Magnetic Resonance Imagery Findings in Androgen Insensitivity
A case series

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ABSTRACT: Androgen insensitivity syndrome (AIS) is a sex-development disorder resulting from mutations in the androgen receptor. In its complete form, patients are genetically male but phenotypically female, presenting with primary amenorrhea. We report three cases of AIS highlighting the multifaceted role of magnetic resonance imaging (MRI) for presurgical planning by evaluating location and type of gonads and detecting complications. All patients presented at the Gynaecology Out-patient Department of Command Hospital, Bangalore, India, between 2013–2016 with primary amenorrhea and MRI accurately localised testes in all; one patient had bilateral inguinal testes; two had intraabdominal testes. Intraabdominal testes were not localised on ultrasonography. MRI also depicted Sertoli cell adenomas and Wolffian duct remnants. MRI provides comprehensive imaging before surgical treatment and can, thus, be considered a ‘one-stop shop’ for AIS imaging. All patients underwent laparoscopic gonadectomy which is the standard of care, with preoperative counselling about fertility. Postoperatively, they were started on oestrogen therapy.

Keywords: Amenorrhea; Androgen Insensitivity Syndrome; Magnetic Resonance Imaging; Case Report; India.

THE PUBERTAL STAGE IS CRUCIAL FOR A female individual during which there is a sequential development of secondary sexual characteristics. Aberrations in the phenotype during this stage need to be treated early so that the female individual is clinically and psychosocially able to lead a normal life. One such condition involving discordance between the genotype and phenotype in pubertal development is the androgen insensitivity syndrome (AIS). AIS is an inherited X-linked recessive disorder, first described by Morris, in which there is an inability of the organs concerned to respond to androgens due to a lack or defect of the androgen receptor (AR). It is associated with Müllerian regression and the presence of testes along its path of descent. In the complete form of this disorder, the individuals are genetically male but phenotypically and psychologically female.

In such cases, early detection of the gonads and their removal is imperative to prevent the malignant transformation of gonads. Ultrasoundography (USG), being the primary modality for localisation of gonads, can miss the intraabdominal gonads. However, magnetic resonance imaging (MRI) provides a comprehensive imaging for both localisation and characterisation of gonads. Existing literature on the abovementioned roles of MRI in these patients is limited. In this case series, three such cases of AIS are presented, showcasing MRI as a ‘one-stop shop’ for visualising the spectrum of AIS and its possible complications.

Case One
A 16-year-old female patient presented at Command Hospital, Bangalore, India, in 2013 with primary amenorrhea. The patient’s clinical and USG findings can be found in Table 1. Tanner staging was used for thelarche and pubarche [Table 2]. Magnetic resonance imaging of the pelvis revealed vagina measuring 5 cm in length and a Gartner’s duct cyst was seen in the posterior vaginal wall [Figure 1A]. Bilateral testes were seen along the lateral pelvic walls, measuring 19 × 14 × 35 mm and 25 × 16 × 37 mm [anteroposterior (AP) × transverse (TR) × craniocaudal (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 visualised. Further, penile structure or phallus was not identified by the 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. The interstitium showed Leydig cell hyperplasia. The hypointense nodules seen on MRI corresponded to Sertoli cell adenomas [Figure 1C].

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A 15-year-old female patient presented at Command Hospital, Bangalore, India, in 2016 with primary amenorrhea. The patient's clinical and USG findings

**Table 1:** Clinical details, hormonal levels and ultrasonography findings of three patients with androgen insensitivity syndrome presenting at Gynaecology out patient department of Command Hospital, Bangalore, India

| Variable/Finding                  | Case I     | Case II    | Case III   |
|-----------------------------------|------------|------------|------------|
| Age (in years)                    | 16         | 15         | 23         |
| Symptom                           | Primary amenorrhea | Primary amenorrhea | Primary amenorrhea |
| Thelarche                         | Tanners III | Tanners III | Tanners V  |
| Pubarche                          | Tanners II  | Tanners II  | Tanners III|
| Labia                             | Well-developed | Ill-developed | Well-developed* |
| Vagina                            | Blind, well-developed vagina | Blind, short vagina | Blind, short vagina |
| Male secondary sexual characters   | Nil        | Short phallus | Nil        |
| Serum testosterone (ng/dl)        | 342        | 1044       | 654        |
| (Normal: 20–80 ng/dl)†            |            |            |            |
| Serum LH (IU/L)                   | 24.7       | 18         | 22.09      |
| (Normal: 5–20 IU/L)‡              |            |            |            |
| Serum FSH (IU/L)                  | 7.14       | 5.2        | 4.94       |
| (Normal: 5–20 IU/L)               |            |            |            |
| Karyotyping                       | 46,XY      | 46,XY      | 46,XY      |
| Transabdominal ultrasonography    | Absent uterus, gonads not located | Absent uterus, gonads in inguinal canal | Absent uterus, gonads not located |

