Prostate gland development and adrenal tumor in a female with congenital adrenal hyperplasia: A case report and review from radiology perspective

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ABSTRACT

We describe a case of a female with simple virilizing congenital adrenal hyperplasia (CAH) reared as a male diagnosed at the late age of 64. Computed Tomography (CT) demonstrated a large adrenal mass, bilateral diffuse adrenal enlargement, female pelvic organs as well as a clearly visualized prostate gland. This is to the best of our knowledge the first case of such a sizable prostate gland in a female CAH patient documented on CT. We review the literature regarding aspects where radiologists may encounter CAH and the finding of presence of a prostate gland in female CAH patients.

CASE REPORT

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A 64-year-old Chinese man presented to the urology clinic for recurrent dysuria and was referred to have ultrasound exam of the scrotum for non-palpable testes. His past medical history was significant for hypospadias with corrective surgery done in childhood. He had also been put on Terazosin for presumed benign prostatic hypertrophy.

Ultrasound findings

At ultrasound exam, he was noted to be of short stature (143cm). Inspection of the perineum revealed a small phallus and fused labioscrotal folds. A ventral scar was seen, in line with previous surgery for hypospadias. No testes could be identified in the perineum, inguinal region nor abdomen on ultrasound. The pelvis was obscured by bowel gas and a full bladder was difficult to obtain due to his urinary symptoms. Incidentally, a 37x35x50mm right adrenal mass was detected while searching for possible undescended testes (Fig1). The mass was sharply demarcated with smooth roundish outline. It was solid, slightly hypoechoic to the liver except for a small focus of hyperechogenicity and relatively homogenous. Moderate vascularity was detected on Color Doppler imaging. CT scan was hence arranged for further investigation.

CT findings

Contrast enhanced CT of the abdomen and pelvis confirmed a large mass arising from the lateral limb of the right adrenal gland. Except for a small focus of hypodensity which showed delayed phase enhancement, the main bulk of the mass was isodense to the rest of the adrenal glands in pre-contrast, post-contrast portovenous phase (75 seconds) and post-contrast 15-minute delayed phase scans. Attenuation measurements in pre-contrast, portovenous phase and delayed phase scans were 41 Hounsefield Units (HU), 167.5HU and 70.6HU respectively with resultant 76.6% absolute contrast washout. There was no evidence of local tumor invasion of the adjacent organs or metastasis to the liver or lymph nodes. The rest of the right adrenal gland as well as the left gland were diffusely thickened with preserved adreniform shape and smooth outline, compatible with hyperplasia (Fig2). No undescended testes could be identified in the abdomen and pelvis. Most strikingly, a uterus complete with bilateral small ovaries were seen. A 36x39x37mm soft tissue mass with appearance and location compatible with a prostate gland was also present (Fig3). A presumptive diagnosis of female with congenital adrenal hyperplasia was made.

Further investigations and management

Subsequent blood tests confirmed grossly elevated 17α-OH-progesterone > 750 nmol/L (Normal male: 0.9-6.6nmol/L), progesterone 342 nmol/L (Normal male: 0.66-4.89nmol/L), DHEA-S 5050 ng/ml (Normal male: 800-5600) and androstenedione 2945 ng/dL (Normal male: 50-220), in line with 21-hydroxylase deficiency. Testosterone level was 33 nmol/L and was within normal range for an adult male (Normal male: 10-35nmol/L). Adrenocorticotropic hormone (ACTH), cortisol and corticosterone metabolites were normal. Serum sodium and potassium levels were normal. Prostate specific antigen was 3.6ng/ml (Normal male: <4ng/ml). Urine catecholamines were not elevated, excluding phaeochromocytoma. Karyotyping returned 46XX.

Uroflometry showed only mild lower urinary tract obstruction and he was taken off Terazosin. His urinary symptoms were attributed to recurrent urinary tract infections which were treated accordingly.

Although the high percentage contrast washout of the adrenal mass was suggestive of adenoma, its large size and presence of heterogeneous component were atypical. Laparoscopic right adrenalectomy, hysterectomy and bilateral salpingooophorectomy were performed with perioperative hydrocortisone supplementation. Due to technical reasons, the right adrenal gland was removed in a piecemeal fashion. Histopathology showed adrenocortical hyperplasia but was unable to differentiate between a hyperplastic nodule and an adenoma due to the piecemeal nature of the specimen. No malignancy was detected. No evidence of testicular tissue was detected in the ovaries. In view of old age and the patient being well all along except for his urinary symptoms, regular corticosteroid replacement was not given. He remained well currently at one year post-operation.

DISCUSSION

Etiology and demographics

Congenital adrenal hyperplasia can be divided into the more severe classical and the milder non-classical or late-onset types. The incidence of classical CAH based on neonatal screening programs is 1 in 15000-16000 live births worldwide with significant geographical and ethnical variations [1, 2]. Non-classical or late-onset CAH has a much higher incidence of 1:1000 worldwide [1]. The disease follows an autosomal recessive inheritance. It is caused by an enzymatic deficiency in the biosynthesis of cortisol and aldosterone. Although the disease can be due to deficiency of five different enzymes, over 90% of cases are due to 21-hydroxylase deficiency [3]. This results in decreased levels of cortisol and aldosterone and shunting of intermediate metabolites towards production of excess androgens. Reduced negative feedback from cortisol leads to continued adrenocorticotropic hormone (ACTH) hyperstimulation, causing adrenal hyperplasia and androgen excess.

