The role of imaging in congenital adrenal hyperplasia

O papel dos métodos de imagem em hiperplasia congênita de suprarrenal

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is an autosomic recessive disorder caused by impaired steroidogenesis. Patients with CAH may present adrenal insufficiency with or without salt-wasting, as well as various degrees of virilization and fertility impairment, carrying a high incidence of testicular adrenal rest tumors and increased incidence of adrenal tumors. The diagnosis of CAH is made based on the adrenocortical profile hormonal evaluation and genotyping, in selected cases. Follow-up is mainly based on hormonal and clinical evaluation. Utility of imaging in this clinical setting may be helpful for the diagnosis, management, and follow-up of the patients, although recommendations according to most guidelines are weak when present. Thus, the authors aimed to conduct a narrative synthesis of how imaging can help in the management of patients with CAH, especially focused on genitography, ultrasonography, computed tomography, and magnetic resonance imaging.

Keywords

Adrenal hyperplasia, congenital; magnetic resonance imaging; computed tomography; ultrasonography; diagnostic imaging

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomic recessive disorder caused by impaired steroidogenesis, in approximately 95% of the cases, secondary to 21-hydroxylase deficiency. Patients may present adrenal insufficiency with or without salt-wasting, as well as various degrees of virilization and fertility impairment, carrying a high incidence of testicular adrenal rest tumors (TART) and increased incidence of adrenal tumors (1). Neonatal screening is recommended because it reduces and prevents morbidity and mortality from salt-losing crisis (2). The diagnosis is made with adrenocortical profile hormonal evaluation and genotyping in selected cases (2).
Utility of imaging in this clinical setting may be helpful for the diagnosis, management, and follow-up of the patients, although recommendations according to most guidelines are weak when present (2). Bone mineral density evaluation in children is not recommended and adrenal imaging is suggested only for patients with an atypical course (2). Conversely, CAH must be excluded in cases of adrenal incidentaloma supposedly asymptomatic or oligosymptomatic. To evaluate gonads, ultrasonography (US) is recommended for screening males from adolescence, but there is no recommendation to screen females (2).

Thus, the authors aim to conduct a narrative synthesis of how imaging can help in the management of patients with CAH, especially focused on genitography (GX), US, computed tomography (CT), and magnetic resonance imaging (MRI).

SEARCH STRATEGY AND SELECTION OF ARTICLES
A systematic search was conducted in MedLine® (from 1950 to July 2013) and in Web of Science® (from 1965 to July 2013) databases for articles published in English, Spanish, Portuguese, and French. On MedLine®, the MeSH term “adrenal hyperplasia, congenital” was searched with the other imaging related MeSH terms with AND at a time using “ultrasonography”, or “magnetic resonance imaging”, or “tomography, X-ray computed”, or “multidetector computed tomography”, or “positron-emission tomography and computed tomography”, or “tomography scanners, X-ray computed radiography”, or “diagnostic imaging”. Web of Science® was searched for articles with the search terms “congenit* and adren* and hyperpl*” “AND imag*”. Books and other selected references cited in the most relevant retrieved articles were also reviewed.

Studies that were conducted in animals and in which only scintigraphy or nuclear imaging modalities were used as imaging modalities were not within the scope of this review. Also, studies that only used X-ray to evaluate bone age or any imaging modalities to assess bone mineral density were not extensively reviewed, as it is well established by the guidelines that bone age should be assessed annually after 2 years of age and regular evaluation of bone mineral density is not recommended (2).

Imaging
Genitography
The urogenital sinus is the embryologic precursor of the bladder, urethra, and distal third of the vagina in females. Excessive androgen exposure in utero leads to virilization of the external genitalia and urogenital malformations in females with CAH (1). Signs of urogenital sinus malformation secondary to virilization are hydrometrocolpos and only two apertures (one of them is the anus) in the perineal region associated with ambiguous genitalia (3). Typically, female patients with classic CAH have ambiguous genitalia at birth. Thus an anatomic detailed image plays an important role in planning strategy for feminizing surgery. Genitography shows the urethra, the level of external sphincter, the presence or absence of the vagina, the urethrovaginal confluence, and the cervical impression of the uterus (3) (Figure 1).

