Female pseudohermaphroditism: strategy and bias in a fast diagnosis.

How tricky could be a diagnosis with a wrong anamnesis

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AIM: *Congenital genitalia anomalies are a spectrum of malformation, difficult to classify because similar or identical phenotypes could have several different aetiology; therefore it's essential to assess an efficient diagnostic algorithm for a quick diagnosis and to develop an efficient therapeutic strategy. The aim of this study is to underline the importance of imaging in case of ambiguous genitalia due to its high sensitivity and specificity in detecting internal organs and urogenital anatomy.*
MATERIAL OF STUDY: *We report a case of a young girl affected by a complex genitor-urinary malformation with an initial wrong anamnesis that led to a tricky diagnosis.*
RESULTS: *Imaging techniques – especially Magnetic Resonance Imaging (MRI) - together with karyotype, hormones and physical investigations, offered complete and reliable informations for the best surgical treatment of our patient.*
CONCLUSION: *Karyotype, hormones investigation, and radiological examinations are the main criteria considered in the diagnostic iter. Ultrasonography (US) is the primary modality for the detection of the presence or absence of gonads and müllerian derivatives, whereas Cystourethrography can define urethral and vaginal tract or the presence of fistulas. In our experience MRI, due to its multiplanar capability and superior soft tissue characterization, proved to be useful to provide detailed anatomic information.*

KEY WORDS: Congenital genitalia anomalies, Disorders of Sex Development (DSDs), Female pseudohermaphroditism.

Introduction

Disorders of Sex Development (DSDs) are congenital conditions in which the development of chromosomal, gonadal or anatomical sex is atypical.

In an epidemiological study, the incidence of ambiguous genitalia in neonates was identified as 1:5000 births, and the most common diagnosis was CAH (Congenital Adrenal Hyperplasia), followed by AIS (Androgen Insensitivity Syndrome) and mixed gonadal dysgenesis. Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) published a consensus statement on management of intersex disorders on the basis of karyotype analysis.[1] The new DSD classification includes three main diagnostic categories: sex chromosome DSD, 46 XY DSD (formerly male PH) and 46 XX DSD (formerly female PH). The category of sex chromosome DSD embraces not only ovotesticular DSD (formerly true hermaphroditism) and 45,X/46,XY mixed gonadal dysgenesis, but

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also Turner's Syndrome (TS) and Klinefelter's Syndrome (KS), which are not included in the previous classifications of intersex disorders.
The chromosomal basis for sex is determined at conception. The internal and external genital structures remain undifferentiated for up to six weeks gestation. Testicular development is guided by testis determining factor (or substance), which is encoded by the SRY (Sex-Determining-region on the Y chromosome) gene located on the short arm of the Y chromosome. In the absence of the Y chromosome, gonads differentiate into ovaries at around 11-13 weeks gestation. Patients with female pseudohermaphroditism have XX karyotype, female internal genitalia and a broad spectrum of external genitalia virilization signs such as hypospadias, micropenis, clitoromegaly, incomplete puberty, amenorrhea and, even, short stature.[2]

Case Report

The case reported describes the management of a 15-years-old patient brought to our attention in June 2010 with a complex genitor-urinary malformation.
The patient was hospitalized with a diagnosis of 21-β-OH deficiency that led astray in the initial treatment. At the examination the patient showed a fusion of the labia majora and a partial union of labia minora, in addition she presented a common urinary and vaginal meatus. She also showed a clitoromegaly (4,5 cm). The patient had a normal sexual hormones development and reported the menarche at 14 years old (Fig. 1).
The patient had a painful family history, was isolated by the family due to malformation, lived in a halfway house and was not able to relate to the medical staff. In addition not being able to understand Italian was accompanied by an interpreter. Her mood was of shame and feelings of inadequacy.

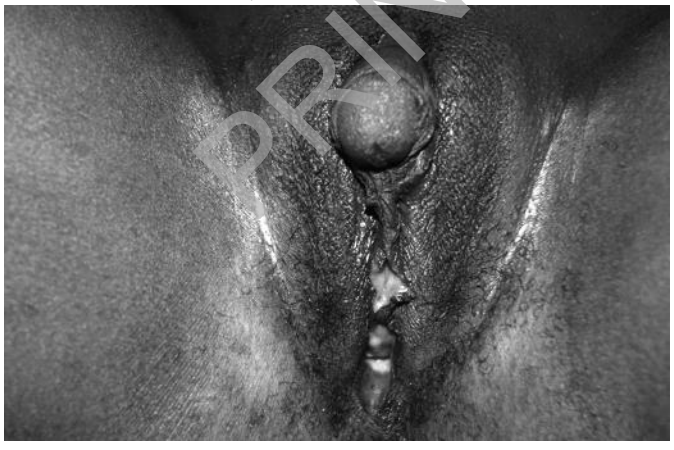

Fig. 1: The clinical examination shows a fusion of the labia majora, a partial union of labia minora and clitoromegaly.

