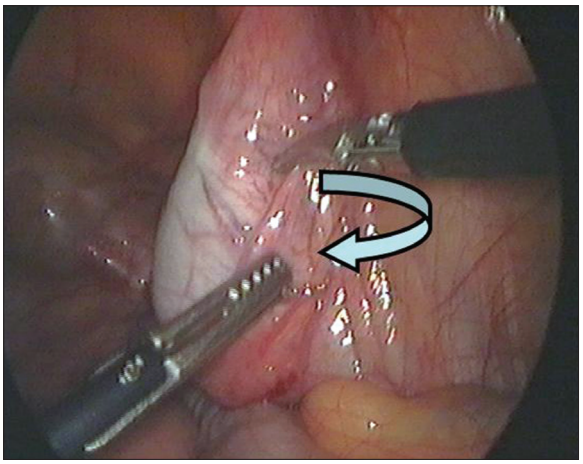


Figure 1: Intra-operative image of gonad—arrow pointing spermatic cord

Table 1: Clinical and histopathological information of patients with androgen insensitivity syndrome

Age (y)	Social sex	Karyotype	Clinical diagnosis	Histopathology right/left	Therapy
9	Female	46 XY	PAIS	Testis bilaterally, microscopic foci of Gonadoblastoma (rt)	Estrogen
8	Female	46 XY	CAIS	Testis, bilaterally, Sertoli cells	Estrogen
8	Female	46 XY	CAIS	Testis bilaterally,	Estrogen
6	Female	46 XY	PAIS	Testis bilaterally, Sertoli cells, Hamartoma (lt)	Estrogen
18	Female	46 XY	CAIS	Testis bilaterally, Leydig cells	Estrogen
18	Female	46 XY	CAIS	Testis bilaterally, Leydig cells	Estrogen
18	Female	46 XY	CAIS	Testis bilaterally	Estrogen
6	Female	46 XY	CAIS	Testis bilaterally, hyperplasia of Leydig cells	Estrogen
13	Female	46 XY	PAIS	Seminoma (rt), Seminoma (lt) with foci of Gonadoblastoma	Estrogen
3	Female	46 XY	PAIS	Testis bilaterally	Estrogen
8	Female	46 XY	PAIS	Testis bilaterally	Estrogen

CAIS = Complete androgen insensitivity syndrome, PAIS = Partial androgen insensitivity syndrome

possible, gonads were individually removed through the 10-mm opening, and for three patients with larger gonads, we used an endobag for evacuation. Specimens were submitted for histological examination, and pelvic cavity and pedicles were inspected to ensure haemostasis. The patients were started on hormone replacement therapy after surgery.

RESULTS

In all cases, gonads were easily identified and no uterus or remnants of adnexa were found. Gonads were with normal "macro" appearance, fixed with pelvic peritoneal attachments and located in different proximity to the internal ring. In three of five PAIS patients, the vas deferens and seminal vesicles were identified. No complication occurred during any of the surgeries. Post-operatively, the patients recovered quickly and were discharged the next dayIn our cohort of 11 patients, microscopic examination revealed bilateral seminoma in 1 (9%) patient with synchronous focci of gonadoblastoma. In a second patient, stage 1 gonadoblastoma was discovered (9%). In a third patient, histopathology revealed benign hamartoma (9%). Table 1 shows the summary of the clinical and histopathological information of all patients with AIS. It is very interesting that the three tumours were found in a subgroup of five patients with PAIS, constituting 60% of all PAIS. In the subgroup of complete AIS, all gonads were histologically normal testes. From five PAIS patients, two had malignant tumours (40%) and one benign tumour (20%). After this evidence, we again reviewed the reports from cytogenetic, hormonal and pathological findings and in cases where malignancy was discovered, we performed an additional cytogenetic evaluation to eliminate misdiagnosis as a possible factor. No other genetic mutations were found and repeat findings confirmed diagnosis of PAIS.

DISCUSSION

Bilateral seminoma in AIS has been reported in an adult patient.[4] However, to our knowledge, this is the first reported case of bilateral seminoma in a 9-year-old child with AIS.

We found in the literature that gonadoblastoma and seminoma are the most frequently occurring malignant tumours in gonadal intersex disorders. They are reported in settings of AIS; however, these findings are much more common in different entities such as pure of mixed gonadal dysgenesis or mosaicism.[5,6] At present, surgical excision is the treatment of choice and further treatment is guided by the stage and histologic type of the malignant component. Sertoli-Leydig hamartomas are well described as well in androgen insensitivity syndrome.[7]

It is possible that in PAIS, the defects underlying this syndrome may develop from a broad spectrum of mutations and genetic mechanisms, sometimes not completely understood, suggesting the possibility that risk of malignancy in this particular entity may be higher than previously thought. It is very important to be aware of the findings associated with AIS, which may be undiagnosed and drastically change the fate of patients.