Clinical presentation

Depending on the severity of the enzymatic defect, the disease could range from being totally subclinical to causing death shortly after or even before birth.

Classical CAH comprises the salt wasting form and the simple virilizing form. The salt wasting form is the most severe form of the disease and accounts for 75% of classical CAH cases [1]. In this form, both aldosterone and cortisol are deficient and marked androgen excess is present. Apart from signs of androgen excess which could be present at birth, most evidently as ambiguous genitalia in girls, affected infants present within weeks after birth with failure to thrive, recurrent vomiting, dehydration and shock in a salt wasting crisis. This is typically fatal without treatment.

The current patient had a partial 21-hydroxylase deficiency that was mild enough not to have caused salt wasting but severe enough to have resulted in masculinized external genitalia. This falls into the category of simple virilizing form of CAH. In this form of the disease, cortisol is not synthesized efficiently, but aldosterone secretion is adequate and sodium balance is maintained. Patients with this form of the disease are mainly affected by hypocortisolism and androgen excess. The former puts them at risk of adrenal crisis while the latter manifests as ambiguous genitalia and menstrual disturbances in girls and hirsutism, pseudoprecocious puberty, advanced skeletal maturity with resultant short final height, acne, alopecia, infertility, etc., in both sexes. As ambiguous genitalia due to 21-hydroxylase deficiency affects only females while males present with penile enlargement which is clinically more subtle, diagnosis in males is often delayed [3]. Classical CAH is by far the most common cause of ambiguous genitalia worldwide.

Non-classical or late onset CAH is the milder form of the disease. The clinical presentation is of androgen excess which is generally milder than in the classical forms. Patients typically present in late childhood or early adulthood although some may remain asymptomatic for life [4]. Hirsutism is the most common symptom [4].

As CAH was only better understood by the medical community in the later decades of the 20th century, it was no surprise that our patient was not diagnosed at birth and was wrongly assigned male gender.

Laboratory diagnosis

The diagnosis of CAH relies on demonstrating accumulation of metabolites upstream of the enzymatic block, typically 17α-OH-progesterone in the case of 21-hydroxylase deficiency. Neonatal screening based on this has become available in many developed countries, allowing early detection and treatment of the classical forms [2]. Specific genetic mutations responsible for the enzymatic deficiencies have been discovered and could nowadays be diagnosed [1, 2, 3].

Radiological findings in CAH

As a metabolic disease, CAH has manifestations in multiple organ systems. The following entities are those which concern radiologists.

The adrenals

Studies on imaging appearance of the adrenal glands in CAH are scarce and mostly comprise small series and case reports.

The potential use of sonography of the adrenal glands as a rapid screening tool for CAH in neonates and infants has been studied. The size of adrenal glands in CAH neonates has been shown to be substantially larger than in normal neonates although significant overlap exists [5-8]. Adrenal length >20mm and width >4mm in the newborn could suggest the diagnosis [8]. Disease severity correlates with adrenal gland size [7, 8]. Later studies showed that "cerebriform" or coiled appearance of the adrenal glands, which reflects the enlarged elongated glands crammed within a confined space is a good discriminator between CAH and normal subjects [9, 10]. In neonates or infants suspected to have classical CAH due to ambiguous genitalia or salt wasting, sonography of the adrenals achieved >90% sensitivity and 100% specificity in diagnosing CAH [9, 10]. With adequate treatment, the size and appearance of the glands typically return to normal in a few months [9, 10]. Adrenal mass is not frequently reported in neonates with CAH, possibly due to the relatively short duration of ACTH hyperstimulation.

Antenatal sonographic visualization of enlarged or "cerebriform" adrenal glands or ambiguous genitalia in fetuses affected by CAH have been reported, but cases are too few to establish its diagnostic reliability [11-19].

In the older pediatric age group and in adults, the most frequently reported imaging abnormalities of the adrenal glands in CAH, treated or untreated, are bilateral enlargement and unilateral or bilateral adrenal mass(es) [20-27]. Adrenal enlargement could be smooth or nodular. The term mass here incorporates nodules which are essentially smaller nodular masses. Jaresch et al. found 82% of CAH patients had adrenal mass on CT with incidence and size of the masses apparently positively correlated with the degree and duration of ACTH stimulation [23]. Reisch et al. showed that total adrenal gland volume on MRI correlated with hormonal control [26]. It was also shown in multiple studies that adequate treatment could lead to morphological normalization of the adrenal glands, with shrinkage or even resolution of some adrenal masses [25, 28-30]. Over-treatment resulting in hypoplastic appearance of the adrenals on imaging has been reported [21, 24]. These are in keeping with the widely held notion that the morphological changes of the adrenals in CAH are largely ACTH dependent thus reflecting disease severity and treatment adequacy. Whether adrenal imaging can be used to help titrate treatment however has yet to be explored.

In another study by Jaresch et al., 82% of homozygotes and 45% of heterozygotes for CAH had adrenal mass [22]. On the other hand, Baumgartner-Parzer et al. showed that 16% and 2% of subjects with adrenal incidentaloma found on CT were heterozygous and homozygous for classical CAH respectively [27]. Thus it seems adrenal tumors are very common in CAH but not vice versa. Nonetheless, the differential of CAH should be borne in mind when an adrenal tumor is encountered, particularly during workup for virilization for one may step into the diagnostic pitfall of solely attributing the hormonal disturbance to the tumor while the underlying problem which may be CAH instead may be completely overlooked [31]. To complicate matters more, functional adrenal tumors may coexist with and biochemically mask underlying CAH [32-34].