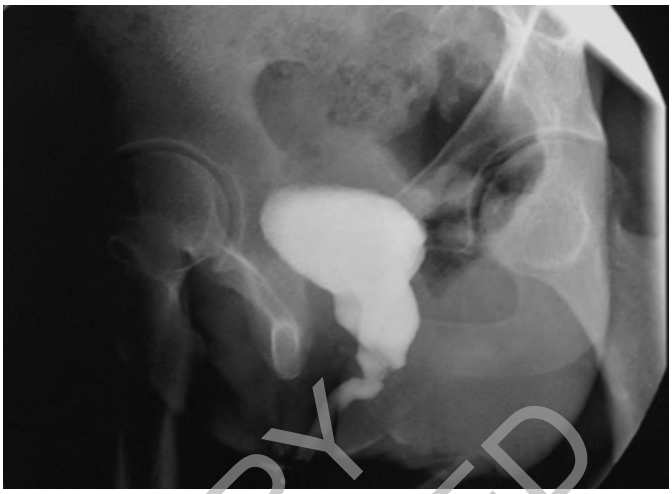

Fig. 2: Retrograde urethrography with voiding cystourethrography shows the continuity between vagina and urethra.

The patient was then subjected to a series of hormonal analysis to determine malformation etiology. Blood tests showed no significant alterations, hormonal tests (FSH, LH, ACTH, 17-oh progesterone, Δ-4-androstenedione, DEHA sulfate, testosterone, prostaglandins, cortisol) showed no changes significant for a 21-β-OH deficiency. She was also tested with Synatchen stimulation for the 17-OH-progesterone production without any evidence of alteration.
After discarded the possibility of a 21-β-OH deficiency was unsatisfactory a mere medical treatment, so instrumental tests were performed to clarify patient's anatomy in view of surgery.
Retrograde urethrography with voiding cystourethrography showed good concentration and elimination of contrast, normal bladder neck and two urethral substenosis. At the end of urination, a vaginal opacification was evident, thus showing continuity between vagina and urethra (Fig. 2).
Transvaginal ultrasound showed normal uterus characteristics. Ovaries had a normal echotexture; vagina was in a normal range for the upper two thirds, while in the lower third of its course had a junction with the urethra.
Subsequent Magnetic Resonance Imaging (MRI) was performed on a 1.5T system, with T2 weighted multiplanar high resolution T2 (T2-TSE= TE 86, TR 6670, SL 3mm, sp 3.75mm; T2-HASTE= TE 85, TR 1000, SL 6mm, sp 7.80mm) and T1 weighted sequences (T1-FLASH 2D= TE 5, TR 137, SL 6mm, sp 7.8, FA 70) without the injection of paramagnetic contrast media. The exam showed the presence of a normal sized uterus with normal signal intensity and normal endometrial thickness. The vagina was well recognizable until the lower third, where an anterior fusion with the urethra was found. At this level it was recognizable the presence of an intermediate signal structure, strongly suspicious