Genitography associated with voiding cistography has also the ability to show upper genitourinary abnormalities, present in 21%-80% (4) of the patients with CAH, mostly seen in girls.

Although some authors concluded that genitography did not add information to endoscopic (5) or surgical findings, many advocate its use as part of routine investigation in female patients with CAH (4), particularly in those infants with ambiguous genitalia.

Ultrasoundography
US is the modality of choice to image abdominal and pelvic organs in children and fetuses. It is widely available, versatile, and portable, with lack of ionizing radiation, there is no need for sedation, and provides high-resolution images in any required plane.

The adrenal glands in young children and fetuses are well depicted with US, especially in the neonate period. Sonographic abnormalities of the adrenal glands in CAH are similar in pre- and postnatal periods. The most prevalent sign is bilateral enlarged glands with width measurements of one limb ≥ 4 mm (6). In addition, adrenal size was positively correlated with plasma concentration of dehydroepiandrosterone sulphate (7). Also, a coiled or cerebriform pattern (8,9) is specific for this condition (Figure 1A). This finding should prompt a thorough investigation in male fetus and whenever a corticoid therapy is initiated serial US will show decrease in size of the adrenal glands (10). In infants, the morphology was shown to be of valuable importance while waiting for laboratory results in patients investigated for suspicious of the disease, enabling earlier diagnosis and treatment (9). However, it is very important to notice that normal adrenal glands do not exclude the possibility of CAH (6).
Although the clinical features of CAH are usually present, testicular adrenal rest tumor (TART) may be the only clinical finding at presentation (11). Based on microscopic studies, TARTs are reported to be present in all males with CAH (12). On US, it has been documented with a prevalence of up to 94% (13). The most common sonographic features are bilateral spikelike appearance intratesticular hypoechoic masses with no sound attenuation, surrounding the mediastinal testis (11). On color Doppler they are hypo or avascular (14) and there is no deviation or changes in caliber of the vessels that course the lesions (11,14). However, TART may also appear as heterogeneous or hyperechoic nodules (11,14,15), and even as an epididymal nodule (11). TART echogenicity is related to the size of the lesions, being hypoechoic in lesions smaller than 2 cm and heterogeneous or hyperechoic in lesions larger than 2 cm (14). These hyperechoic areas may represent fibrosis or calcifications (14). In addition, larger lesions may not be confined to the mediastinal testis and smaller lesions are more often seen unilaterally (14). On follow-up, TART can vary in size (15), but there is no correlation between hormonal control or hormonal markers and TART (15-17). TARTs are thought to be responsible for testicular parenchymal damage that contributes to reduced fertility (17,18). It can be found even in young children with a prevalence of 21% (19) and it is suggested that gonadal dysfunction is already present before puberty (19). Therefore, early detection of testicular lesions is advised (20) to improve treatment and prevent longstanding gonadal impairment function. Thus, some authors advocate that not only adolescents should undergo US (21) (Figure 2).

High prevalence of impaired fertility is not restricted to men as it was reported also in women with CAH (13,17). The prevalence of polycystic ovaries is increased in women with classical and nonclassical CAH (22). Bilateral enlarged ovaries (23), bilateral ovarian cysts, and ovarian adrenal rest tumors (OART) (24) may occur and can also be depicted by US. OART may present as hypoechoic nodules on US (24,25), similar to TART.

