MRI Findings in Androgen Insensitivity

Case series

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Abstract

Androgen insensitivity syndrome is a disorder of sex development resulting from mutations in androgen receptor. In complete form of this disorder, patients are genetically males, but phenotypically females, presenting with primary amenorrhea. We report three cases of Androgen Insensitivity Syndrome highlighting multifaceted role of MRI for presurgical planning by evaluating location, type of gonads and detecting possible complications. All patients presented with primary amenorrhea and MRI accurately localised testes in all, one patient had bilateral inguinal and two had intra-abdominal testes. Intra-abdominal testes were not localised on USG. MRI also depicted Sertoli cell adenomas and Wolffian duct remnants in these patients. MRI can provide comprehensive imaging prior to surgical treatment and thus can be considered a ‘One Stop Shop’ for imaging in androgen insensitivity syndrome. All the patients underwent laparoscopic gonadectomy which is the standard of care, with preoperative counseling about fertility. Postoperatively, they were started on estrogen therapy.

Keywords: Amenorrhea; Androgen-insensitivity syndrome; magnetic resonance imaging.
Introduction

Pubertal stage is a crucial time in a girl’s development where there is a sequential development of secondary sexual characters. Many aberrations in the phenotype during this stage need to be treated early so that the girl is clinically and psychosocially able to lead a normal life. One such condition involving discordance between genotype and phenotype in pubertal development is Androgen Insensitivity Syndrome (AIS). AIS is an inherited X-linked recessive disorder, first described by Morris, in which there is inability of organs to respond to androgens due to lack or defect of androgen receptor (AR). It is associated with Müllerian regression and presence of testes along its path of descent. In the complete form of this disorder the individuals are genetically males but phenotypically and psychologically females.

In such cases, early detection of gonads and their removal is imperative to prevent the malignant transformation of gonads. Ultrasonography (USG) being the primary modality for localisation of gonads, can miss the intra-abdominal gonads. Magnetic Resonance Imaging (MRI) provides a comprehensive imaging for both localisation and characterisation of gonads. There is limited literature available highlighting the above mentioned roles of MRI in these patients. In this series, three such cases of androgen insensitivity syndrome are presented, showcasing MRI as a ‘One Stop Shop’ for visualizing the spectrum of AIS and its possible complications. Consent was obtained from all three patients for use of the clinical and radiological data maintaining strict confidentiality about patient’s identity.

Case Reports

Case One

A 16-year-old female presented with primary amenorrhoea with clinical and USG findings as in [Table 1]. Tanner staging was used for thelarche and pubarche [Table 2]. MRI of pelvis revealed vagina measuring 5cm in length and a Gartner’s duct cyst was seen in posterior vaginal wall [Figure 1A]. Bilateral testes were seen along lateral pelvic walls, measuring 19×14×35 mm and 25×16×37 mm (AP×TR×CC) on the right and left sides respectively. There were multiple well-defined hypointense nodules on T2 weighted imaging (T2WI) seen within these structures bilaterally suggestive of Sertoli cell adenomas [Figure 1B]. The uterus and cervix were not visualized. Penile structure or phallus was not identified on MRI. A diagnosis of complete AIS
was given. The patient underwent laparoscopic gonadectomy and histopathology of specimen revealed stroma separating lobules of seminiferous tubules, consisting of only Sertoli cells. No spermatogonia / spermatocytes were seen. Interstitium showed leydig cell hyperplasia. The hypointense nodules seen on MRI corresponded to sertoli cell adenomas [Figure 1C].

Case Two
A 15-year-old female presented with primary amenorrhea with clinical and USG findings as in [Table 1]. Tanners Staging was used for thelarche and pubarche [Table 2]. MRI imaging of pelvis showed bilateral undescended small testes (measuring 2.5 cm on the right side and 2.3 cm on the left side) in the distal inguinal canal. No focal lesions were seen within the testes. There were paratesticular cysts seen bilaterally [Figure 2A]. Small penile shaft with corpora cavernosa and bilateral seminal vesicles were also seen along with rudimentary vagina [Figure 2B]. The uterus and bilateral ovaries were not visualized. These findings were suggestive of incomplete AIS. The patient underwent laparoscopic bilateral inguinal gonadectomy and histopathology of the specimen revealed decreased size of seminiferous tubules with thickened tubular walls and foci of hyalinization. There was loss of germ cells in the tubules with immature Sertoli cells. There was leydig cell hyperplasia. No atypia or dysplasia were seen [Figure 2C].