A few cases of normal adrenal morphology on CT or MRI in untreated non-classical CAH in adults have been reported [23, 35]. However, to our knowledge, such finding has not been reported in untreated classical CAH in adults despite the sizable number of untreated adult classical CAH cases reported in the literature. Thus abnormal adrenal morphology on CT or MRI is probably a very sensitive marker for untreated classical CAH in adults. Adrenal mass or enlargement is however not specific for CAH.

Adrenocortical adenomas are well known to occur in CAH. Less well known is that adrenal myelolipoma is also associated with CAH [24, 36]. The imaging diagnosis of the latter is rather straightforward, requiring visualization of macroscopic fat. The only documented prevalence of myelolipomas in a heterogeneous group of CAH patients is 6% (4 in 62) [24]. The imaging and histopathological distinction between adenomas and hyperplastic macronodules is often not possible, as was the case in our patient. Fortunately, such a distinction is not of great clinical importance. The high prevalence of masses reported by Jaresch et al. and Reisch et al. of 82% and 73% respectively likely represented the combined prevalence of adenomas and hyperplastic macronodules [23, 26]. A low prevalence of 3% adenomas and 0% hyperplastic macronodule was reported by Nermoen et al. [24]. Such large discrepancy may reflect different hormonal control between the studied populations.

Studies on radiological characterization of adrenal masses in CAH are lacking, thus whether adrenocortical adenomas and myelolipomas occurring in CAH have different imaging characteristics from those generally described is unknown.

Only a few cases of adrenal carcinoma and one case of phaeochromocytoma occurring in CAH have been reported [24, 37, 38]. No definite association between these two entities and CAH has been established.

Urogenital tract anomalies

Pelvic sonography for identification of the uterus is routinely done for patients with ambiguous genitalia. Female infants with completely masculinized external genitalia may present at sonography as boys with bilateral cryptorchidism who require localization of the testes. Female pseudohermaphrodites due to CAH should always have a normal uterus. For those who need corrective urogenital surgery, further delineation of the internal portions of the urogenital tract with sonography or urogenitography might be needed preoperatively [39].

Nabhan et al. found 21% (14 out of 66) of girls with ambiguous genitalia due to CAH had upper urinary tract abnormalities which included vesicoureteric reflux, hydronephrosis and duplicated collecting system [40]. Thus sonography of the kidneys and micturating cystourethrography should probably be performed for all patients in this subgroup. The incidence of urinary tract abnormalities in boys with CAH is unknown.

Adrenal rest tumors

Chronically increased ACTH can lead to tumor formation in adrenal rests in the body, most commonly in the testes. In the largest cohort of patients with CAH due to 21-hydroxylase deficiency (n=244, 46% male), testicular adrenal rest tumor (TART) was found on sonography in 44% men (>18 years of age) and 33% boys (4-18 years of age; youngest patient with TART was 4.1 year-old) with classical CAH [41]. Reported cases of TART in CAH occurred almost exclusively in the classical form. Since TARTs are usually not palpable unless larger than 2cm, diagnosis relies heavily on imaging. Sonography and MRI are equally good in this regard [42]. The typical appearance on sonography is multiple nodular hypoechoic foci arising from the testicular hilar region, bilateral in 80%. Hyperechogenicities appear in the later stages due to fibrosis and fatty infiltration, which irreversibly impair spermatogenesis [42]. On MRI, TARTs are T1 isointense to slightly hyperintense and T2 hypointense to normal testicular tissue and diffusely enhance [43]. Malignant change in TART has not been documented thus recognition of this association is important to avoid unnecessary orchidectomy. Imaging differentiation of mass forming TARTs from other testicular tumors may be difficult. Presence of vessels crossing the lesion without deviation has been described as a feature of TART [43]. Other useful differentiating features include negative testicular tumor markers, increased cortisol on gonadal vein sampling and suppressibility by gluccocorticoid treatment [43].

In contrast to TART in males, ovarian adrenal rest tumors (OART) in CAH are rare with occurrences limited to isolated case reports [44-48]. Limited radiological information in these reports suggests that they are solid echogenic masses.

Adrenal rest tumors in CAH have also been reported to have occurred at the renal hilar region and in the retroperitoneum with encasement of the aorta and renal arteries [49, 50]. Successful use of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) in detecting adrenal rest tumors have been reported in two cases, one in the ovaries and the other in the para-ovarian tissues [47, 51]. In the latter case, the lesions were undetectable in the initial PET scan but showed high uptake in the second PET scan which was preceded by injection of Cosyntropin, which is a synthetic analogue of ACTH.

Polycystic ovaries

Increased prevalence of polycystic ovaries has been shown by Hague et al. [52]. They found 85% (29 of 34) adults, 40% (4 of 10) post-pubertal girls (aged 11-16) and 3% (1 of 31) pre-pubertal and peri-pubertal girls (aged 0.1-13 years) who had CAH had polycystic ovaries on sonography. Stikkelbroeck et al. however found only 15.4% (2 of 13) CAH patients aged 14.8-24.5 years had sonographic polycystic ovaries, which was similar to the incidence in the general population [44]. It is noteworthy that different hormonal control and imaging criteria used may have led to different results in these studies.