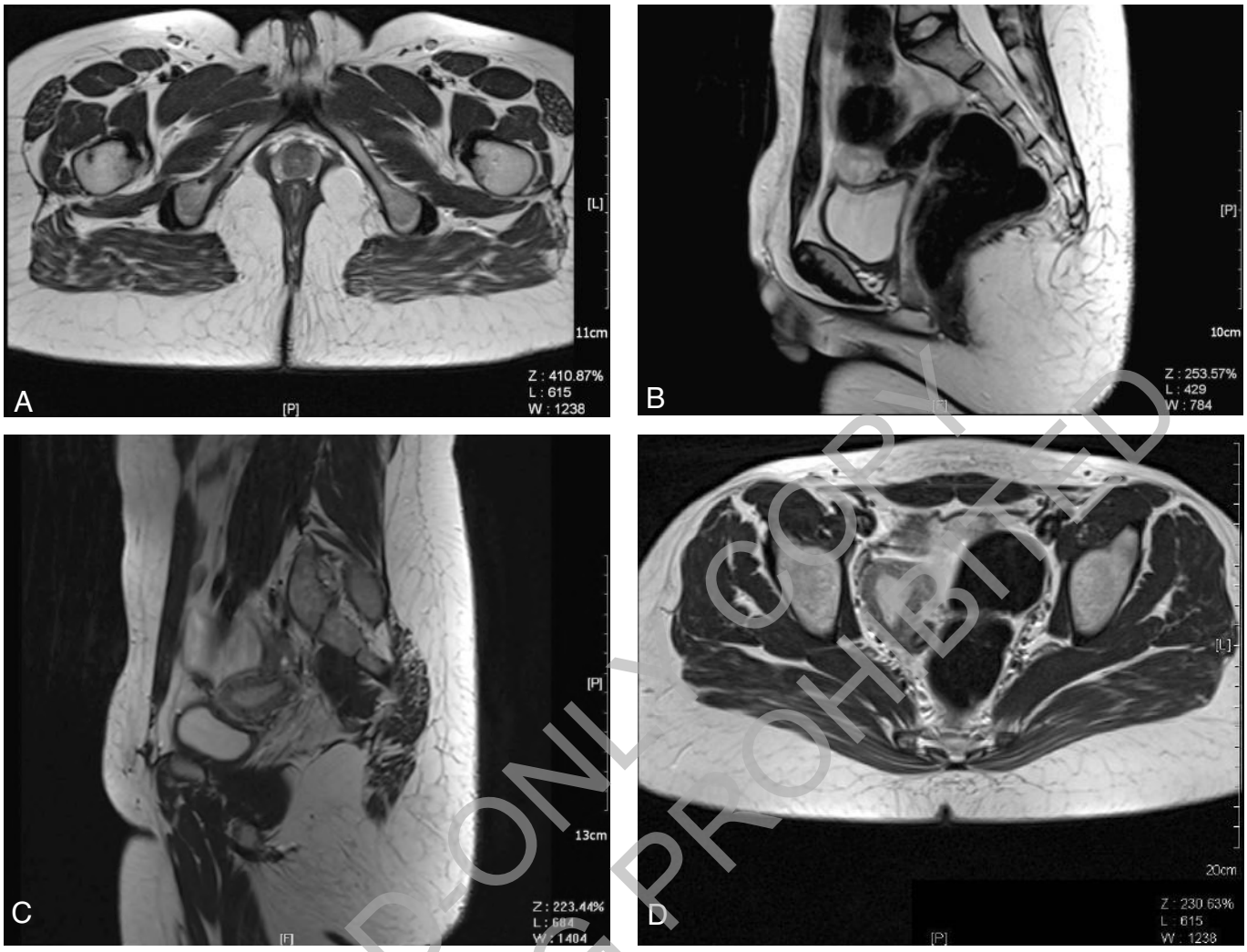

Fig. 3: T2 TSE high resolution sequences of the pelvis (TR 6410 msec; TE 89 msec; Fov 270x270mm; SL 3mm). A) Axial plane: inhomogeneous signal intensity tissue characterized by a central hypointensity and a pheripheral hyperintense signal localized contiguous to the urethra likely referable to prostatic tissue; B) Sagittal plane: vagina well recognizable until its lower third where it results fused with urethra; C-D) Sagittal and Axial planes: ovary characterized by the presence of functional cystic formations, uterus is laterodeviated to right showing enlarged endometrial cavity.

for prostatic tissue because of its typical MR appearance. In fact, on T2-W images, it was evident a central hypointense area corresponding to the central and transitional zones and a peripheral hyperintense area corresponding to the peripheral zone (Figs. 3 a-d).
Ovaries were normal sized and characterized by the presence of several functional cystic formations.
Clitoromegaly was found together with a partial fusion of the small and big labia.
The exam, extended to the adrenal region, showed the presence of a left adrenal gland with normal size and signal whereas the right gland was not detectable.
The patient underwent vaginoplasty with the formation of neovagina and a subsequent intervention for clitoromegaly reduction. After surgical treatment the patient was submitted to a test for assessing the sensitivity of the clitoris (Genito Sensory Analyzer).

Discussion and Comments

Female pseudohermaphrodites have a 46,XX kariotype and present normal ovaries and uterus. Although their external genitalia are ambiguous, they do not have testicular tissue or internal wolffian-duct derivatives.
The most common cause of female pseudohermaphroditism is congenital adrenal hyperplasia resulting from 21-OH deficiency. This type of congenital adrenal hyperplasia causes virilization due to an excess of androgenic steroids and may cause salt wasting due to diminished mineralocorticoids in the severe form. The extent of masculinization is determined by the time and degree of androgen exposure [1].
Unusual causes of female pseudohermaphroditism include maternal drug ingestion (usually progestational agents) and androgen-producing tumors of the adrenal gland or ovary [1].

Besides the clinical evaluation (family and prenatal history, general physical examination, assessment of genital anatomy in comparison to norms), the diagnostic evaluation of disordered sexual differentiation (DSD) includes karyotyping, imaging, measurements of hormone levels, and if needed, endoscopy, laparoscopy and gonadal biopsy [2].

Ultrasonography is always the first imaging modality in working-up DSD patients. Ultrasound (US) easily shows the presence or absence of Mullerian structures (uterus) at all ages, locate the gonads (pelvic, inguinal, perineal) and characterize their echo texture (ovaries, testes, streak gonads). US diagnoses CAH, in untreated patients, by displaying adrenal abnormalities such as: increased size (limb>4 mm in width, >20 mm in length), abnormal echo structure (cerebriform, lobular) and irregular surface. According to the literature, US is 92% sensitive and 100% specific in untreated CAH patients. Following treatment, adrenal US returns to normal [2,3].