*Both labia and clitoris; †Taylor et al.18; ‡Taylor et al.19

**Table 2:** Tanner staging for thelarche and pubarche in patients with androgen insensitivity syndrome

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

**Figure 1:** A: A multiplanar T2 weighted magnetic resonance image (sagittal view) showing absent uterus and presence of a vagina (star) and hyperintense Gartner's duct cyst (arrow); B: multiplanar T2 weighted magnetic resonance image (coronal view) showing bilateral testes (stars) with well-defined hypointense Sertoli cell adenomas (right arrows); and C: haematoxylin and eosin histopathological stain of the intraabdominal testes at 100x magnification showing Sertoli cell adenoma (star) of a 16-year-old female patient with primary amenorrhea.

**Figure 2:** A: A multiplanar T2-weighted magnetic resonance image (coronal view) depicting bilateral inguinal testes with paratesticular cysts (left arrow) and corpora cavernosa (star); B: multiplanar T2-weighted magnetic resonance image (axial view) showing bilateral inguinal testes (arrows) and seminal vesicles (star); and C: haematoxylin and eosin histopathological stain at 400x magnification showing seminiferous tubules with thickened hyalinised walls (white arrow) lined with immature Sertoli cells (red arrow) of a 15-year-old female patient with primary amenorrhea.

**Figure 3:** T2-weighted magnetic resonance image showing axial views of the (A) bilateral testes (four point star) and (B) seminal vesicles (left arrow) and (C) a haematoxylin and eosin histopathological stain of abdominal testes at 400x magnification showing seminiferous tubules lined by Sertoli cells (red arrows) with surrounding stroma showing Leydig cell hyperplasia (white arrows) of a 23-year-old female patient with primary amenorrhea.

**Case Two**

A 15-year-old female patient presented at Command Hospital, Bangalore, India, in 2016 with primary amenorrhea. The patient's clinical and USG findings...
can be found in Table 1. Tanner staging was used for thelarche and pubarche [Table 2]. MRI imaging of the 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]. A 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 visualised. 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 hyalinisation. There was loss of germ cells in the tubules with immature Sertoli cells. Moreover, there was Leydig cell hyperplasia and no atypia or dysplasia was seen [Figure 2C].

Case Three
A 23-year-old female patient presented at Command Hospital, Bangalore, India, in 2016 with primary amenorrhea. The patient’s clinical and USG findings can be found in Table 1. Tanner staging was used for thelarche and pubarche [Table 2]. The MRI showed bilateral intraabdominal testes. On the right side, the gonad anterior to the external iliac vessels was seen near a deep inguinal ring measuring 9.3 × 16.4 × 29 mm (AP × TR × CC). On the left side, the gonad posterior to the external iliac vessels was seen measuring 19 × 9.8 × 23 mm (AP × TR × CC) [Figure 3A].

Bilateral seminal vesicles were observed [Figure 3B]. The penile structure or phallus was not identified on MRI. These MRI findings were consistent with complete AIS. The patient underwent laparoscopic bilateral gonadectomy and histopathology revealed seminiferous tubules lined by Sertoli cells with 50% showing luminal formation and Leydig cell hyperplasia. No spermatocytes or matured spermatids were seen [Figure 3C].

It is to be noted that written consent has been obtained from all three patients for the use of their clinical and radiological data while maintaining strict confidentiality about patient identity.

Discussion
Morris coined the term ‘testicular feminisation syndrome’, now known as AIS, in 1953 after his study on 82 patients. Complete AIS constitutes males with female phenotype who are raised as females. Partial AIS reflects a phenotype with varying degrees of masculinisation of the external genitalia due to variation in the levels of response to androgen. The incidence of AIS has been variably reported and based on molecular proof of diagnosis, one study in Denmark has reported it to be from one in 40,800 to one in 99,000. In complete AIS, there is mutation of the AR gene located on the long arm of the X chromosome and it follows X-linked recessive inheritance. Approximately 40% of the patients with AIS may have no family history of mutations of the AR gene.

The AR in AIS is unresponsive to androgen action and androgens are converted into oestrogens with action of aromatase. This leads to development of female secondary sexual characteristics. The secretion of the Müllerian-inhibiting substance (MIS) by the testes results in the absence of the Müllerian system and hence, the 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 are anchored in position by the cranial suspensory ligament (CSL) cranially and gubernaculum caudally during the transabdominal stage at 10–15 weeks.

