Section: Radiodiagnosis

Case Series

RADIOLOGICAL PERSPECTIVES ON INTERSEX DISORDERS: FROM DIAGNOSIS TO TREATMENT

Suriyaprakash Nagarajan[1], R S Satiish[2], P Lavanya[2], B Kaveri[3]

[1]Assistant Professor, Department of Radiodiagnosis, Govt Medical College and Hospital, Tiruppur, Tamil Nadu, India
[2]Senior Resident, Department of Radiodiagnosis, Govt Medical College and Hospital, Tiruppur, Tamil Nadu, India
[3]DRP PG, Department of Radiodiagnosis, Govt Medical College and Hospital, Tiruppur, Tamil Nadu, India

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Corresponding Author:
Dr. Suriyaprakash Nagarajan,
Email: cbesuriya@gmail.com

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Abstract

Intersex disorders (ISD) are sexual development disorders that challenge clinicians and it is a medical and social emergency. ISD involves atypical chromosomal, gonadal, or anatomical sex development, making accurate and early diagnosis essential for optimal patient care. Early diagnosis is crucial for appropriate management, including hormone therapy and, in some cases, surgery. Imaging is vital for identifying the presence and structure of internal gonads and reproductive organs, detecting abnormalities, and guiding surgical planning. MRI provided detailed anatomical information due to its better soft tissue resolution. This case series underscores the importance of imaging techniques in the diagnosis of intersex disorders, advocating for their routine integration into clinical practice to enhance patient care and outcomes. Radiologists must be part of the multidisciplinary team involved in diagnosing and managing patients with ISD.

INTRODUCTION

Intersex disorders, involving atypical development of chromosomal, gonadal, or anatomical sex, often require precise imaging for accurate diagnosis and management. Advanced imaging techniques, including ultrasound, MRI, and CT scans, play a crucial role in evaluating internal structures, guiding treatment decisions, and ensuring comprehensive care for individuals with these complex conditions. We present three rare cases of disorders of sexual differentiation.

CASE 1

A 21 years old female with history of primary amenorrhoea was sent to radiology department for imaging evaluation. On physical examination, the breast is underdeveloped with only breast bud without glandular tissue. No axillary or pubic hair seen. No significant family history was present. No history of fever, burning micturition, abdominal pain, diarrhoea or constipation. On clinical examination, the patient had normal stature. Pelvic ultrasound did not reveal uterus or ovaries. No mass lesions seen in the pelvis and abdomen. MRI of the pelvis confirmed the absence of uterus and ovaries [Figure 1 - A, B, C]. There was a clinico-pathologic meeting regarding this case, and most of the specialists including the surgeon, obstetrician, endocrinologist and plastic surgeon were of the opinion to proceed with laparoscopy to look for gonadal tissue. Laparoscopy revealed a rudimentary testis close to the inguinal ring which was confirmed by histo-pathological examination [Figure 1-D&E]. A retrospective review of the MRI images shows small hypointense lesions close to the deep inguinal ring. Meanwhile sample was sent for Karyotyping, which revealed 46XY confirming the diagnosis of Swyers syndrome [Figure 1-F]. The patient was first stunned by the diagnosis and found it difficult to accept, but she was able to do so after reassurance. It is planned to do vaginoplasty for the patient for normal sexual function.

Swyers syndrome is a rare disorder of sexual differentiation with female phenotype and 46 XY genotype. Imaging plays a vital role in the evaluation of patients with Swyers syndrome in addition to Karyotyping and other hormonal evaluation. Presence of the Y chromosome makes these patients more vulnerable for the development of germ cell tumours. Since preventive gonadectomy lowers the likelihood of developing germ cell cancers in these situations, early detection of Swyers syndrome is essential.