Brain lesions

Increased prevalence (27-45%) of abnormal white matter T2 or FLAIR hyperintensities in the brain, typically at the periventricular region has been reported [53-56]. An association with temporal lobe structure dysgenesis including amygdala atrophy and hippocampal dysgenesis has also been reported [53, 57]. Evidence on how these are associated with neuropsychological disturbances is scanty and inconclusive. The cause and clinical significance of these have yet to be fully elucidated.

Skeletal system

Advanced skeletal maturation with early epiphyseal plate closure and short resultant final height are common in CAH. Bone age advanced by 2-3 years is common in children with classical CAH. Advanced bone age is more pronounced in boys and in the simple virilizing form [58]. A final height of 1.55 and 1.25 standard deviations below mean were observed for boys and girls respectively in one study [58]. There is also increased prevalence of osteopenia and osteoporosis in CAH patients older than 30 years of age and in postmenopausal women with CAH compared to healthy controls, postulated to be related to gluccocorticoid over-treatment [59]. Bone mineral density in children and young adults are generally normal [59].

Prostate gland development in female CAH patients

The paraurethral Skene gland in the female is homologous to the prostate gland in the male [60-62]. Although it has been shown that androgen excess could stimulate prostate gland development in females, the conditions such as timing with respect to embryological development, duration, androgen level and underlying genetic predisposition required for this to happen are still uncertain [63]. To the best of our knowledge, there are to date 11 published articles documenting development of prostatic tissue in female CAH patients with a total of 16 reported cases [64-74], making our patient the 17th case. Only one case of adenocarcinoma of the prostate and one case of benign prostatic hypertrophy in female CAH patients have been reported [67, 68]. In the largest study by Paulino Mda et al., 15.6% (5 out of 32) of female patients with classical CAH had MRI evidence of prostate gland development [66]. However in the series by Doherty et al., all 11 adult female CAH patients who underwent pelvic MRI had no evidence of prostate gland development despite 7 of them had marked androgen excess [75]. If the true prevalence is anywhere close to that reported by Paulino Mda et al., then this phenomenon is very much under-reported.

In the study by Paulino Mda et al., all female CAH patients with MRI visible prostate gland development had a prostate specific antigen (PSA) level of >0.1ng/mL [66]. PSA has also been recently found to be a marker for hyperandrogenism in females outside the context of CAH [76-

79]. However, elevated levels could also result from breast fibroadenomas and cysts [80]. Whether the imaging appearance of the Skene/prostate gland in females may also serve as a marker for hyperandrogenism outside the context of CAH may be worth exploring.

Although our patient showed such a sizable prostate gland on CT, it was deemed at most only partly responsible for his urinary symptoms, with the most likely cause being repeated episodes of urinary tract infection related to his lower urinary tract malformation. The extreme case of acute retention of urine due to prostate enlargement in a female CAH patient has only been reported once in the literature [68].

Treatment and prognosis

The mainstay of treatment for all forms of CAH is corticosteroid replacement. The salt losing form is typically fatal without treatment. Prognosis is generally good with adequate treatment. A significant cause of mortality is inadequate treatment particularly during times of stress such as infection especially in early childhood [81]. Fertility can be achieved with treatment in both female and male. In affected pregnancies, corticosteroid replacement in the mother can prevent ambiguous genitalia in the female fetus. Short final height is unfortunately common in the classical forms despite treatment [58, 59]. Other sources of morbidity may arise from metabolic consequences of under- or over-treatment such as obesity, insulin resistance, hypertension and osteoporosis [59].

Differential diagnosis

The appearance of the adrenal glands in CAH is indistinguishable from that in ACTH dependent Cushing syndrome, which comprises Cushing's disease (pituitary ACTH producing adenoma) and ectopic ACTH. This is expected as the changes in adrenal morphology are due to the same cause, i.e. chronically increased ACTH levels. Cushing's disease and ectopic ACTH are however clinically evidently different from CAH as they present with hypercortisolism instead. Primary adrenal hyperplasia, typically presenting as Conn's syndrome, is another differential which may have similar adrenal morphology but has distinguishably different biochemical profile. Differentiating between these entities is beyond CT or MRI and has to rely on biochemistry.

As for the solitary adrenal mass in our patient, the large size and intense contrast enhancement raised suspicion for phaeochromocytoma. Although rapid contrast washout of >60% (absolute) at 15 min delayed scan is generally diagnostic of adenomas, phaeochromocytomas are known to overlap with adenomas in this regard. This differential was however considered unlikely given the non-elevated catecholamine levels and normal blood pressure. Malignancy was also a consideration given the large size, pre-contrast attenuation >30HU and lack of intralesional macroscopic fat which if present would suggest myelolipoma which is typically large. But the largely homogenous texture, well defined regular outline and rapid contrast washout were features against malignancy.

As for the presence of a uterus in a phenotypic male, the differentials include true hermaphroditism and other intersex conditions, all of which are extremely rare.

However, when bilateral diffuse adrenal enlargement is combined with presence of a uterus in a phenotypic male, the only unifying diagnosis is CAH in a female patient.

