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Complete Androgen Insensitivity Syndrome: Role of Imaging for Diagnosis

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Abstract

Androgen insensitivity syndrome (AIS) is a rare disorder of sexual differentiation, characterized by impaired responsiveness to androgens, resulting in the development of typically female external genitalia, despite having a male chromosomal pattern (XY). In this case report, we describe the radiological findings of two young siblings diagnosed with AIS who presented with primary amenorrhea. The diagnosis was confirmed on laparotomy and gonads were surgically removed in both the siblings.

Keywords

- androgen insensitivity syndrome
- androgens
- ultrasound
- magnetic resonance imaging
- primary amenorrhea
- Mullerian structures
- gonads
- secondary sexual characteristics

Introduction

Androgen insensitivity syndrome (AIS) is a rare X-lined genetic disorder resulting in impaired androgen receptor function in 46,XY individuals, which leads to varying degrees of feminization of external genitalia. Depending on the degree of receptor response to androgens and clinical features, AIS is categorized into three subtypes[1,2]:

(1) Complete AIS: Individuals with complete insensitivity to androgens. They have female external genitalia with undescended testis as gonads.
(2) Partial AIS: Androgen receptor function is limited leading to an ambiguous external genitalia and secondary sexual characteristics.
(3) Mild AIS: The least severe form, with an XY karyotype, male external genitalia, normal male secondary sexual characteristics, and subtle androgen receptor abnormalities.

Radiological imaging, such as pelvic ultrasound (USG) and magnetic resonance imaging (MRI), plays a crucial role in assessing the internal reproductive anatomy, localization, and characterization of gonads, thereby aiding in the clinical evaluation of AIS patients. Diagnosis is confirmed by karyotyping, which shows an XY pattern in a phenotypically female pattern.

Case Presentation

This case report discusses two siblings, aged 18 (case 1) and 17 (case 2), highlighting the role of imaging in the diagnosis and management of AIS. Both patients were referred from the gynecology department for radiological evaluation of primary amenorrhea.

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USG scanning was performed for both patients followed by an MRI, which revealed nonvisualization of internal genital structures and the presence of bilateral inguinal testis in both cases

Case 1

An 18-year-old female patient presented to the department of radiodiagnosis for evaluation of primary amenorrhea. The patient's clinical details, laboratory investigations, and USG findings are summarized in ►**Table 1**. Thelarche and pubarche were assessed using the Tanner staging system. There was a similar family history of similar clinical complaints in one of the maternal aunt, however, no records of genetic testing were available.

MRI of the pelvis (►**Fig 1C, D**) revealed nonvisualization of uterus and cervix in a retrovesical location with the presence of a blind vaginal pouch of length 4 cm. Bilateral ovaries were not seen. A well-defined, ovoid structure measuring 25 × 22 mm appearing hypointense on T1 and heterogeneously hyperintense on T2 was noted in the right inguinal region (►**Fig 1D, E**). Similar structure measuring 15 × 12 mm appearing hypointense on T1 and hyperintense on T2 was observed in the left inguinal region (►**Fig 1D, F**) as well, suggesting the possibility of bilateral undescended testis.

A diagnosis of complete AIS was given, corroborated by karyotyping and histopathology (►**Fig 2A, B**).

The patient underwent laparoscopic gonadectomy and histopathology of the specimen revealed testicular tissue with spermatogenesis arrest, vas deferens, and epididymis.

Case 2

A 17-year-old female patient (younger sibling of case 1) presented to the department of radiodiagnosis for evaluation of primary amenorrhea. The patient's clinical details, laboratory investigations, and USG findings are summarized in ►**Table 1**. Thelarche and pubarche were assessed using the Tanner staging system.

MRI of the pelvis (►**Fig 3C, D**) revealed the absence of uterus and cervix with the presence of a small distal vaginal pouch measuring 1.6 cm in length. Bilateral ovaries were absent, while distinct ovoid structures, appearing T1 isointense and T2 hyperintense, resembling testis were seen in the bilateral inguinal region measuring 14 × 8.5 mm on the right side and 24 × 14 mm on the left side (►**Fig 3E, F**).

