A Review of Radiologic Imaging in Patients with Androgen Insensitivity

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Abstract
Androgen insensitivity (AIS) is a disorder of sex development that results from mutations in the androgen receptor. In complete AIS, patients are genetically XY, but phenotypically female and frequently present with primary amenorrhea in the teenage years. In partial AIS, patients are also genetically XY, but the phenotype varies based on the amount of activity of the androgen receptor and commonly present with ambiguous genitalia. These disorders have enormous physical and psychological impacts on patients and their families. At the time of diagnosis of AIS, whether complete or partial, imaging should be ordered to evaluate the internal genitalia and location of the gonads. There are a variety of imaging modalities, which can be employed including ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), or a combination of these techniques. We will review the role of each imaging modality in the diagnosis and evaluation of androgen insensitivity.

Keywords
Androgen insensitivity; MRI; Gonadectomy; Orchiectomy

Introduction
Disorders of sex development (DSD) are a group of disorders resulting from congenital abnormalities in development of the reproductive organs. Androgen Insensitivity (AIS), previously known as testicular feminization, is a DSD resulting from a relatively rare condition affecting the androgen receptor (AR). The incidence is approximately 1 in 20,000 to 1 in 64,000 births [1]. The pathophysiology of the condition begins with the XY genotype, which all AIS patients are born with. The SRY gene of the Y chromosome directs the gonad to become a testicle, and produce the Sertoli and Leydig cells. The Sertoli cells then secrete Anti-Mullerian Hormone (AMH), resulting in regression of the Mullerian ducts that would have formed into the uterus, fallopian tubes and upper vagina. The Leydig cells secrete testosterone, which would normally stabilize the Wolffian ducts and cause masculinization of the external genitalia. In AIS, however, there is a mutation in the AR gene resulting in defective binding of testosterone and therefore lack of masculinization of the external genitalia and failure to stabilize the Wolffian ducts.

The phenotype of AIS is variable depending on the functionality of the AR receptor. Complete AIS occurs when the androgen receptor (AR) is completely unresponsive to circulating androgens. Patients with complete AIS are phenotypically female from birth and often present with primary amenorrhea during the teenage years. These patients usually present with normal breast development, although breast composition is abnormal and scant or absent pubic and axillary hair. Furthermore, they are often found to have a shortened vagina, but invariably absent uterus, cervix, and fallopian tubes. Instead of ovaries, they have undescended testicles and testosterone in the normal range for males. Patients with partial AIS have some function of the AR. The phenotypic presentation of partial AIS can vary from mildly virilized female appearance to under-virilized male appearance and is frequently diagnosed at birth with ambiguous genitalia [2,3]. Internally, these patients lack Mullerian structures but have variable development of the Wolffian ducts depending on the amount of AR functionality. The inheritance pattern of AIS is X-linked recessive; however, approximately 40% of patients with complete androgen insensitivity have no family history and are thought to be denovo mutations [3].

Patients and their families have to deal with the psychological and physical consequences of the diagnosis. For patients with partial AIS, gender reassignment, timing of surgery for genital reconstruction and gonadectomy need to be considered generally in infancy. For complete AIS, the decision of when to do gonadectomy is weighed against the need for hormone therapy for secondary sexual characteristic development. Delaying the diagnosis of AIS can result in malignancy of the gonads or make surgical correction more difficult for patients with partial AIS [4]. Therefore the correct diagnosis and proper characterization of the pelvic anatomy are paramount in patients with AIS [5]. This review will discuss the imaging modalities that have been used in the evaluation of patients with AIS including the strengths and weaknesses of each.

Malignant transformation of gonads
Patients with AIS have traditionally been counseled on the need to remove the gonads at the time of diagnosis secondary to risk of malignancy. The actual risk of malignancy and timing of removal are under debate in the pediatric and adolescent gynecology literature [4,6]. Previously it was recommended that gonads were removed prior to puberty because of an increased risk of malignant transformation after puberty.