The most common cause of disorders of sex differentiation in the perinatal period is CAH. A clue to the prenatal diagnosis of CAH is usually the presence of ambiguous genitalia that may be present by the second trimester. The most often presentation is of an enlarged clitoris, but more complex abnormalities can be seen (26).
In postnatal period, to assess internal anatomy of the pelvis, US is the first choice (Figure 1C). It is easily performed and must include images of the pelvis, scrotum, inguinal, perineal, renal, and adrenal regions (27). The main purpose of the pelvic sonography is to depict accurately the size and morphology of the Mullerian structures, the uterus, the vagina, and the gonads (3). In addition to the adrenal glands findings described above, the presence of a uterus in a patient with ambiguous genitalia indicates that the diagnosis is mostly likely CAH (9). Ultrasound evaluation of the pelvic structures is not only performed for diagnosis but also as part of the preoperative approach for surgery, often in conjunction with other exams, such as genitography and MRI (3). US provides adequate information about the vagina and urogenital sinus for preoperative decision-making (28).

Many other abnormalities in patients with CAH can also be demonstrated by US: cardiac dysfunction that reverses with therapy (29), vascular dysfunction and increased carotid intima media thickness (30), skeletal and midface malformations associated with P450 oxidoreductase deficiency in prenatal diagnosed fetuses (31), hydrops of placental stem villi in a 46,XX fetus (32), association with increased nuchal translucency detected in the prenatal period (33), bilateral ovarian steroid cell tumor in a girl with CAH 11 beta-hydroxylase deficiency (34), and adrenal rest tissue extending from the lower pole of the kidney (35).

**Computed tomography**

Adrenocortical tumors in patients with CAH are not rare. A prevalence of up to 83% of adrenocortical masses in homozygote patients is reported (36). Despite this high frequency, adrenocortical tumors in this setting are most likely to be benign, as malignant lesions are rare (36). In many reports CT scans showed nodules (36-38) that may regress with adequate therapy (37), adenomas (23), myelolipomas (39), and the typical pattern of diffuse enlargement (38) with a heterogeneous enhancement (Figure 3).

Positron emission tomography with CT scan (PET-CT) was used in 3 case reports. In one, PET-CT was used to evaluate an adrenal mass in an untreated patient and showed a mass proved to be an adrenocortical tumor of uncertain prognosis (40). In the other two, PET-CT depicted OARTs (25,41), interestingly, in one of these reports both MRI and CT could not shown this finding. On the other hand, adrenal rest tumors have already been described on conventional CT as a soft tissue masse in the ovary, OART (42), and in the perirenal region (43).

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**Figure 2.** Testicular adrenal rest tumor (TART) in a 14 year-old male, with simple virilizing congenital adrenal hyperplasia. On ultrasonography (A-B), there is a round heterogeneous, predominantly hypoechoic nodule (*) within both testicles, in the region of the mediastinal testis. On magnetic resonance imaging (C, axial; D, coronal) the TARTs are hypointense on T2-weighted images.
Magnetic resonance imaging

Studies based on MRI are in accordance with others performed with CT (36) demonstrating a high prevalence of adrenal nodules (73%) in adults with CAH (16). Moreover, adrenal MRI imaging in CAH patients showed findings such as normal or diffuse enlarged adrenal glands (44), adrenal nodules (16,37,45), and myelolipomas (46,47), which is consistent with US and CT findings (Figure 3). The size of the adrenal glands and presence of nodules may relate to hormonal control status; a significant correlation between adrenal and nodule sizes and hormonal parameters has been described (16). Moreover, these morphological adrenal features are more prevalent in patients with a poor hormonal control status (48), even as the prevalence of adrenal masses increases with adrenal volume (16), which may regress with adequate treatment (49).

Excellent soft-tissue contrast, spatial resolution, and capability of multiplanar imaging make MRI more sensitive than other imaging modalities to evaluate the pelvis. MRI is indicated when US fails to adequately demonstrate the morphology, size, and relationship between Mullerian duct derivatives in virilized female infants (3,27) (Figure 1). It is the primary imaging modality when evaluation of pelvic organs and morphology in older children, adolescents, and adults are needed. In addition, although rare, prostatic tissue has been shown in females with CAH with a prevalence of up to 15% (50).