The descent of the testis in the groin is achieved by testicular enlargement and gubernacular swelling reaction. Subsequently, CSL regression occurs under the influence of androgens. Both of these factors facilitate the 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 virilisation to under-virilised males presenting with ambiguous genitalia. These patients have variable development of the Wolffian duct system. Complete AIS presents with female secondary sexual characteristics such as well-developed breasts, scanty pubic or axillary hair with shortened vagina and no evidence of male characteristics. Incomplete AIS patients may have normal breasts and sparse pubic and axillary hair, with some abnormal form of male external genitalia. In the above series, cases one and three showed no virilisation and a well-formed vagina, whereas case two showed partial virilisation with the phallus. Instead of ovaries, all the three cases showed undescended testes.

For genetic diagnosis of AIS, karyotyping is usually the first step and it reveals a 46, XY state as was seen in all of the above cases. The most definitive
way for diagnosis is to look for the AR gene mutation by molecular genetic tests; however, facilities for these tests are not readily available and hence not routinely done.\textsuperscript{11} Hormonal assays in these patients reveal normal to mildly elevated serum gonadotropins with normal to high androgen levels.\textsuperscript{12} It must be noted that hormonal assays are non-specific as a diagnostic tool as far as AIS is concerned. In the above series, mildly elevated levels of serum testosterone and normal or mildly increased gonadotropins were detected [Table 1].

Imaging plays a vital role in locating and characterising the gonads.\textsuperscript{4} Although ultrasonography (USG) is usually the first imaging ordered, 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.\textsuperscript{4} Exact localisation of gonads is valuable to decide the surgical approach. Nakhal \textit{et al.} have reported bilateral intraabdominal testes in 62% patients (n = 15) and at least one inguinal testes in 37% patients (n = 9).\textsuperscript{5} It must be noted that two of the cases reported in this article (case one and case three) had bilateral intraabdominal testes and case two had bilateral inguinal testes. The potential risk of malignancy in these gonads has been reported to be 0.8–30% in complete AIS\textsuperscript{13,14} and up to 50% in partial AIS.\textsuperscript{15}

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.\textsuperscript{5} Detection of these on USG has not been reported in the literature till date. Although Sertoli cell adenomas are usually considered benign, Nakhal \textit{et al.} found one out of 10 patients to have premalignant intratubular germ cell neoplasm which could not be detected on MRI.\textsuperscript{3} 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-Küster-Hauser syndrome and Müllerian duct anomalies wherein ovaries are. Wolffian duct remnants including vas deferens and epididymis have been reported in the literature; however, presence of seminal vesicles, as seen in two of the above cases, has not been reported.\textsuperscript{15}

The morphology of external genitalia including length of the vagina and thickness/length of the phallus are essential for gender-assignment surgical planning in partial AIS.\textsuperscript{12} Secaf \textit{et al.} have defined objectively the criterion for diagnosing phallic/clitoral hypertrophy on MRI.\textsuperscript{16} 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.\textsuperscript{17} There is a felt need for monitoring these patients for \textit{in situ} or invasive neoplasm. Although micro-RNA-based and single-nucleotide-polymorphism-based tests have shown some promise, their clinical use is still not in vogue.\textsuperscript{11} Until a reliable screening tool is developed, MRI may be used to detect neoplastic changes in these testes, although MRI cannot detect \textit{in situ} tumour.\textsuperscript{5,17} Gonadectomy done at puberty may prevent occurrence of germ cell tumours in the abnormally placed gonads.\textsuperscript{3} Laparoscopic gonadectomy was performed in all of the cases reported in as part of this article. The histological correlation of these gonads revealed maturation arrest without any dysplastic changes. The patients were extensively counselled preoperatively about their future fertility prospects and were started on oestrogen 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. Magnetic resonance Imaging (MRI) appears to be a ‘one stop shop’ for visualising 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 a screening tool for detection of neoplastic changes in patients of AIS who retain their gonads into late adolescence or adulthood, although it cannot detect \textit{in situ} neoplasm.

### Authors’ Contribution

IM contributed to the conception and design of the report. RA and SM were involved in acquisition of the data. RA and DM contributed to the analysis and interpretation of the data. IM and SM drafted the initial version of the manuscript. IM and RA revised the manuscript. All authors approved the final version of the manuscript.

### References

1. Morris JM. The syndrome of testicular feminization in male pseudohermaphrodites. Am J Obstet Gynec 1953; 65:1192–211. https://doi.org/10.1016/0002-9378(53)90359-7.
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2. Hughes IA, Davies JD, Buncl TJ, Pasterski V, Mastroyannopoulou K, Dougall JM. Androgen insensitivity syndrome. Lancet 2012; 380:1419–28. https://doi.org/10.1016/S0140-6736(12)60071-3.