TEACHING POINT

Congenital adrenal hyperplasia (CAH) is a metabolic disease with imaging manifestations in various organ systems. When bilateral diffuse adrenal enlargement is seen in combination with presence of a uterus in a phenotypic male, the only unifying diagnosis is CAH in a female. Do not be surprised if a prostate gland is seen.

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FIGURES

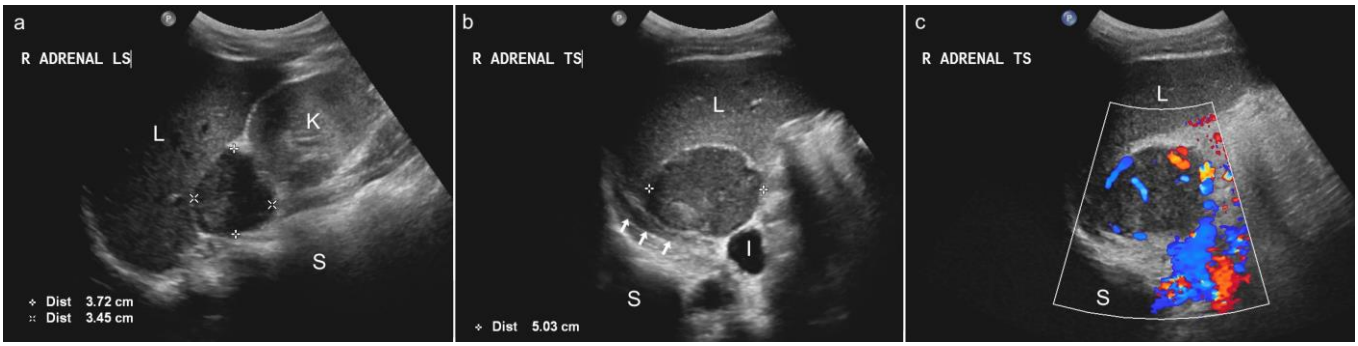

Figure 1: Sonography of the right adrenal gland of a 64 year old phenotypic male with 46XX karyotype affected by congenital adrenal hyperplasia.
Abdominal ultrasound with 5MHz curvilinear probe: (a) Oblique sagittal and (b) horizontal sections through the right adrenal gland showed a 37x35x50mm sharply demarcated roundish mass (bounded by markers) with smooth outline, slightly hypoechoic to the liver and relatively homogenous except for a small internal focus of hyperechogenicity. The thickened medial limb of the right adrenal gland was also seen (arrows). (c) Horizontal section color Doppler image showed moderate vascularity over the right adrenal mass. (L: Liver; K: Right kidney; I: Inferior vena cava; S: Spine)

