Mini-Review

Timing of Gonadectomy in Patients with Complete Androgen Insensitivity Syndrome– Current Recommendations and Future Directions

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A B S T R A C T

This review highlights the controversy regarding timing of gonadectomy in patients with complete androgen insensitivity syndrome (CAIS). We will review the published literature regarding frequency of gonadal malignancy and summarize historical findings. Recent research suggests that gonadectomy may be deferred until adulthood due to the low risk of malignancy. An algorithm is also provided to help guide clinicians in management of patients with complete androgen insensitivity syndrome who have deferred gonadectomy.
Key Words: Complete androgen insensitivity syndrome, Gonadectomy, Testicular feminization syndrome

Introduction

Androgen insensitivity syndrome (AIS) is an X-linked recessive disorder caused by a mutation in the gene encoding the androgen receptor (AR) resulting in androgen resistance. The estimated prevalence of AIS is between 1:20,000 and 64,000 births.[1] There is variable phenotypic expression of the disorder, and therefore it is classified into complete and partial androgen insensitivity syndrome. Individuals with complete androgen insensitivity syndrome (CAIS) have female external genitalia, whereas ambiguous genitalia are often present in patients affected by partial insensitivity syndrome (PAIS). Our focus highlights recommendations for patients with CAIS as the complete form of AIS presents with a known phenotype, unlike PAIS, which presents with heterogeneity in phenotype. Also, there is a higher risk of gonadal malignancy in patients with PAIS (50%) and possible virilization in individuals raised as women; thus, gonadectomy is usually recommended in these cases.[2]

It has been established that there is an increased risk of gonadal tumors in patients with CAIS. Controversy in timing of gonadectomy has been a well-known debate over the years in which some providers advocate for gonadectomy before puberty to decrease the risk of malignancy, while others are in favor of delaying gonadectomy to allow for spontaneous puberty.[3] Patient advocates from the Androgen Insensitivity Syndrome Support Group (AISSG) have supported delaying gonadectomy into adulthood closer to the natural age of puberty due to a low malignancy potential. We will summarize the current literature regarding reported estimates of malignant tumors in these patients, along with a review of surveillance options if gonadectomy is deferred.

Clinical Description

Initially coined as a "testicular feminization syndrome" by Morris[4] in 1951, the disorder was characterized by the presence of a male karyotype with a female phenotype. Due to a defect in the gene encoding the androgen receptor on the long arm of the X chromosome,[5] there is resistance of the target organs to the actions of testosterone. Succinctly stated by Dr. R.P. Shearman, "If the target cells lack this (androgen) receptor, testosterone passes like a stranger in the night and neutral female absolutism reigns supreme."[6]

The characteristic features of this disorder include a female phenotype with normal breast development but absent or scanty growth of pubic and axillary hair.[5] The disorder also includes a vagina of varying lengths along with the absence of the uterus, fallopian tubes, and ovaries. Gonads, in the form of testes, are located at the internal inguinal ring or can be palpated in the labia majora for patients with CAIS.[7] There have also been cases in which intra-abdominal gonads were observed in patients with CAIS.[1] Androgens, in the form of testosterone, are produced by these gonads and in the range of a typical male adult.[5] Also, estrogen and aromatase activity are both preserved, which is responsible for breast development in these patients.

It has been well established that there is an increased risk for the development of germ cell tumors in patients with AIS. The invasive type II germ cell tumor that are encountered are the seminoma (if the gonad is testes) and dysgerminoma, if the gonad is considered an ovary[8]; early

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precursors of these tumors are seen as a gonadoblastoma (GB) or carcinoma in situ (CIS). If the gonads are removed due to the risk of future malignancy, hormone replacement therapy should be initiated and continued until the age of menopause.

Historical Evidence for Timing of Gonadectomy

The OVID MEDLINE database was searched to gather articles written within the time frame of 1996 to 2014. Articles were cross-referenced and earlier papers were also obtained dating to as early as the original papers published in 1953. These articles were then reviewed, and the findings are summarized in Table 1. Published literature regarding the estimated risk of gonadal malignancy have varied from 0.8% to 22%[8] from ages 14 to 51. The majority of these reports are based on case reports and anecdotal evidence.