Case Three
A 23-year-old female presented with primary amenorrhea with clinical and USG findings as in [Table 1]. Tanners Staging was used for thelarche and pubarche [Table 2]. MRI showed bilateral intra-abdominal testes. On right side the gonad anterior to external iliac vessels were seen near deep inguinal ring measuring 9.3×16.4×29 mm (AP×TR×CC). On the left side the gonad posterior to external iliac vessels were seen measuring 19×9.8×23 mm (AP×TR×CC) [Figure 3A]. Bilateral seminal vesicles were seen [Figure 3B]. Penile structure or phallus were not identified on MRI. These MRI findings were consistent with complete AIS. The patient underwent laparoscopic gonadectomy and histopathology revealed seminiferous tubules lined by Sertoli cells with 50% showing luminal formation and leydig cell hyperplasia. There were no spermatocytes nor matured spermatids seen [Figure 3C].
Discussion
Morris coined the term Testicular Feminisation Syndrome in 1953 after his study on 82 patients, which is now known as AIS. Complete AIS are males with female phenotype and are raised as females. Partial AIS reflects a phenotype with varying degrees of masculinisation of the external genitalia due to levels of response to androgen. Incidence of AIS is approximately 1 in 20,400 to 1 in 99,100 births. In Complete AIS, there is mutation of the AR gene located on long arm of X chromosome and it follows X linked recessive inheritance. Approximately 40% of patients with AIS may have no family history of mutations of AR gene.

The AR in AIS is unresponsive to androgen action and androgens are converted into estrogens with action of aromatase. This leads to development of female secondary sexual characteristics. The secretion of Müllerian-inhibiting substance (MIS) by testes results in absence of mullerian system and hence uterus and fallopian tubes are not developed. Low prenatal androgenic effect in AIS also results in inadequate testicular descent. The testes develop on the anteromedial surface of the mesonephros in the urogenital ridge and is anchored in position by cranial suspensory ligament (CSL) cranially and gubernaculum caudally during the transabdominal stage at 10–15 weeks. The descent of testis in groin is achieved by testicular enlargement and gubernacular swelling reaction. Subsequently, CSL regression occurs under the influence of androgens. Both of these factors facilitate migration of testes through the inguinal canal. The inguinoscrotal phase at 25–35 weeks gestation is androgen-dependent and consists of the passage of the testes from the internal inguinal ring down into the scrotum. Testicular descent can get arrested at either of the two stages in AIS.

Clinical presentation of incomplete AIS can vary from phenotypic females with mild virilization to under-virilized males presenting with ambiguous genitalia. These patients have variable development of the Wolffian ducts system. Complete AIS presents with female secondary sexual characteristics like well-developed breasts, scanty pubic or axillary hair with shortened vagina and no evidence of male characteristics. Incomplete AIS patients may have normal breast, sparse pubic and axillary hair, with some abnormal form of male external genitalia. In our series, cases
One and Three showed no virilization and well formed vagina, whereas Case Two showed partial virilization with phallus. Instead of ovaries, they have undescended testes as in all our cases.

For genetic diagnosis of AIS, karyotyping is usually the first step and it reveals a 46 XY state as was seen in our cases. The most definitive way for diagnosis is to look for AR gene mutation by molecular genetic tests; however, facilities for these are not readily available and hence not routinely done. 8 Hormonal assays in these patients reveal normal to mildly elevated serum gonadotropins with normal to high androgen levels. 9 In our series, mildly elevated male levels of serum testosterone and normal or mildly increased gonadotropins were detected [Table 1]. Hormonal assays are however non-specific as a diagnostic tool in AIS.

Imaging plays a vital role in locating and characterizing the gonads. Although USG is usually the first imaging ordered, but operator/ equipment dependence, interference with bowel gas on transabdominal approach, requirement of transvaginal/transperineal approach and inherently smaller gonads in AIS are some of the reasons for low gonadal detection rates on USG. These are better with MRI as it has better soft tissue contrast and multiplanar capability. 10 Exact localization of gonads is valuable to decide surgical approach. Nakhal et al. have reported bilateral intraabdominal testes in 62% patients (n= 15) and at least one inguinal testes in 37% patients (n= 9). 11 Two of our cases had bilateral intraabdominal testes and Case Two had bilateral inguinal testes. Potential risk of malignancy in these gonads has been reported to be 0.8%–16% in Complete AIS and up to 50% in partial AIS. 9,12

MRI can detect heterogeneity of these gonads which may represent neoplastic changes. Well-defined hypointense nodules on T2WI represent Sertoli cell adenomas which occur in up to 83% of testes. 11 Detection of these on USG has not been reported in the literature till date. Although Sertoli cell adenomas are usually considered benign, Nakhal et al. found one out of 10 patients to have premalignant intratubular germ cell neoplasm which could not be detected on MRI. Paratesticular cysts appearing homogenously hyperintense on T2WI, have been reported in up to 96% of testes and Case Two also showed these cysts.
MRI also helps in ruling out other differential diagnosis of Mayer Rokitansky Kustner Hauser syndrome and Müllerian duct anomalies wherein ovaries are present. Wolffian duct remnants including vas deferens and epididymis have been reported in the literature; however, presence of seminal vesicles as seen in two of our cases has not been reported. The morphology of external genitalia including length of vagina and thickness/length of phallus are essential for gender-assignment surgical planning in partial AIS. Secaf et al. have defined objectively the criterion for diagnosing phallus/clitoral hypertrophy on MRI. These measurements can be accurately recorded on MRI.