US examination should always include the evaluation of kidneys looking for associated malformations. US is valuable for identification of the uterus or testes but may have some limitations (inadequate field of view and poor demonstration of complex anomalies) [4].

We believe that MRI is the most useful method to evaluate genital anatomy because of the excellent soft-tissue contrast resolution, multiplanar capability, and no radiation exposure. Previous reports have shown that MR imaging is useful to evaluate congenital pelvic abnormalities and ambiguous genitalia. The strength of MRI lies in the multiplanar capability and tissue characterization by means of T1- and T2-weighted sequences. MRI contributes to an accurate morphological evaluation of mullerian duct structures, gonads and the development of the phallus, all of which are essential in order to define the appropriate gender and to plan the most suitable surgical reconstruction.

Image analysis included evaluation of the presence or absence of the uterus, vagina, ovaries, testes, penis, and clitoris. Moreover Radiologits evaluated localization, size, shape, and signal intensities of the genitalia.

Concerning structural architecture, uterus presents different tissue layers which are clearly reproduced on T2-weighted images; on the contrary, an hypoplastic uterus is not only small but demonstrates low signal intensity of the entire myometrium on T2-weighted images.

In order to complete the evaluation of the uterus, both axial and sagittal T2-weighted images are necessary. The vagina is best demonstrated on axial T2-weighted images; sagittal images are complementary to the axial images. On T2-weighted images, the hypointense vaginal wall can be distinguished from the central canal and surrounding adipose tissue. Axial T2-weighted images are preferred in order to highlights the connection between vagina and urethra, which represents the urogenital sinus, although clear identification of this structure is not easy. Normal ovaries and testes show medium to low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The normal penis is composed of the corpora cavernosa and corpus spongiosum characterized by a medium signal intensity on T1-weighted images and an high signal intensity on T2-weighted images which allows to differentiate these structures from the supporting muscles and urethra. The mentioned structures are held in position by the supporting muscles such as the bulbocavernous muscle (seen on coronal and sagittal images) and transverse perineal muscle (seen on axial images). Secaf et al. demonstrated their utility to differentiate the penis from the hypertrophic clitoris because of the usual absence of these muscles in female pseudohermaphrodites with clitoral hypertrophy [5]. Nevertheless, differentiating between the penis and a hypertrophic clitoris is not easy.

Conclusions

In patients with anomalies of sexual differentiation, the external genitalia are deformed and frequently ambiguous. Accurate demonstration of genital anatomy is essential for proper gender assignment and for treatment of intersexual disorders. Imaging modalities can play an important role in the diagnosis of DSDs together with karyotype, hormones and physical investigations, offering complete and reliable informations for the best clinical or surgical treatments.

In our experience MRI proved to be feasible for a morphologic evaluation of pelvic anatomy, offering a complete visualization of mullerian duct structures, gonads, and clitoris because of its multiplanar capability and due to the excellent soft-tissue contrast.

Moreover, in this case, MRI allowed the demonstration of the prostate gland. This is important to avoid the risk of benign prostatic hyperplasia or prostatic carcinoma, which can occur after long term exposure to excessive androgens.

Riassunto

Le anomalie congenite dei genitali rappresentano uno spettro di malformazioni di difficile classificazione, in quanto è frequente il riscontro di fenotipi simili o addirittura identici che presentano un'eziologia del tutto differente. Pertanto, risulta essenziale un algoritmo diagnostico efficace che consenta una diagnosi rapida e conseguentemente la pianificazione di un'efficiente strategia terapeutica. A tale riguardo lo studio del cariotipo, le indagini ormonali e gli esami radiologici costituiscono i principali strumenti utilizzati nel contesto dell'iter diagnostico.

Lo scopo del nostro studio consiste nel sottolineare l'importanza delle procedure di Imaging nei casi clinici di genitali ambigui in virtù della loro elevata sensibilità

e specificità nel rilevare gli organi interni e nella visualizzazione dell'anatomia urogenitale.
In particolare, l'Esame Ultrasonografico risulta essere lo strumento principale per il rilevamento della presenza o assenza di gonadi e derivati mülleriani; mentre la Cistouretrografia consente lo studio del tratto uretrale e di quello vaginale e l'eventuale identificazione di tramiti fistolosi.
In base alla nostra esperienza, riteniamo che la Risonanza Magnetica, grazie alla sua proprietà multiplanare e alla raffinata capacità di caratterizzazione dei tessuti molli, sia una tecnica di imaging estremamente utile per ottenere informazioni anatomiche dettagliate nello studio delle malformazioni congenite dei genitali.

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