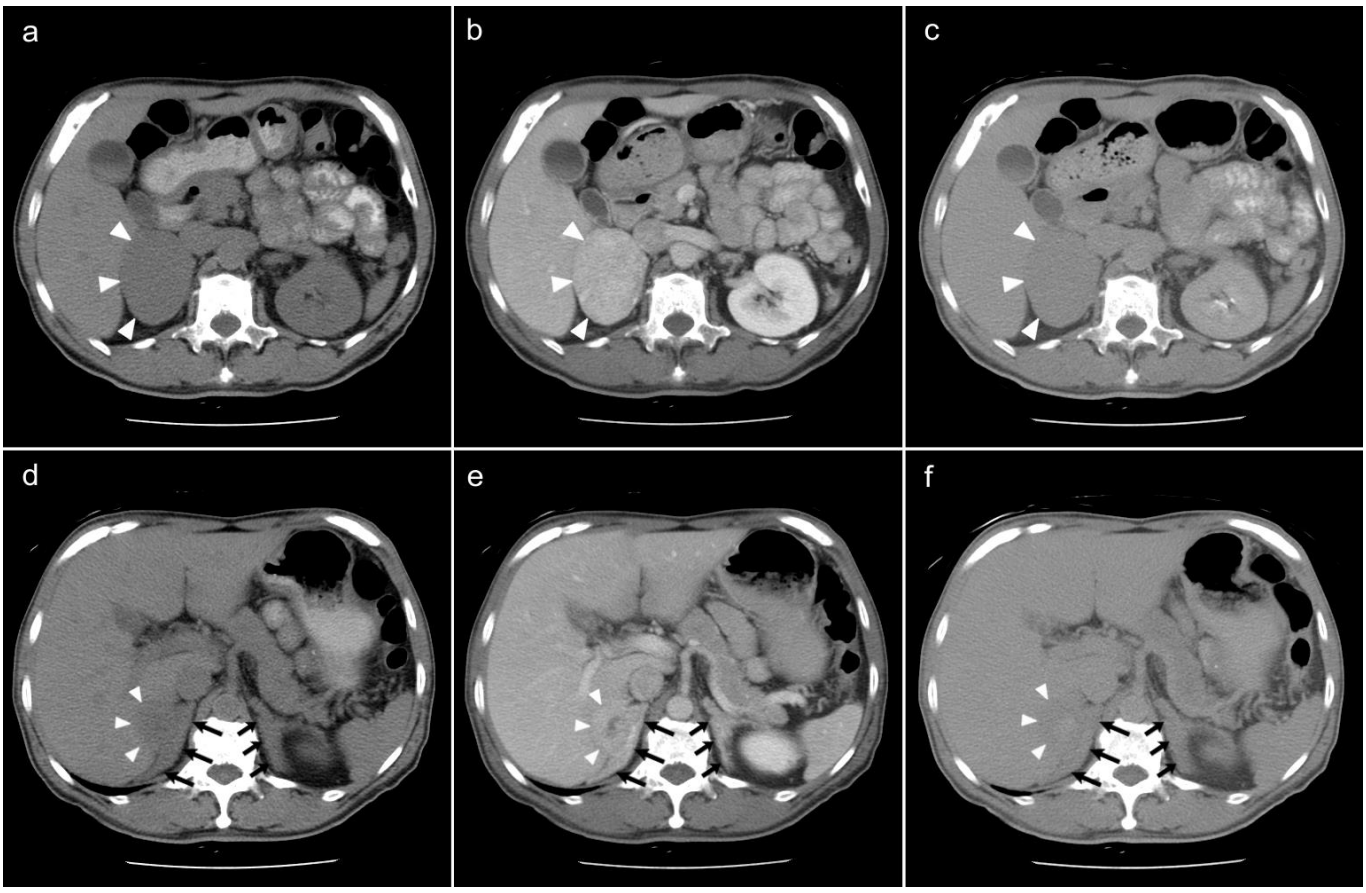

Figure 2: Computed tomography images of the adrenals of a 64 year old phenotypic male with 46XX karyotype affected by congenital adrenal hyperplasia.
Left column (a,d): Pre-contrast scan.
Middle column (b,e): Portovenous phase scan.
Right column (c,f): 15 minutes delayed phase scan.
Upper row images (a,b,c) are at level of the right adrenal mass.
Lower row images (d,e,f) are at level of the adrenal glands and superior part of the adrenal mass.

CT showed a large mass (white arrow heads) arising from the lateral limb of the right adrenal gland. Except for a small intralesional focus of hypodensity (d,e) which showed delayed phase enhancement (f), the main bulk of the mass was isodense to the rest of the adrenal glands in pre-contrast, portovenous phase and 15min delayed phase scans. There was no evidence of local tumor invasion of the adjacent organs or metastasis to the liver or lymph nodes. The rest of the right adrenal gland (1ong black arrows) as well as the left gland (short black arrows) were diffusely thickened with preserved adreniform shape and smooth outline, compatible with hyperplasia.

(CT protocol: Voltage:120kV; Current: modulated, 120-214mA; Slice thickness: 5mm; Scanner: General Electric Lightspeed 16 CT; Intravenous contrast: 90mL Omnipaque 300 given at 2mL/second; Portovenous phase taken at 75 seconds after contrast injection; Delayed phase taken at 15 minutes)