A diagnosis of complete AIS was given which was then confirmed by karyotyping and histopathology (►**Fig 4A, B**).

The patient underwent laparoscopic gonadectomy and histopathology of the specimen revealed testicular tissue with spermatogenesis arrest, vas deferens, and epididymis.

Table 1 Clinical features, laboratory, and imaging findings of both the siblings

Clinical and imaging features	Elder sister, age 18 y		Younger sister, age 17 y	
Presentation	Primary amenorrhea		Primary amenorrhea	
Secondary sexual characteristics	Normal breast development (Tanner stage III) Sparse pubic hair (Tanner stage II) Absent axillary hair (Tanner stage I)		Normal breast development (Tanner stage III) Absent pubic and axillary hair (Tanner stage I)	
Physical examination	Normal external genitalia		Normal external genitalia	
Hormonal levels				
Serum testosterone (ng/dL) (normal: 8.4–48 ng/dL)	Raised (330 ng/dL)		Raised (370 ng/dL)	
LH and FSH (normal LH: 2.5–75 IU/L; FSH: 3.5–25 IU/L)	Normal (LH: 20 IU/L, FSH: 12 IU/L)		Normal (LH: 35 IU/L, FSH: 17 IU/L)	
USG				
Uterus	Not seen (►**Fig 1A**)		Not seen (►**Fig 3A**)	
Cervix	Not seen		Not seen	
Bilateral ovaries	Not seen		Not seen	
Bilateral testis	Right location: deep inguinal ring Characteristics: heterogeneously hypoechoic (►**Fig 1B**)	Left location: left inguinal canal Characteristics: homogenous (►**Fig 1B**)	Right location: right inguinal canal Characteristics: homogenous in echotexture (►**Fig 3B**)	Left location: superficial inguinal ring Characteristics: heterogeneous in echotexture (►**Fig 3B**)
Karyotype	XY		XY	

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; USG, ultrasound.