Due to highly variable rates of malignancies in these patients, many patients prefer to retain their gonads till late adolescence or even adulthood. There is a felt need for monitoring these patients for in situ or invasive neoplasm. Although micro RNA based and single nucleotide polymorphisms based tests have shown some promise, their clinical use is still not in vogue. Until a reliable screening tool is developed, MRI may be used to detect neoplastic changes in these testes although MRI cannot detect in situ tumour. Gonadectomy done at puberty may prevent occurrence of germ cell tumours in the abnormally placed gonads. In all our cases, laparoscopic gonadectomy was performed. Histological correlation of these gonads revealed maturation arrest without any dysplastic changes. The patients were extensively counseled preoperatively about the future fertility prospects and they were started on estrogen therapy.

**Conclusion**

In AIS, imaging should be done to evaluate the internal genitalia. USG continues to remain the primary modality for evaluation as it is inexpensive and easily accessible. However, USG can miss detection of these gonads. MRI is a ‘One Stop Shop’ for visualizing the spectrum of AIS including its possible complications. It plays a key role in decision-making for management by gonadectomy or gender assignment surgery. Finally, MRI may be used as screening tool for detection of neoplastic changes in patients of AIS who retain their gonads into late adolescence or adulthood although it cannot detect in situ neoplasm.
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Table 1: Clinical details, hormonal levels and ultrasonography findings

| Finding                   | Case One          | Case Two         | Case Three        |
|---------------------------|------------------|------------------|-------------------|
| Age                       | 16               | 15               | 23                |
| Symptom                   | Primary          | Primary          | Primary           |
|                           | amenorrhoea      | amenorrhoea      | amenorrhoea       |
| Thelarche                 | Tanners III      | Tanners III      | Tanners V         |
| Pubarche                  | Tanners II       | Tanners II       | Tanners III       |
| Labia                     | Well developed   | III developed    | Well developed labia and clitoris |
| Vagina                    | Blind ,well      | Blind ,short     | Blind ,short      |
|                           | developed Vagina | vagina           | vagina            |
| Male secondary sexual     | Nil              | Short Phallus    | Nil               |
| characters                |                  |                  |                   |
| Serum Testosterone(ng/dl) | 342              | 1044             | 654               |
| (Normal:20–80 ng/dl)      |                  |                  |                   |
| Serum LH (IU/L) (Normal:5–20 IU/L) | 24.7 | 18 | 22.09 |
Table 2: Tanners Staging for Thelarche and Pubarche

| Stage | Breast                  | Pubic Hair                                                                 |
|-------|-------------------------|----------------------------------------------------------------------------|
| One   | Elevation of papilla only | No pubic hair                                                              |
| Two   | Elevation of breast and papilla as small mound, increased areola diameter | Sparse, long, pigmented hair, primarily on labia majora                     |
| Three | Further enlargement without separation of breast and areola              | Dark, coarse, curled hair sparsely distributed over mons                     |
| Four  | Secondary mound of areola and papilla above the breast                    | Adult-type hair, abundant but limited to the mons                          |
| Five  | Recession of areola to contour of the breast                             | Adult-type hair, extending onto the medial thigh                           |

Figure 1: Multiplanar T2 weighted MRI images & histopathology section for a 16-year-old female with primary amenorrhea. A: Sagittal image showing absent uterus and presence of a
vagina (four point star) and hyperintense Gartner’s duct cyst (left arrow). B: Coronal image depicting bilateral testes (four point star) with well defined hypointense sertoli cell adenomas (right arrows). C: Histopathology section of intraabdominal testes showing Sertoli cell adenoma (four point star) (H&E, 100x).

**Figure 2:** Multiplanar T2 weighted MRI images & Histopathology section for a 15-year-old female with primary amenorrhea. A: Coronal image depicting bilateral inguinal testes with paratesticular cysts (left arrow) and corpora cavernosa (four point star). B: Axial image showing bilateral inguinal testes (white arrows) and seminal vesicles (four point star). C: Histopathology section showing seminiferous tubules with thickened hyalinised walls (black arrow) lined with immature Sertoli cells (red arrow) (H&E, 400x).
Figure 3: T2 weighted MRI images & Histopathology section for a 23-year-old female presented with primary amenorrhea. A: Axial image depicting bilateral testes (four point star) B: Axial image showing seminal vesicles (left arrow). C: Histopathology section of abdominal testes showing seminiferous tubules lined by Sertoli cells (blue arrows) with surrounding stroma showing leydig cell hyperplasia (red arrows) (H&E, 400x).