As can be seen from the findings in Table 1, there have been many discrepancies in the literature regarding the timing of gonadectomy. These discrepancies have stemmed from a lack of data in the majority of these cases. Diagnosis of the syndrome based on clinical criteria before the advent of karyotyping may have led to misdiagnosis in early reports. Other weaknesses in the literature include discrepancies in the age at gonadectomy and pathology of the gonads.

The trend toward gonadectomy in these patients appears to have been implemented as early as the 1950s when Morris suggested "after adolescence surgical removal then appears advisable to avoid the very real danger of neoplasm."[4] In a subsequent study by Morris in 1963, 14 malignant tumors were seen in a total of 181 cases of CAIS; 3 tumors were seen in patients younger than 30 years (3/131, 2.3%) and 11 tumors were reported in patients older than 30 years (11/50, 22%). However, he concluded that this estimated malignancy rate of 22% may be an overestimation as he states the indication of the procedure may have prompted the patient to seek care with this physician. Ultimately, the conclusion to continue with gonadectomy in these patients was reemphasized.

Studies published in the 1970s aimed to look at the incidence of malignant gonadal tumors in patients of varying ages undergoing gonadectomy. Dewhurst et al analyzed a group of 44 patients with a known XY karyotype and exhibiting clinical characteristics of AIS.[10] Although the exact age at which gonadectomy had been performed was unknown, the majority of patients underwent gonadectomy after age 16. There were no cases of malignancy found in the gonads of these patients leading the authors to favor delay in gonadectomy to a postpubertal state in which secondary sex development is complete.

Similarly, in a study by Manuel et al,[11] 23 cases of "testicular feminization syndrome" were described and none of the gonads were found to contain a tumor. This study also contained a review of 82 cases in the literature in which they found 7 malignant tumors in patients with an age range of 14 to 51, leading these authors to conclude that a delay in gonadectomy may be entertained until the age of 30.

Case reports published in the 1980s were the first to describe true malignant tumors in adolescent patients.[12,13] Horcher et al[12] first described a case report of a 15-year old girl with AIS based on an XY karyotype and physical attributes. This patient was allowed to complete puberty without intervention and underwent a gonadectomy at age 16. Both gonads were removed, and one was found to contain a seminoma. This patient did not require any further postoperative radiation or chemotherapy as surgery was curative. Later in the same decade, Hurt et al[13] reported a stage IIA testicular seminoma in a 14-year-old girl with AIS. Radiation therapy was used for this patient, leading to a disease-free interval of 18 months at the time of published report. Both patients in these studies did receive conjugated estrogen hormone replacement therapy. These 2 case studies represented the earliest reported cases of malignant gonadal tumors in teenage patients.

As techniques in gene sequencing improved in the 1990s and early 2000s, more studies were published regarding gonadectomy in AIS patients. One of the largest reports, published by Ahmed et al,[1] contained 105 cases of CAIS in which 81 had undergone gonadectomy. These patients were identified based on clinical diagnosis as well as autosomal recessive mutational studies. The majority of these patients had undergone gonadectomy before puberty. No cases of malignancy were reported.

Hannema et al[7] described the risk of malignancy in 44 patients with CAIS, also with confirmation of the an AR

Table 1
Historical Evidence for the Timing of Gonadectomy

Study author	Year	Number of Patients	Karyotype Available	Age at Gonadectomy	Pathology	Malignancy
Morris and Mahesh[9]	1963	181	No	Unknown	Germinoma	22%
Dewhurst et al[10]	1971	44	Yes	55 years	Dysgerminoma	2.2%
Manuel et al[11]	1976	23	Yes	Unknown	–	3.6% (age 25); 33% (age 50)
Horcher et al[12]	1983	1	Yes	16 years	Seminoma	N/A
Hurt et al[13]	1989	1	Yes	14 years	Seminoma	N/A
Rutgers and Scully[14]	1991	40	No	35, 51, 71 years	Seminoma; malignant sex cord tumor	9%
Ahmed et al[1]	2005	105	No (AR mutational studies)	Average 14 years	Normal testes	0%
Hannema et al[7]	2006	44	Yes	14 days to 53 years (average 5.5 years)	Carcinoma in situ	0% (in situ lesion)
Nakhal et al[15]	2013	13	Yes	17 to 37 years (average 22 years)	Sertoli cell adenoma; paratesticular cysts	0%
Liu et al[16]	2014	30	Yes	17 to 34 years (average 22.3 years)	Gonadoblastoma	30%