CASE 2

A 20-year-old unmarried female patient came with complaints of primary amenorrhea and the absence of

secondary sexual characteristics. She is the second child of phenotypically normal parents born by normal vaginal delivery and her birth weight was approximately 3kg. Her parents were of normal stature. Physical examination revealed prepubertal features, thelarche and pubarche were both Tanner stage II. Genital inspection revealed the clitoris to be normal in size and shape, whereas the labia majora and minora were hypoplastic. Axillary hair and pubic hair were absent. The hormone laboratory results were: Thyroid stimulating hormone (TSH) 5.968 IU/ml. Follicle stimulating hormone (FSH) 128.2 IU/ml. Luteinizing hormone (LH) 18.9IU/ml were in higher values. Blood lipid levels were normal. All other biochemical and hematologic parameters were normal. In abdominal ultrasonography, the uterus was hypoplastic, and bilateral ovaries were not visible. Bilateral kidneys and other solid abdominal organs appeared normal. MRI pelvis imaging revealed a mildly retroverted uterus and appeared hypoplastic for age-measuring 3.6 x1.4 x 1.8 cm [Figure 2-A&C], with non-visualization of both ovaries [Figure 2-B&D]. The result of karyotype analysis performed by the fluorescence in situ hybridization technique reported the absence of a Y chromosome and had a 46, XX karyotype [Figure 2-E]. Oral contraceptive treatment was initiated to support secondary sexual characteristics and to prevent long-term complications. Now, the patient is clinically stable with regular monthly menstruation.

This case is a co-existence of gonadal dysgenesis and uterine hypoplasia in 46 XX female. A review of the literature on the subject did not reveal any case of bilateral ovarian agenesis in association with the rudimentary uterus, normal fallopian tubes, and vagina in a patient with 46, XX karyotype. The absence of a uterus and vagina, together with the absence of ovaries, is called Mayer-Rokitansky-Küster Hauser syndrome. Our case is discriminated from this syndrome by the presence of a rudimentary uterus, together with gonadal agenesis but with a normal vagina and normal fallopian tubes, in a patient with a 46, XX karyotype and no other associated organ system anomaly. Initially, undifferentiated gonads present as a mass in front of the coelomic epithelium at the fourth to fifth week of embryonic development. Later on, the cortex and medulla appear within the mass. In males, the cortex regresses, whereas the medullary part develops. In females, the cortex develops and the medulla regresses. The migration of primordial germ cells from the yolk sac to the gonads is one of the most important steps of embryonic development (fifth to sixth week). If this step fails, the gonads cannot develop completely, and gonadal agenesis occurs. In our case, we could not detect any factor that might have led to gonadal agenesis and a rudimentary uterus, and we consider this to be a sporadic case.

CASE 3

A 2-year-old child with ambiguous genitalia was brought to our department for imaging analysis. Antenatal and postnatal history was unremarkable. Clinical examination showed the child was alert, vitals within normal limits, a large phallus and rugose labioscrotum with a single perineal opening at the base of the phallus. Ultrasound of the abdomen shows no uterus or ovaries. Bilateral adrenal glands were normal. Two well-defined hypoechoic structures were seen in the bilateral inguinal canal. MRI pelvis was done which revealed a rudimentary bifid scrotum [Figure 3-A], small penis-like musculature [Figure 3-B] with rudimentary undescended supra scrotal testis (Figure 3-C&D) in the inguinal canal with normal cord structures [Figure 3 -E]. Hormonal analysis revealed 5 alpha reductase deficiency (5-ARD) and karyotyping shows 46XY [Figure 3-F]. The parents were informed about this disorder.

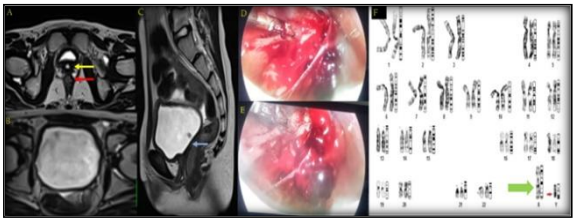

Figure 1: (A-Axial T2WI, B-Axial T2WI, C-Sag T2WI, D&E-Intraoperative images, and F-Karyotyping) A-C Absent uterus and ovaries in MR imaging. The red arrow shows the urethra and the yellow arrow points to the anal canal with absent middle compartment structures. D & E - Presence of rudimentary testis intraoperatively. F – Karyotyping reveals 46 XY DSD with Y chromosome indicated by a small red arrowhead.