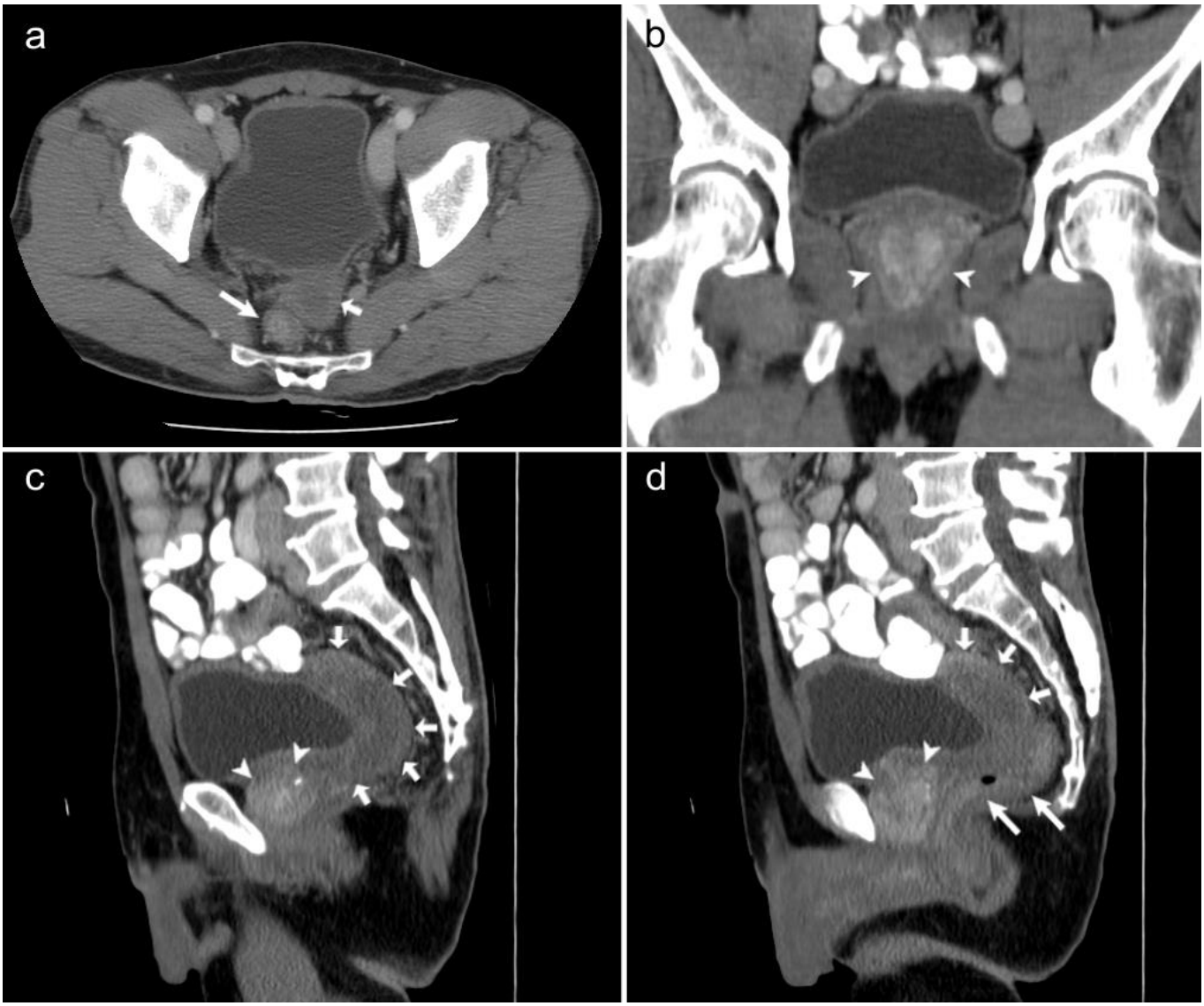

Figure 3: Computed tomography images of the pelvis of a 64 year old phenotypic male with 46XX karyotype affected by congenital adrenal hyperplasia.
(a): Axial image at pelvis showing the uterus (short arrow) and rectum (long arrow). The uterus was mildly distended with hypodense fluid.
(b): Coronal reformatted image showing the prostate gland (arrow heads) with differential zonal enhancement.
(c): Sagittal reformatted image showing the prostate gland (arrow heads) and uterus (short arrows). The uterus was mildly distended with hypodense fluid. A speck of calcification could be seen within the prostate gland.
(d): Sagittal reformatted image at a plane slightly right of (c) showing the prostate gland (arrow heads), rectum (long arrows) and part of the uterus (short arrows).
(CT protocol: Voltage:120kV; Current: modulated, 120-214mA; Axial image (a) slice thickness: 5mm; Coronal and sagittal reformatted images (b,c,d) slice thickness: 2.5mm; Scanner: General Electric Lightspeed 16 CT; Intravenous contrast: 90mL Omnipaque 300 given at 2mL/second; All images were from portovenous phase scan performed at 75 seconds after contrast injection)

Etiology	Autosomal recessive inherited enzymatic defect in cortisol biosynthesis. >90% due to 21-hydroxylase deficiency. Problems result mainly from corticosteroid insufficiency, androgen excess and increased adrenocorticotropin (ACTH). Clinical presentation is variable and depends on severity of the enzymatic defect.
Incidence	*Classical forms:* • 1 in 15000-16000 live births worldwide. • 1 in 14203 live births in US and Canada. • 1 in 19000 live births in Japan. • 1 in 5000 live births in Saudi Arabia • 1 in 21270 live births in New Zealand. • Exceptionally high incidence in Yupik Eskimos of Alaska at 1 in 282 live births. *Non-classical form:* • 1:1000 worldwide. • Up to 1:27 in Ashkenazi Jews.[1,2]
Gender ratio	No gender predilection
Presentations	*Classical forms (salt wasting form and simple virilizing form):* • Ambiguous genitalia in females; Enlarged penis in males • In salt wasting form: Failure to thrive, repeating vomiting, dehydration and shock early in infancy. • Very early puberty and accelerated growth and skeletal maturation with short final height • Disturbance of menstruation and impaired fertility in both sexes • Other signs of virilization including hirsutism, alopecia, acne, deepened voice…etc. *Non-classical or late onset form:* • Clitoromegaly and other signs of virilization. • Early puberty and accelerated growth and skeletal maturation with short final height • Disturbance of menstruation. • Impaired fertility mainly in females
Age at presentation	Neonatal screening which detects classical CAH is nowadays available in many developed countries, allowing early recognition and treatment. For undiagnosed patients, age at presentation depends on disease severity. Classical forms present earlier in life, usually in infancy or early childhood. Non-classical form presents later in life, usually late childhood or early adulthood but may remain asymptomatic for life.
Risk Factors	Risk is in accordance with genetic makeup of parents which is reflected in geographical and ethnical background.
Treatment	• Corticosteroid (usually glucocorticoid with or without mineralocorticoid) replacement. • Corrective surgery for ambiguous genitalia in girls.
Prognosis	• Salt losing form is usually fatal without treatment. With treatment, prognosis is generally good. Mortality is often due to inadequate corticosteroid replacement, especially during times of stress such as infection. • Fertility can be achieved with adequate therapy. • Short final height common despite treatment.
Findings on imaging	• Normal adrenal morphology in untreated adult classical CAH has not been reported. The most common adrenal abnormalities on imaging are bilateral adrenal gland enlargement and adrenal mass(es). Adrenal enlargement could be diffuse with smooth contour or nodular. Up to 82% has adrenal mass. Adenoma, myelolipoma and hyperplastic macronodules are among the known predisposed adrenal masses. • Phenotypic males who are actually female CAH patients may present with bilateral cryptorchidism for sonographic localization of testes. Imaging would reveal normal female pelvic organs. • Female patients with ambiguous genitalia due to CAH have increased risk (~21%) of upper urinary tract abnormalities including vesicoureteric reflux, hydronephrosis and duplicated collecting system. • Advanced bone age by 2-3 years is common in classical CAH. • Increased prevalence of osteopenia and osteoporosis in adults >30 years of age and in post-menopausal women. • 0-15.6% females with classical CAH have MRI evidence of prostate gland development. • Male patients with classical CAH are predisposed (~33% in 4-18 year-olds and ~44% in >18 year-olds) to testicular adrenal rests tumors (TART) due to ACTH hyperstimulation. These are bilateral in 80% cases. At sonography, these appear as multiple hypoechoic nodules at the testicular hilar region. Later may show hyperechogenicities due to fibrosis and fatty infiltration. On MRI, these are hypointense on T2W and isointense to slightly hyperintense on T1W imaging and diffusely enhance. • Adrenal rest tumors rarely occurred in the ovaries, para-ovarian tissues and retroperitoneum. Increased uptake on F18-Fluorodeoxyglucose-PET especially after Cosyntropin injection has been reported. • Increased incidence of polycystic ovaries detected on sonography in up to 85% adults, 40% post-pubertal girls (aged 11-16) and 3% pre-pubertal and peri-pubertal girls (aged 0.1-13 years). • Increased prevalence (27-45%) of abnormal cerebral white matter T2/FLAIR hyperintensities. Also higher incidence of dysgenesis of temporal lobe structures including amygdala atrophy and hippocampal dysgenesis.

