INTERHOSPITAL CONFERENCE CASE 3

136 ปี ศิริราช

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Patient Profile

ผู้ป่วยชาย อายุ 33 ปี

อาการสำคัญ : ปัสสาวะแสบขัดเป็นๆหายๆ 6 เดือน

ประวัติปัจจุบัน

- 2 ปีก่อน ผู้ป่วยมีอวัยวะเพศแข็งตัวร่วมกับมีอาการปวดขณะหลับเป็นบางครั้งจนต้องตื่นนอน ตอนเช้ามีอวัยวะเพศแข็งตัวได้ปกติ
- 6 เดือนก่อน ผู้ป่วยมีปัสสาวะแสบขัด เป็นๆหายๆ ไม่มีไข้ มาโรงพยาบาล ได้ตรวจกับศัลยแพทย์ทางเดินปัสสาวะตรวจพบ hypospadias และ คลำไม่พบ testes ร่วมกับส่งตรวจเพิ่มเติมพบความผิดปกติจึงปรึกษา endocrine ร่วมประเมิน

ประวัติปัจจุบัน

- มีอาการอ่อนเพลียบ้างตั้งแต่อายุ 12ปี ถึงวัยทำงาน พักแล้วหายเป็นปกติ
- ไม่มีคลื่นไส้อาเจียน หน้ามืดหรือวูบเป็นๆหายๆมาก่อน
- สีผิวพอเดิม ไม่รู้สึกผิวคล้ำขึ้น
- น้ำหนักตัวคงที่
- ไม่เคยตรวจพบความดันโลหิตสูงหรือต่ำ

ประวัติพัฒนาการ

- คลอดครบกำหนด น้ำหนักแรกเกิดประมาณ 3000 กรัม หลังคลอดมีตัวเหลือง ได้รับการส่องไฟและทำการเปลี่ยนถ่ายเลือดร่วมด้วย นอนโรงพยาบาลประมาณ 1 เดือน ได้ยากลับมารับประทานต่อที่บ้านหลังจากนั้นไม่ได้ไปพบแพทย์ต่อเนื่อง
- ตั้งแต่จำความได้ผู้ป่วยคลำไม่ได้ลูกอัณฑะบริเวณถุงอัณฑะทั้ง 2 ข้าง ไม่เคยไปรักษาที่ใด ไม่มีคลำได้ก้อนที่ท้อง หรือขาหนีบ แต่ยังสามารถยืนปัสสาวะได้ปกติ ไม่เคยมีประวัติติดเชื้อทางเดินปัสสาวะ

ประวัติพัฒนาการ

- อายุ 6 ปี เริ่มมีหนวด ขนรักแร้ ขนหน้าแข้ง ขนอวัยวะเพศ ลักษณะเป็นขนอ่อน ขณะนั้นตัวสูงที่สุดในห้องเรียน
- อายุ 10 ปี เริ่มมีอวัยวะเพศชายแข็งตัวและขนาดใหญ่ขึ้น หยุดสูง มีกล้ามแขนชัดขึ้น เสียงแตกห้าวขึ้น
- อายุ 12 ปี มีหนวด เครา และขนที่อวัยวะเพศเยอะหนาขึ้น ต้องโกนหนวดและเครา มีผมร่วง

ประวัติพัฒนาการ

- อายุ 12 ปี มีหนวด เครา และขนที่อวัยวะเพศเยอะขึ้น เป็นขนหนาขึ้น ต้องโกนหนวดและเครา สัปดาห์ละ 1-2 ครั้ง สังเกตว่ามีผมร่วงเริ่มจากบริเวณหน้าผากและกลางกระหม่อม
- เรียนจบปริญญาตรี เกรดเฉลี่ยประมาณ 3