The prevalence of ectopic adrenal rest tumors in the testicles showed by MRI is high, ranging from around 29% (32) to 94% (14). Despite this high incidence, presence of TART did not show any correlation with short hormonal parameters in adults (16). On MRI, TARTs are typically isointense relatively to parenchyma on T1-weighted images, hypointense on T2-weighted images (14,51), and present well-defined margins (14). After intravenous injection of gadolinium they have a significant enhancement (51). Although MRI has the same sensitivity as US in detecting TART (51), when testis sparing surgery is considered MRI is recommended due to its better depiction of the tumor margins (14). Adrenal rest tissue was also documented in the retroperitoneum encasing the aorta with regression of the size after glucocorticoid treatment (52).

Concerning brain changes in patients with CAH, MRI showed white matter abnormalities (53), smaller amygdalas (54), and temporal lobe atrophy in young population (55). White matter abnormalities may also be secondary to electrolytic complications of the disease (56). Pituitary abnormalities (57) and hypothalamic hamartoma (58) were described in CAH patients.

Figure 3. Adrenal glands in three different patients with congenital adrenal hyperplasia (CAH). Enlarged adrenal glands (arrows) can be seen on computed tomography (A) and magnetic resonance imaging (B), in different patients. On "A", the left adrenal gland had nodular margins (dashed arrow). On "B" the left adrenal gland (dashed arrow) is larger than the right adrenal gland, which was within normal limits. Another adult patient with abdominal pain in which ultrasonography (not shown) depicted an adrenal mass. Computed tomography (C) and magnetic resonance imaging (D-E) showed a right adrenal myelolipoma (circles). CAH was confirmed posteriorly. Axial contrast-enhanced computed tomography (A); coronal T1-weighted magnetic resonance imaging (B); axial computed tomography (C) and T1-in-phase (D) and out-of-phase (E) magnetic resonance imaging.
in anecdotal case reports. Functional MRI demonstrated different patterns of activation in emotional memory comparing CAH patients with controls (59), and a virilized amygdala function in females affected (60).

CONCLUSIONS
Although the diagnosis of CAH is based on hormonal dosages and genetic analysis, imaging still has an important role in the management of these patients regarding a proper clinical setting. In addition to radiographs evaluating bone age included as a tool in the clinical follow-up, genitography, US, MRI, CT, and other imaging modalities add important information for diagnosis, follow-up, and surgical planning (Table 1).

The detection of TART is essential to be done as early as possible, as the patients can be monitored and treated more intensively, in order to prevent fertility impairment and testicles damage (20). US figures as the modality of choice for this purpose (20,51). Therefore, it should be used routinely and not only from adolescence. While laboratorial results are pending, US may show a specific coiled pattern and/or enlargement of the adrenal glands (6), enabling early treatment of neonates with suspicious of CAH. Furthermore, US is the first modality to evaluate neonates and young infants with ambiguous genitalia (27), a feature frequently present in virilized females. As a tool to help early detection of risk for cardiovascular diseases, US may be used to evaluate carotid vessels (30).

MRI is a problem solving for detailed depiction of pelvic structures when US in not sufficient, mainly in cases of ambiguous genitalia (3,27). It is recommended to evaluate TART before testes sparing surgery (14). Also, MRI can evaluate in detail adrenal nodules. Due to its lack of radiation and better soft tissue contrast, MRI may be considered as the method of choice to follow-up patients, as adrenal changes on MRI correlate to hormonal parameters (16). CT is mainly used to evaluate the adrenal glands but with the drawback of

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* If MRI is not available, which has higher sensitivity and specificity than CT and lack of ionizing radiation exposure.
ionizing radiation. To assess pelvic anatomy, genitography is used for planning feminizing surgery (3).

For radiologists and sonographers, the detection of enlarged adrenal glands, adrenal gland nodules, and coiled adrenal glands in any imaging study should prompt raise the possibility of CAH. Also, they must keep in mind the possibility of CAH in cases of ambiguous genitalia, testis lesions, ovarian solid nodules, abnormal retroperitoneum solid tissues, and even white matter abnormalities seen in brain MRI.

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REFERENCES