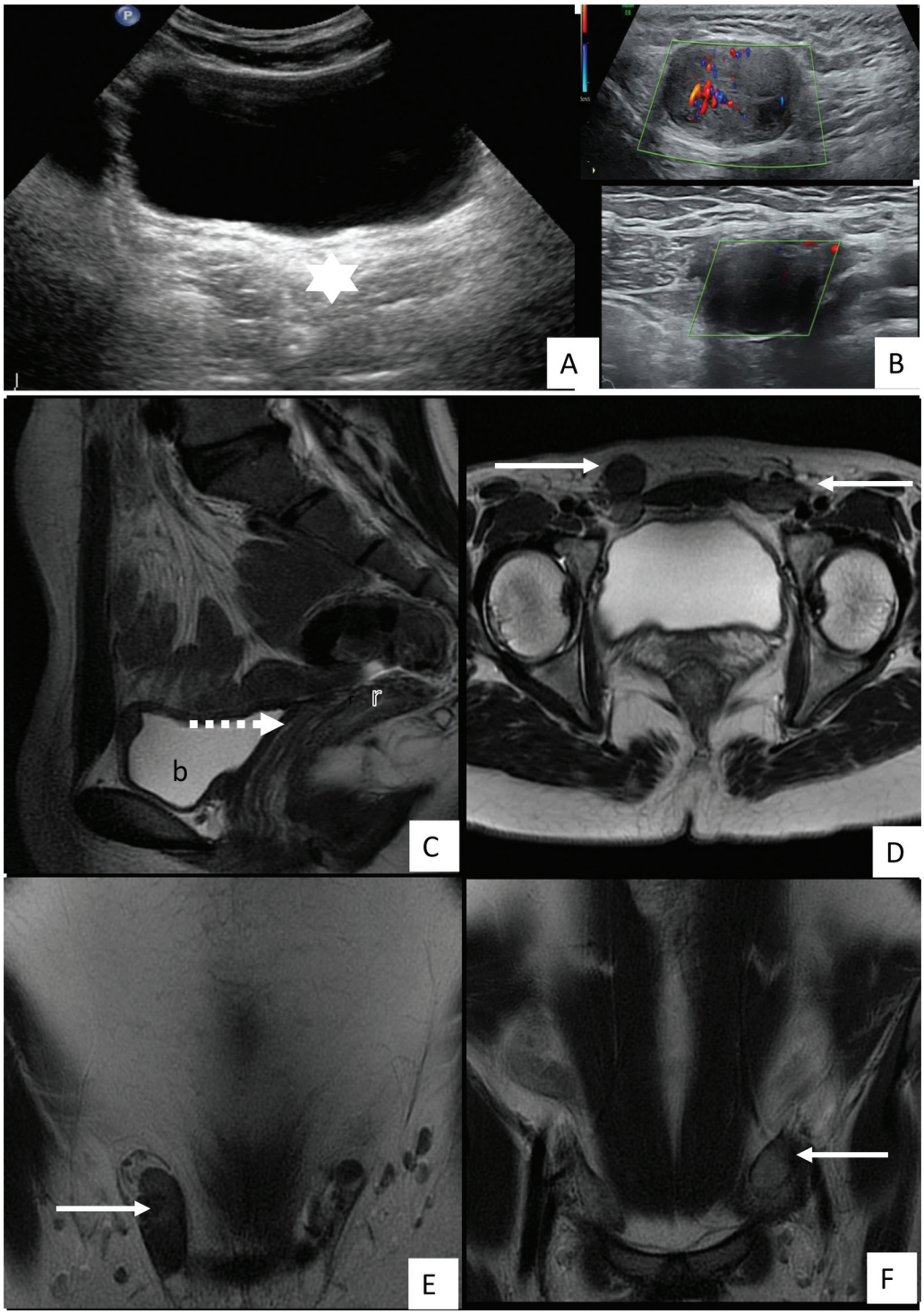

Fig. 1 Transabdominal ultrasound in elder sister aged 18 years reveals absence of uterus posterior to urinary bladder (star in **A**) with presence of testis in the bilateral inguinal regions. Sagittal (**C**) T2 weighted magnetic resonance imaging (MRI) image reveals absent uterus in the expected location between the urinary bladder (**B**) and rectum (r) with blind ending at the lower vagina (dotted arrow). Axial (**D**) and coronal (**E**, **F**) T2- weighted MRI images show the presence of testes in the bilateral inguinal region anterior to external iliac vessels (arrow).

Discussion

Primary amenorrhea, characterized by the absence of menstruation by age 16 in the presence of normal growth and secondary sexual characteristics, necessitates a thorough diagnostic evaluation. Imaging modalities play a pivotal role in delineating structural abnormalities of the reproductive organs and guiding targeted management strategies.

The imaging approach to primary amenorrhea involves a systematic and multimodal process aimed at comprehensive assessment and characterization of pelvic anatomy. Initially, ultrasonography emerges as the frontline imaging modality,

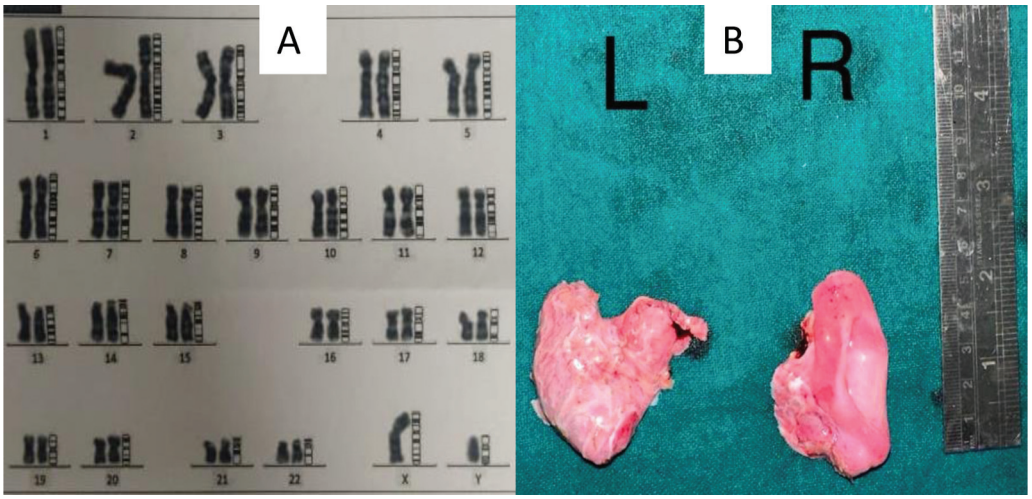

Fig. 2 (**A**) Karyotyping of the elder sister shows presence of XY chromosomes. (**B**) Surgically removed gonads.