AIS includes a group of disorders in which the genetic sex is male with XY sex chromosome complement. The gonads are testicles but the phenotype is female. Deleterious mutation of the androgen receptor gene on the only X chromosome can cause several forms of AIS. Complete form seems to be the most common (CAIS), but prevalence of partial (PAIS) and other milder forms is not well established.[8]

In CAIS, individuals cannot respond to testosterone and only the non-androgenic aspects of male development take place: formation of testes, production of testosterone and anti-Müllerian hormone which suppress Müllerian ducts, preventing formation of the uterus and upper vagina. The testes usually remain in the abdomen, or occasionally move into the inguinal canals. The testes make sufficient amounts of testosterone but no androgenic sexual differentiation occurs and internal male genital ducts fail to form because of lack of testosterone response. At birth, a child with CAIS appears to be a normal girl, with no reason to suspect an incongruous karyotype. Puberty tends to begin slightly later; some of the testosterone is converted to the estradiol, inducing normal breast development. Little or no pubic hair or other androgenic hair appears and acne is rare as well. Primary amenorrhea is the most common complain.

In PAIS, associated mutations do not entirely eliminate all responsiveness to androgens and mild testosterone effects occur. These individuals also have a female body lacking a uterus, ovaries and full vagina. The most obvious testosterone effect seen in PAIS is pubic and axillary hair, which are usually normal. The clitoris may be enlarged and the labia partially fused. These features are usually not pronounced enough to cause noticeable ambiguity of the genitalia at birth, or may be subtle enough to be ascribed to normal anatomic variation

during childhood. Internally, traces of undeveloped Wolffian structures (epididymis, vas deferens, seminal vesicles and ejaculatory ducts) may be present.

When the diagnosis of complete form of AIS is made before puberty, there are two schools of thought regarding management. The traditional approach is to leave the testes in place so that breast development occurs spontaneously at puberty. However, malignancy *in situ* has been observed before puberty, albeit occurring more frequently in the partial form of androgen insensitivity.[9] The estimated risk prevalence is quoted to be 2 to 5%.[10] "*In situ*" malignant lesions can be excluded only with histopathological examinations of gonads. Studies in adults have shown that 50% of testes containing carcinoma *in situ* develop a tumour within 5 years of diagnosis, if not treated.[11] When reviewing the literature, we found several reports of malignancy in adolescent and young adult AIS patients.[12] A premalignant form of gonocytes can give rise to choriocarcinoma, gonadoblastoma, seminoma teratoma, yolk sac and embryonal tumours.

Benign tumours such as hamartomas, Sertoli cell adenomas and rarely Leydig-cell tumours have been reported in association with AIS. The hamartomas associated with AIS do not have an endocrine effect, whereas ovarian Sertoli-Leydig cell tumours are often virilising or occasionally estrogenic.[13] By reviewing images (CT/MRI) of these tumours, it is difficult to exclude possible neoplastic nature and preclude surgery for definitive diagnosis. Uncommon conditions such as AIS are difficult to analyse with prospective studies because of the large sample size required to capture sufficient number of cases.

Currently, there is no worldwide consensus on the stage at which testes should be removed from AIS patients reared as female. We strongly encourage the tendency to perform an early gonadectomy in female phenotype-assigned patients whenever the diagnosis of PAIS is made. For male-assigned patients, a minority, orchiopexy allows "close" follow-up and should follow reconstructive surgeries. This approach allows gonadal tumours to be detected at an early, asymptomatic phase of their development. Based on our study, it seems to be particularly important in PAIS patients in whom broad spectrum of defect mutations and genetic mechanisms underlying this syndrome may "hide" significant risk for malignancy.

In post-pubertal patients with androgen insensitivity syndrome, literature review revealed quite standardised approach among the centres and prophylactic removal of gonads is usually recommended. Estrogen replacement is needed thereafter; ethinyloestradiol is commonly used, although delivering estrogen for selected patients through a transdermal patch is a suitable alternative. In pre-pubertal AIS patients with female-assigned gender, breast development can be induced at 11 to 12 years of age, starting with ethinyloestradiol and increasing gradually to an adult dose by the end of puberty. The requirement to use combined estrogen-progesterone treatment in cyclical fashion has been controversial because of the absence of a uterus. However, there is the possibility of an increased risk of breast cancer and cardiovascular disease with the use of long-term unopposed estrogen. For patients with suspected AIS, a thorough investigation and evaluation by a paediatric endocrinologist and geneticist is essential and in recent years, laparoscopy has been used as a method for the evaluation and treatment of intersex patients.[14,15]

At present, laparoscopy has gained acceptance as the ideal method of surgical treatment of the internal genital organs in patient with variety of intersex disorders. Laparoscopic gonadectomy has efficiency equivalent to that of open surgery with lower morbidity, quicker postoperative recovery and excellent cosmetic results. This latter aspect is especially important for patients with intersex disorders who need reaffirmation of their body image and self esteem.

Laparoscopic procedure has created a new diagnostic and treatment standard, well tolerated by patients and widely accepted by surgeons. In complementation to hormonal tests and cytogenetic techniques, early laparoscopic gonadectomy is the final, definite step in completing the diagnostic work up for these patients. This therapeutic approach thereby eliminates the risk of malignancies of gonadal origin with low operative risk and huge benefit. We strongly suggest consideration of early laparoscopic gonadectomy in routine management of the practice for PAIS female phenotype-assigned patients.

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Cite this article as: Kravarusic D, Seguier-Lipszyc E, Feigin E, Nimri R, Nagelberg N, Freud E. Androgen insensitivity syndrome: Risk of malignancy and timing of surgery in a paediatric and adolescent population. Afr J Paediatr Surg 2011;8:194-8.

Source of Support: Nil. **Conflict of Interest:** None declared.