The most commonly described tumors in AIS are Sertoli-Leydig cell tumors as well as Intratubular Germ Cell Tumors (ITGCT). ITGCTs are considered precursor lesions of malignant gonocytes, which can give rise to all types of non-seminomatous germ cell tumors [7]. Morris reported an incidence of malignancy of 22% in a cohort of 50 patients over the age of 30 with AIS [3]. Manuel et al. calculated a risk of malignancy of 3.6% by age 2.5 years, which increased to 30% by age 50 years [8]. The risk of malignancy is higher in patients with partial AIS as compared to complete AIS [9]. The risk of malignancy for partial AIS exists even prior to puberty. Cassio et al found that in a group of 11 patients with partial AIS that 63% had a pre-pubertal malignancy [10]. In a study by Bangsbo et al all cases of complete
AIS were reviewed in Denmark over a seven-year period. During that time, 21 patients were diagnosed with CAIS and four were noted to have gonadal tumors; however none were malignant [11]. Supporters of delaying gonadectomy argue that patients with complete AIS have a lower risk of malignancy than previously stated, require less exogenous hormone, improved development of secondary sexual characteristics, and improved patient coping and compliance [6].

Need for imaging

The location of the gonads in AIS is highly variable. The testes can be anywhere along the tract of normal descent including the intraperitoneal cavity, in the inguinal canal either cephalad or caudal to the inguinal ring, or in the labia. The gonads are usually fibrosed, atrophic and can be very small in size. Intra-abdominal gonads are typically removed via laparoscopy. When the gonads are located within the inguinal canal, they can sometimes be removed laparoscopically, but may require bilateral inguinal dissection, which may be outside the expertise of the reproductive endocrinologist. Therefore, it is important to order imaging prior to surgery to plan the best surgical approach (and arrange for surgeons with proper expertise) to remove the gonads and to characterize the surrounding anatomy to minimize damage to surrounding structures. We will describe the various imaging modalities that have been explored to aid in identifying the location of testes before gonadectomy including the strengths and weaknesses of each.

Another argument for delineating the best imaging modality for AIS patients is to better explore the pelvic anatomy, both internal and external. This is of particular significance in patients with partial AIS, as the phenotype can be quite variable. Therefore in addition to having an imaging modality, which can best identify the location of the gonads, it is important to have a modality which can clearly identify altered pelvic anatomy for other reference or potential future need for corrective surgery, especially in the setting of gender assignment in partial AIS.

Ultrasound

Patients with AIS were originally compared to males with cryptorchidism. Sonography has typically been utilized in patients with cryptorchidism. Vijayaraghavan performed a review of 197 cases of no palpable testes and the location of the testicle was predicted by ultrasound in 191 cases even when the testes was abdominal, torsed or atrophic. The smallest testis identified was 4.8x3 mm. The authors credit the “following the cord” technique. Testes were unable to be localized in 5.1% of cases; however 4 cases were confirmed to have vanishing testis. Laparoscopy was needed for diagnosis in 2.5% of cases. Ultrasound was initially employed with AIS patients as well. Ultrasound is inexpensive, safe, and widely available. However, as mentioned previously, AIS gonads can be smaller and have a different character than normal testes, making sonographic detection of the gonads challenging. This modality is sensitive at locating testes in other locations [12].

As the imaging modality applied to locate cryptorchid testes, ultrasound was initially employed with AIS patients as well. Ultrasound is inexpensive, safe, and widely available. However, as mentioned previously, AIS gonads can be smaller and have a different character than normal testes, making sonographic detection of the gonads challenging. This modality is sensitive at locating testes within or caudal to the inguinal ring; however, it is less sensitive at locating testes in other locations [13]. Mansour et al. performed both ultrasound and MRI on 25 patients being assessed for DSD’s including 12 patients ultimately diagnosed with complete AIS. They used a multi-approach ultrasound (including transabdominal, transvaginal, transperineal and occasionally transrectal) to identify the pelvic anatomy. They found that multi-approach ultrasound was 89.8% accurate compared to 85.7% with MRI. They concluded that ultrasound should be ordered initially as a more cost effective modality with good accuracy and that MRI should be reserved for situations in which ultrasound is inconclusive. They had more success with ultrasound than previous studies with DSD and this is attributed to the addition of the multi-approach [14].

Ultrasound is the most inexpensive imaging modality and is widely available. However, it is important to note that skilled sonographer with the specialized probes used in the multi-approach method by Mansour et al. [14] may not be available at all facilities. Ultrasound, especially the abdominal approach, is considered to be non-invasive. However, a multi-approach ultrasound could be considered quite invasive, especially in a virginal teenage girl presenting with pubertal development issues.