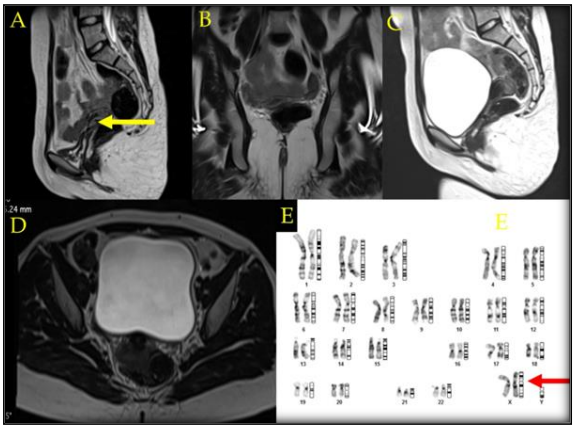

Figure 2: (A-Sag T2WI, B-Coronal T2WI, C- Sag T2WI with distended urinary bladder, D- Axial T2WI, and E - Karyotyping) A & C - Hypoplastic retroverted uterus as indicated by yellow arrow B and D - Absent bilateral ovaries in MR pelvic imaging. E – Karyotyping red arrow shows 46XX female genotype.

5-ARD is an autosomal recessive sex-linked disorder with the inability to convert testosterone into a more physiologically active form of Dihydroxy testosterone (DHT) during embryogenesis. DHT

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plays a vital role in the development of external male genitalia in contrast to testosterone in the development of internal male genitalia and secondary sexual characteristics. 5 Alpha reductase deficiency in males presents at birth with female phenotype with a varying degree of hypospadias or clitoromegaly. Management for 5-ARD includes sex assignment, androgen supplementation, and external genitalia reconstruction.

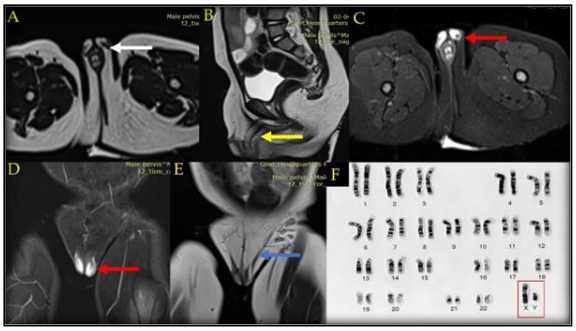
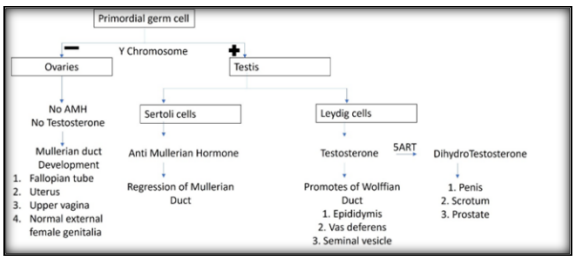


Figure 3: (A-Axial T2WI, B-Sag T2WI, C-Axial STIR, D- Coronal STIR, E- Coronal T2WI and F - Karyotyping). A - Bifid scrotum indicated by white arrow. B - Yellow arrow shows a phallus with penile musculature. C & D – Red arrow shows the supra scrotal location of testis. E - Blue arrow indicates normal cord-like structures. F – Karyotyping shows 46XY (red box).



Flow chart 1 – Schema of development of different gonadal structures

DISCUSSION

Disorders of sexual differentiation (DSDs) are complex conditions where there is a discrepancy between chromosomal, gonadal, and phenotypic sex. These disorders cover a wide spectrum of conditions from ambiguous genitalia to total sex reversal, and they can manifest at birth, throughout puberty, or even later in life. It is essential to comprehend the etiology, development, imaging modalities, and therapeutic modalities to diagnose and treat DSDs accurately.[1]

DSDs are relatively rare, with an estimated incidence of 1 in 4,500 live births. However, this figure varies significantly depending on the specific type of DSD.[2] The epidemiology of DSDs is also influenced by geographical and ethnic factors.