offering versatility through both transabdominal and transvaginal approaches. Transabdominal ultrasonography provides an overview of pelvic structures, while transvaginal ultrasonography offers enhanced resolution, particularly beneficial for visualizing the uterus, ovaries, and surrounding soft tissues. This dual approach enables the identification of congenital anomalies such as Mullerian duct abnormalities (e.g., Mayer-Rokitansky-Küster-Hauser [MRKH] syndrome, septate uterus), ovarian cysts, or tumors.

Subsequently, MRI assumes a pivotal role, providing unparalleled soft tissue contrast and multiplanar capabilities. MRI serves as a complementary tool to ultrasonography, particularly in cases where USG findings are equivocal or further characterization of complex pelvic anatomy is warranted. Notably, MRI plays a crucial role in evaluating associated anomalies such as spinal dysraphism in patients with suspected Mullerian duct anomalies, ensuring a comprehensive assessment of the entire genitourinary tract.

In the evaluation of primary amenorrhea, a thorough understanding of the diverse differentials is essential for guiding the diagnostic workup and formulating appropriate management strategies. These differentials encompass a wide range of conditions, including anatomical anomalies, endocrine disorders, and chromosomal abnormalities.[1,3]

1. Mullerian duct anomalies: These congenital abnormalities involve malformations of the Mullerian ducts, which give rise to the uterus, fallopian tubes, and upper two-thirds of the vagina. MRKH syndrome is characterized by congenital absence or underdevelopment of the uterus and upper two-thirds of the vagina, often associated with normal ovaries and secondary sexual characteristics. There are various subtypes of Müllerian duct anomalies, among which uterine aplasia/hypoplasia without functional endometrium most commonly presents with primary amenorrhea.
2. Endocrine disorders:
   a. Congenital adrenal hyperplasia (CAH): CAH results from enzymatic deficiencies in cortisol biosynthesis, leading to excess androgen production. In females, this can manifest as virilization of external genitalia and primary amenorrhea due to ovarian dysfunction.
   b. Hypothalamic-pituitary axis dysfunction: Disorders affecting the hypothalamic-pituitary axis, such as hypothalamic amenorrhea or pituitary adenomas, can disrupt the normal hormonal regulation of menstruation, resulting in primary amenorrhea.
3. Disorders of sex development (DSD), which encompass congenital conditions characterized by atypical development of chromosomal, gonadal, or anatomical sex, imaging assumes a crucial role. The major categorizes include three main groups based on karyotype: 46,XX DSD, 46,XY DSD, and sex chromosome DSD.[4] Imaging serves as a cornerstone in the process of gender assignment and plays a pivotal role in identifying gonads and Müllerian structures.

The phenotypic spectrum of AIS encompasses individuals with a complete female phenotype with normal female external genitalia (as in complete AIS) to a male phenotype with undervirilization depending on the residual androgen receptor activity. Clinical symptoms vary based on the patient's age and receptor sensitivity. In infancy, they may present with inguinal hernia or labial swelling in phenotypically female children.[2,5]

The majority of patients with complete AIS typically present with primary amenorrhea during puberty, accompanied by some degree of thelarche and sparse to absent pubic or axillary hair. These changes are often attributed to converting androgens to estrogen.[2] The development of Mullerian structures is suppressed due to the production of anti-Mullerian hormones by the testis, inhibiting normal uterine development.

The diagnosis of AIS relies on clinical evaluation, hormonal profiling, and genetic testing. Radiology plays an important role in the comprehensive assessment and management of patients with AIS, providing valuable insights into the underlying anatomical abnormalities and guiding treatment decisions.