Computed tomography

Computed Tomography (CT) is commonly used for detection or characterization of malignancy. CT has been described for the detection of tumors in patients with AIS in a variety of studies. These studies suggest that if concerns for malignancy are present, CT scan or PET/CT may be a useful adjunct to other imaging used for diagnosis and surveillance [15-17]. However, little has been published about the use of CT in the initial evaluation of patients suspected of having AIS. A case report by Hales and Rosser described how the cross sectional ability of CT made this modality a good tool for localization of the gonads in AIS, which helped in planning the surgical approach as well as decreased anesthesia time during surgery [18]. CT has the disadvantage of being less accessible and more costly than ultrasound, and there is exposure to ionizing radiation. CT scan does not characterize soft tissues as well as MRI, which can be important in the evaluation of DSD’s, especially those presenting with ambiguous genitalia.

Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) has been studied more extensively than CT in the evaluation of patients with AIS. In 2011, a review by Fenner stated that ultrasound is not ideal for the assessment of undescended testes and MRI and diffusion weighted imaging are the preferred methods for their location [19]. MRI has the same advantage of CT by imaging in multiple planes and good contrast resolution. MRI has improved detection of intraabdominal gonads as compared to ultrasound but without the exposure to ionizing radiation as in CT imaging. MRI has been the imaging modality of choice for patients with DSD’s to characterize abnormal internal anatomy because of the good soft tissue resolution. This is especially important in patients with partial AIS who can have drastically varying phenotypes and therefore pelvic anatomy that needs to be characterized accurately [2]. Another quality stated by proponents of MRI is that the parameters can be adjusted to optimize the contrast between the testes and surrounding tissues. Tanaka et al described the use of MRI to locate the gonads in this patient population. Since the testes are often fibrosed, they result in hypo-intense T2 weighted images as compared to normal testes [20] (Figure 1). Other authors have described differences in gonad appearance on MRI, specifically the T2 relaxation times of AIS gonads as compared to normal, which helps in detection of smaller testes [21]. In a case series, Khan...
et al found that MRI aided in pre-surgical planning for removal of the gonads by accurately characterizing the location of the testes, allowing for appropriate pre-surgical consultation when inguinal dissection was expected to be performed (Figure 2). Furthermore, MRI prevented unnecessary surgical dissection in a case of unilateral testis [22].

One prospective study compared normal females to patients with complete AIS in terms of MRI findings, sexual function and physical exam findings. MRI was found to be helpful in understanding vaginal depth that was not adequately assessed on physical examination [23]. Nezzo et al. published a case series regarding the role of imaging in complete AIS. They concluded that MRI is the study of choice for evaluation because it provides superior tissue characterization of Mullerian anomalies and is better at detection of intraabdominal gonads compared to ultrasound [24]. Mansour et al. recommended MRI as the imaging modality of choice for patients with ambiguous genitalia prior to surgical correction, specifically when differentiating between micropenis and clitoral hypertrophy [14].

Drawbacks of MRI include exposure to the contrast agent gadolinium, which has a low rate of adverse reactions [25]. However, contrast is not absolutely necessary during the evaluation of DSD’s such as AIS. Additionally, MRI may not be used in patients with metal implants. Finally, MRI is the most costly and least accessible of all imaging modalities described.

Conclusion

At the time of diagnosis of AIS, whether complete or partial, imaging should be ordered to evaluate the internal genitalia and to locate the gonads. Ultrasound continues to remain the best choice for initial evaluation as it is inexpensive, easily accessible and has a high sensitivity and specificity for location of gonads in complete AIS patients. Drawbacks of ultrasound are that is operator dependent, more invasive than other options when using the multi-approach, and may be inferior to other methods for characterization of abnormal internal pelvic anatomy. CT is rarely used for this patient population at present however may be a resource if MRI is not available to describe internal pelvic anatomy and locate intraabdominal gonads. As compared to other methods CT does have the drawback of exposure to ionizing radiation and does not have the same soft tissue characterization as MRI. MRI has the ability to image in multiple planes and good contrast resolution without exposure to ionizing radiation. MRI has been recommended as the preferred method of imaging in AIS, not only because it correctly characterizes the location of the gonads, but also because it arranges for proper surgical expertise at the time of their surgical removal. Additionally, MRI is less invasive than multi-approach ultrasound. If ultrasound is not able to locate gonads or if a description of internal pelvic anatomy is needed for surgical reconstruction planning, MRI is the imaging modality of choice. All methods have utilities and drawbacks depending on the clinical situation. Providers should be familiar with benefits and drawbacks of each as well as the resources at their institution to make the best choice for their patient with AIS.

References


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