The process of sexual differentiation begins early in embryogenesis. Around the sixth week of gestation, the bipotential gonads develop, which have the potential to differentiate into either testes or ovaries. This process is primarily driven by genetic and hormonal factors.

The presence of the SRY gene on the Y chromosome typically leads to testis development, while its absence results in ovarian development (Flow chart 1).[3] However, mutations or alterations in the SRY gene or other genes involved in the sexual differentiation pathway can lead to DSDs. Testicular development is associated with the secretion of two critical hormones: Anti-Müllerian hormone (AMH) and testosterone.[4] AMH leads to the regression of the Müllerian ducts, preventing the development of female internal genitalia. Testosterone and its more potent derivative, dihydrotestosterone (DHT), are crucial for the development of male internal and external genitalia, respectively.[5] Any disruption in these pathways, whether due to genetic mutations, hormone receptor defects, or enzyme deficiencies, can result in a spectrum of DSDs.[6]

Radiological imaging plays a pivotal role in the evaluation of DSDs.[7] The goals of imaging are to assess the anatomy of the internal and external genitalia, identify gonads, and detect associated anomalies. The choice of imaging modality depends on the patient's age, clinical presentation, and the specific DSD being investigated.[8]

Ultrasound is often the first-line imaging modality used in the evaluation of DSDs due to its non-invasive nature, lack of ionizing radiation, and ability to provide real-time assessment.[9] In neonates and infants, pelvic ultrasound is particularly useful for visualizing the uterus, ovaries, and any masses or ambiguous structures. The identification of Müllerian structures, such as the uterus, can help differentiate between 46XX DSDs and 46XY DSDs. In cases where gonads are not identified, ultrasound can also help locate intra-abdominal or inguinal testes, which may be important for both diagnosis and future management.

Magnetic Resonance Imaging (MRI) is often used as a complementary tool to ultrasound, particularly when detailed anatomical assessment is required.[10] MRI offers superior soft tissue contrast and can provide detailed images of the internal genitalia, gonads, and associated structures. It is particularly useful in complex cases where ultrasound findings are inconclusive or when planning surgical intervention. However, in most cases, both USG and MRI are indicated for prompt diagnosis and proper presurgical planning.

The management of DSDs is multidisciplinary, involving pediatricians, endocrinologists, surgeons, radiologists, psychologists, and genetic counsellors.[11] The goals of treatment are to address any life-threatening conditions, assign a gender that is most congruent with the individual's likely future gender identity, and provide appropriate hormonal and surgical treatments.

Hormonal therapy is often a cornerstone of DSD management, particularly in cases where there is a deficiency or resistance to sex hormones.

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Surgical interventions in DSDs are often complex and controversial, particularly when it comes to early genital surgery.[12] The timing and extent of surgery depend on the specific condition, the degree of ambiguity, and the psychosocial implications. Gonadectomy is a common surgical intervention, particularly in cases where there is a high risk of gonadal malignancy.[13]

Psychological support is crucial for individuals with DSDs and their families.[14] The diagnosis of a DSD can be distressing, and ongoing counselling is often necessary to help individuals and families navigate the complexities of gender identity, social relationships, and medical decision-making.

Long-term follow-up is essential in the management of DSDs. Individuals with DSDs require ongoing medical care, including hormone replacement therapy, surveillance for potential complications such as gonadal tumors, and support for psychosocial and sexual health issues.[15]

CONCLUSION

Intersex disorders are complex and delicate problems that require a nuanced and multidisciplinary approach. Imaging is essential for the prompt detection of intersex diseases, which allows for the early assignment of a child's gender. Advances in imaging, genetics, and hormonal therapies have significantly improved the diagnosis and management of DSDs, but many challenges remain, particularly in terms of ethical considerations and long-term outcomes. Radiologists must be part of the multidisciplinary team along with Gynaecologists, Paediatric endocrinologists, and Plastic Surgeons in genetic counselling to improve patient quality of life. Radiologists must be aware of the basic genetics and have an organized approach for making the appropriate diagnosis. Continued research and collaboration among healthcare professionals are essential to optimize care for individuals with DSD.

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