Table 1: Summary table for congenital adrenal hyperplasia (CAH)

	General features	USG/CT/MRI	Nuclear scan
Congenital adrenal hyperplasia (CAH)	• Virilization, hypocortisolism, hypoaldosteronism	• Variable diffuse enlargement of bilateral glands with or without hyperplastic nodules. • Associated with adenomas and myelolipomas. • Coiled or "cerebriform" gland may be seen in infants and antenatal fetal ultrasound.	
Adrenocorticotropic hormone (ACTH) dependent Cushing syndrome – Cushing's disease (pituitary adenoma) and ectopic ACTH	• Hypercortisolism	• Variable diffuse enlargement of bilateral glands with or without hyperplastic nodules. • Nodules >1cm in 18% in Cushing's disease and 30% in ectopic ACTH. • Nodules are usually T1W and T2W isointense to normal parts of the gland.	
Adrenocorticotropin-independent macronodular adrenal hyperplasia (AIMAH)	• Hypercortisolism, mild in many cases. • Rare	• Both glands massively enlarged with multiple hyperplastic nodules 0.1-5.5cm in size. • Internodular parts of glands usually distorted and obscured, but if visible, may be normal, hypoplastic or hyperplastic. • Nodules are T1W hypointense and usually T2 hyperintense to liver.	• Bilateral increased uptake on ^{131}I-iodomethylnorcholesterol scintigraphy.
Adrenal hemorrhage	• Associated with trauma, stress, bleeding diatheses and underlying adrenal tumors including myelolipoma, hemangioma, pheochromocytoma, adenoma, adrenocortical carcinoma and metastasis • 20% bilateral in non-traumatic cases. • 77% right side if traumatic. • May present as acute adrenal insufficiency. • Most common neonatal lesion of adrenal gland	• Rapidly appear and evolve over serial scans. • Attenuation and signal intensity follow evolution of hematomas in general. • May be diffuse with preserved adreniform shape if small, showing peripheral tramtrack enhancement of normal gland. Ball-like if larger. • Can be >10cm. • Peri-glandular infiltration in acute phase. • May show active extravasation. • Cystic appearance later with rim enhancement. • Resolves over time or in chronic cases appear as thin-walled pseudocyst which are mostly unilocular and may be peripherally calcified. • Post-insult gland may atrophy	
Granulomatous infection	• Tuberculosis, histoplasmosis, blastomycosis • Bilateral adrenal gland destruction eventually leads to Addison's disease	• Enlargement in acute phase. Mass like in 50-65%, adreniform in 35-50%. • More commonly homogenous in unenhanced CT with one-third heterogeneous. • Peripheral enhancement with central necrosis in 40-50% in contrast enhanced scan. May also show heterogeneous gland enhancement. • Cystic change, calcifications and atrophy in chronic phase.	
Metastases	• Lung, breast and colon, renal cancers and melanomas are the most common primaries. • 50-75% chance an adrenal mass is a metastasis if known history of malignancy. Unlikely if no history of malignancy.	• Ill-defined outline and heterogeneous density are more common in metastases than in benign entities. • Typically >10 HU on unenhanced CT and do not show signal loss on chemical shift imaging. • Slow contrast washout.	• High uptake on F18-FDG-PET, showing 100% sensitivity and 98% specificity for differentiating malignant from benign adrenal neoplasms

Table 2: Differential diagnosis table for diffuse bilateral adrenal enlargement [82-88]

ABBREVIATIONS

ACTH: Adrenocorticotropic hormone
CAH: Congenital adrenal hyperplasia
CT: Computed tomography
FDG: Fluorodeoxyglucose
HU: Hounsfield unit
MRI: Magnetic resonance imaging
OART: Ovarian adrenal rest tumor
PET: Positron emission tomography
TART: Testicular adrenal rest tumor

KEYWORDS

Congenital adrenal hyperplasia; adrenogenital syndrome; radiology; imaging; prostate; CT; computed tomography; sonography; ultrasound; MRI; magnetic resonance imaging

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