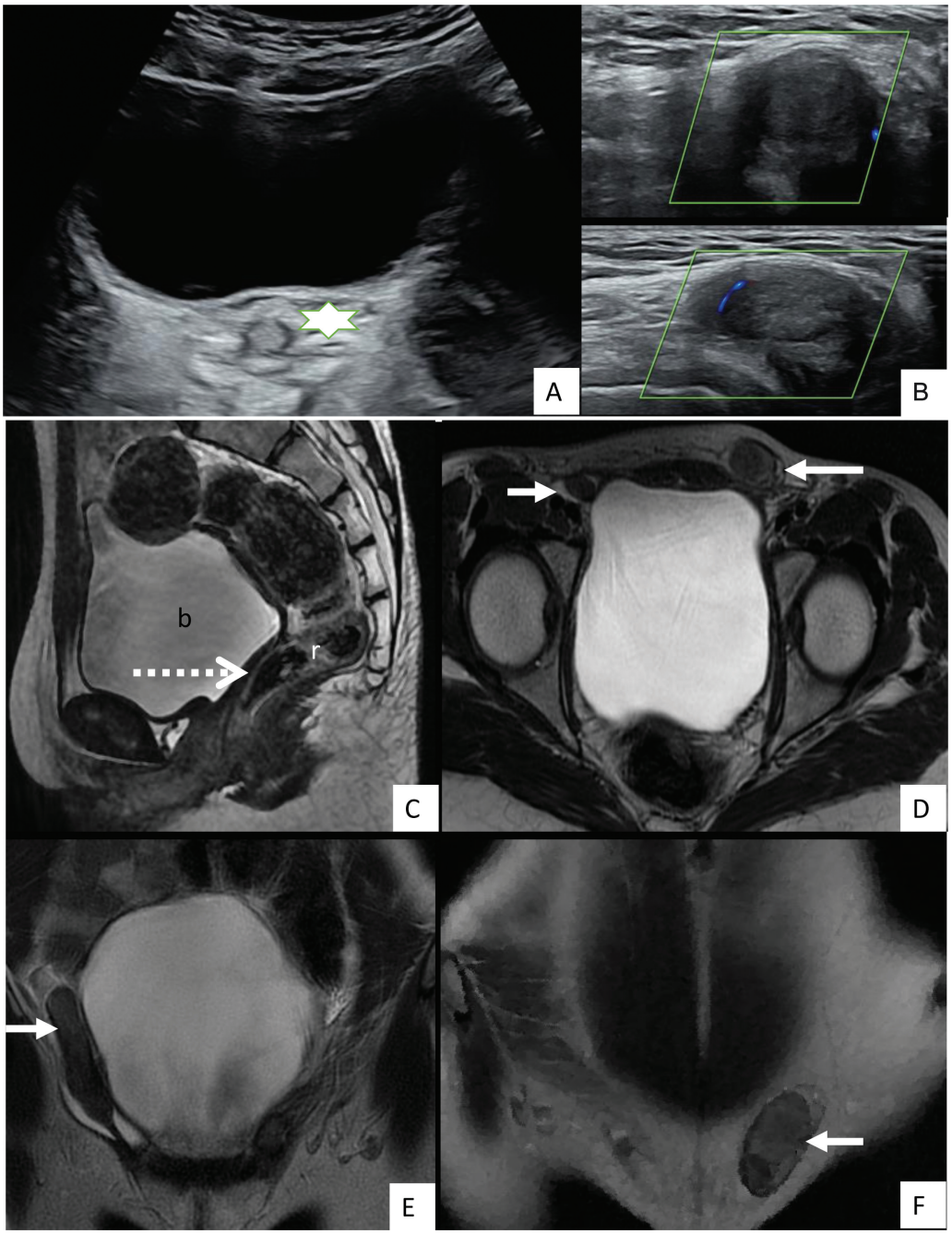

Fig. 3 Transabdominal ultrasound of the pelvis in the younger sister aged 17 years reveals (**A**) absence of uterus in the retrovesical location (marked by star) and presence of testes (**B**) in the right and left inguinal canals, respectively. Sagittal T2-weighted magnetic resonance imaging (MRI) image (**C**) reveals absence of uterus (dotted arrow) between the urinary bladder (**B**) and rectum (r). Axial T2-weighted MRI image (**D**) shows presence of ectopic testes in the bilateral inguinal canals anterior to the urinary bladder (arrows). Coronal T2-weighted images (**E**) and (**F**) confirm the presence of testis in the bilateral inguinal regions (arrows).