3. Döhnert U, Wünsch L, Hiort O. Gonadectomy in complete androgen insensitivity syndrome: Why and when? Sex Dev 2017; 11:171–4. https://doi.org/10.1159/000478082.

4. Khan S, Craig LB. A review of radiologic imaging in patients with androgen insensitivity. J Genit Syst Disor 2013; S1. https://doi.org/10.4172/2325-9728.s1-003.

5. Nakhal RS, Craggs MH, Freeman A, Kirkham A, Conway GS, Arora R, et al. Evaluation of retained testes in adolescent girls and women with complete androgen insensitivity syndrome. Radiology 2013; 268:153–60. https://doi.org/10.1148/radiol.13121068.

6. Taylor HS, Pal L, Seli E. Normal and abnormal growth and pubertal development. In: Speroff’s Clinical Gynecologic Endocrinology and Infertility, 9th ed. Philadelphia: Wolters Kluwer, 2020. Pp. 321.

7. Boehmer ALM, Brinkmann O, Bruggenwirth H, Assendelft CV, Otten BJ, Verleen-Mootijn MC, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. J Clin Endocrinol Metab 2001; 86:4151–60. https://doi.org/10.1210/jcem.86.9.7825.

8. Chauhan P, Rani A, Singh SK, Rai AK. Complete androgen insensitivity syndrome due to mutations in the DNA-binding domain of the human androgen receptor gene. Sex Dev 2018; 12:269–74. https://doi.org/10.1159/000492261.

9. Touzon MS, Garrido NP, Marino R, Ramirez P, Costanzo M, Giarcio G, et al. Androgen insensitivity syndrome: Clinical phenotype and molecular analysis in a single tertiary center cohort. J Clin Res Pediatr Endocrinol 2019; 11:24–33. https://doi.org/10.4274/jcrpe.galenos.2018.2018.0185.

10. Hutson JM, Southwell BR, Li R, Lie G, Ismael K, Harisaj G, et al. The regulation of testicular descent and the effects of cryptorchidism. Endocr Rev 2013 Oct; 34:725–52. https://doi.org/10.1210/er.2012-1089.

11. Raza J, Zaidi SZ, Warne GL. Management of disorders of sex development with a focus on development of the child and adolescent through the pubertal years. Best Pract Res Clin Endocrinol Metab 2019; 33:1–14. https://doi.org/10.1016/j. beem.2019.101297.

12. Lee PA, Nordenström A, Hook CP, Ahmed SF, Aucus R, Baratza A, et al. Global disorders of sex development update since 2006: Perceptions, approach and care. Horm Res Paediatr 2016; 85:158–80. https://doi.org/10.1159/000442975.

13. Cooks M, Drop SL, Wölfinduth KL, Oosterhuis JW, Looijenga LH. Germ cell tumors in the intersex gonad: Old paths, new directions, moving frontiers. Endocr Rev 2006; 27:668–84. https://doi.org/10.1210/er.2006-0005.

14. Huang H, Wang C, Tian Q. Gonadal tumour risk in 292 phenotypic female patients with disorders of sex development containing Y chromosome or Y-derived sequence. Clin Endocrinol (Oxf) 2017; 86:621–7. https://doi.org/10.1111/cen.13255.

15. Kathrins M, Kolon TF. Malignancy in disorders of sex development. Trans Androl Urol 2016; 5:794–98. https://doi.org/10.21037/tau.2016.08.09.

16. Secaf E, Brinkmann O, Bruggenwirth H, Assendelft CV, Otten BJ, Verleen-Mootijn MC, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. J Clin Endocrinol Metab 2001; 86:4151–60. https://doi.org/10.1210/jcem.86.9.7825.

17. Cools M, Looijenga L. Update on the pathophysiology and risk factors for the development of malignant testicular germ cell tumors in complete androgen insensitivity syndrome. Sex Dev 2017; 11:175–81. https://doi.org/10.1159/000477921.

18. Taylor HS, Pal L, Seli E. Hirsuitism. In: Speroff’s Clinical Gynecologic Endocrinology and Infertility, 9th ed. Philadelphia: Wolters Kluwer, 2020. Pp. 452.

19. Taylor HS, Pal L, Seli E. Amenorrhea. In: Speroff’s Clinical Gynecologic Endocrinology and Infertility, 9th ed. Philadelphia: Wolters Kluwer, 2020. Pp. 349.