USG is the first modality generally employed in females presenting with primary amenorrhea to assess the uterus and ovaries and detect the presence of male gonads. It has the advantages of being readily available, inexpensive, and rapid. The presence of ovarian/testicular tissue on USG helps to differentiate Mullerian agenesis versus pure gonadal dysgenesis as normal ovaries are seen in the former condition whereas testis are noted in the latter. The location of the ectopic testis is variable as they can be found in the inguinal canal, sublabial, or intra-abdominal.[5,6] USG has limited sensitivity in detecting gonads located above the inguinal canal. MRI is a problem-solving tool, especially in the identification of streak gonads and gonads located intra-abdominally. Due to its excellent soft tissue resolution and multiplanar capability, it is the modality of choice to evaluate the Mullerian structures. It can detect suspicious intratesticular nodules like Sertoli cell adenoma, which are more common in the undescended testis in AIS patients and guide therapeutic procedures. Paratesticular cysts have been commonly observed with the undescended testis.[1]

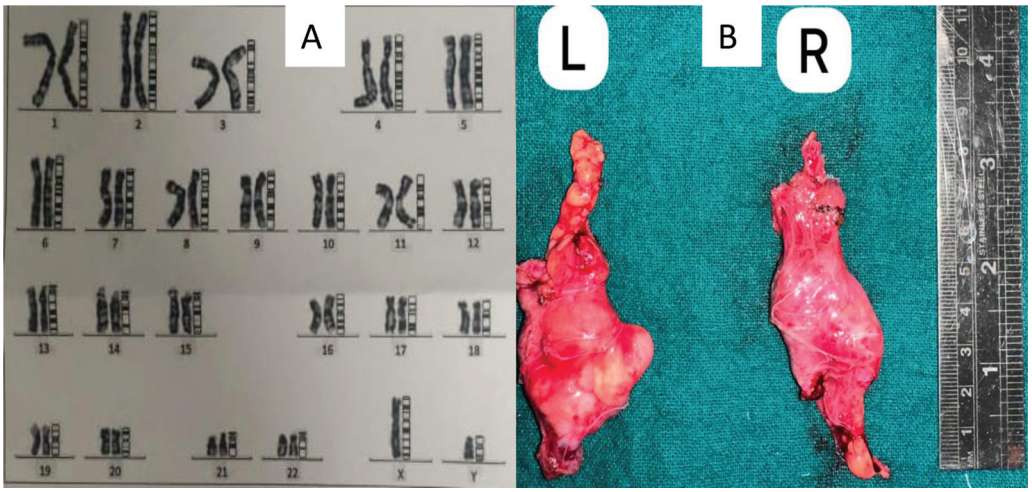

Fig. 4 (**A**) Karyotyping of the younger sister shows presence of XY chromosomes. (**B**) Surgically removed gonads.

The presence of uterus on imaging favors the possibility of 46,XX DSD like CAH whereas presence of testicular tissue or streak gonads on imaging suggest the possibility of 46,XY DSD, which include conditions like pure gonadal dysgenesis, androgen insensitivity syndrome, and sex chromosome DSD (including Klinefelter, Turner, and mixed gonadal dysgenesis).

Each of these differential diagnoses requires specific diagnostic approaches for confirmation. A comprehensive approach to patient management in AIS is essential considering both the psychological and physical well-being of the patient. The management strategy is tailored to their receptor sensitivity and can include medical as well as surgical interventions. Gonadectomy is generally advised to mitigate the risk of underlying malignancy.

Conclusion

AIS is a complex disorder of sexual differentiation, which is a rare but important cause of female infertility. Radiology plays a key role in the diagnosis and management planning in such cases and ruling out other causes associated with female infertility. MRI has proven to be an indispensable tool for the visualization of the spectrum of anatomical features associated with AIS, such as the absence of a functional uterus and ovaries, the presence of testicular tissue in the abdomen, pelvis, or inguinal regions, and the detection of neoplastic changes in the ectopic gonads.

Conflict of Interest
None declared.

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