ประวัติพัฒนาการทางเพศ

- ผู้ป่วยมีแฟนเป็นเพศชาย มีเพศสัมพันธ์ได้ มีสารคัดหลั่งเป็นน้ำขุ่นๆ

ประวัติอดีต

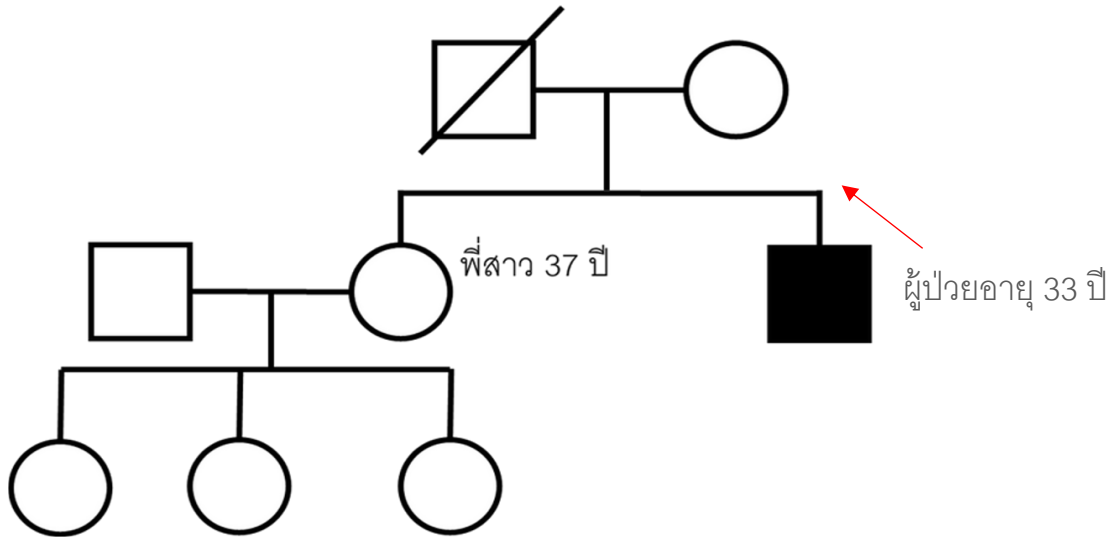
- เคยผ่าตัดไส้ติ่งเมื่อ 5 ปีก่อนไม่มีภาวะแทรกซ้อน
- เคยติดเชื้อ COVID-19 เมื่อ 1 ปีก่อน ได้รับการรักษาแบบผู้ป่วยนอก ไม่มีภาวะแทรกซ้อน

ประวัติส่วนตัว

- ปฏิเสธยาต้ม/ยาหม้อ/ยาสมุนไพร/ยาลูกกลอน/ยาฮอร์โมน/อาหารเสริม
- ปฏิเสธดื่มสุรา สูบบุหรี่หรือใช้สารเสพติดอื่นๆ
- ไม่มียาที่รับประทานเป็นประจำ

ประวัติครอบครัว

- บิดาสูง 160 เซนติเมตร เสียชีวิตจากอุบัติเหตุขณะอายุ 40ปี
- มารดาสูง 165 เซนติเมตร ปัจจุบันอายุ 57ปี ปฏิเสธโรคประจำตัว
- Midparental height 156 ± 8 เซนติเมตร (148-164 เซนติเมตร)
- มีพี่สาว 1 คน สูง 171 เซนติเมตร ปัจจุบันอายุ 37 ปี ปฏิเสธโรคประจำตัว
- พี่สาวมีบุตรสาว 3 คน ทุกคนแข็งแรงดี
- ปฏิเสธการแต่งงานในเครือญาติ



Physical examination

Vital signs:	BT 36.9°C, BP 106/64 mmHg, PR 88 bpm, RR 20 /min
	BW 54 kg, Ht 147 cm, BMI 24.99 kg/m2, Arm span 147 cm, upper:lower 77.5/69.5 = 1.1
GA:	Normosthenic built, not pale, no jaundice, no edema, no Cushingoid appearance,
	no acromegalic feature, short stature, no cubitus valgus
HEENT:	No thyroid gland enlargement
CVS:	Regular and equal peripheral pulse, no heaving, no thrill, normal S1S2, no murmur
RS:	Equal breath sound, no adventitious sound
Abd:	No distension, soft, no tenderness, liver and spleen not palpable, no palpable mass
NS:	Alert and cooperative

Physical examination

Breast:	No gynecomastia
Hair:	Male pattern hair loss, normal axillary hair
Skin:	No hyperpigmentation at gingivae, oral mucosa, hyperpigmentation at palmar creases, knuckles
Genitalia:	Pubic hair Tanner stage 5
	Penile length 5 cm, midshaft hypospadias with 60-90 degree ventral curvature
	Testes are not palpable at scrotal sac and inguinal area
	Well-formed pigmented scrotum, normal rugae

136 ปี ศิริราช

Problem List

Problem List

A 33-year-old man with

1. History of male precocious puberty
2. Proportionate short stature
3. Testes are not palpable
4. Midshaft hypospadias
5. Hyperpigmentation at palmar creases, knuckles
6. Male-pattern hair loss

Lab Investigation

- CBC: Hb 16.9 g/dL, Hct 50.5%, WBC 6910 /mm3, N 49.9%, L 41.7%, Plt 239,000/mm3
- LFT: AST 19 U/L, ALT 29 U/L, ALP 59 U/L, TB 1.54 mg/dL, DB 0.37 mg/dL , Alb 4.9 g/dL, Glb 3.6 g/dL
- Blood sugar 77 mg/dl, Cholesterol 174 mg/dl, HDL 28 mg/dl, LDL 115 mg/dl, Triglyceride 155 mg/dl
- Blood chemistries: Na 137 mmol/l, K 4.1 mmol/l, CL 103 mmol/l, HCO3 23 mmol/l, BUN 15 mg/dl,

  Cr 0.98 mg/dl
- UA: pH 7.5, Sp.gr. 1.010, WBC 0-1/HPF, RBC 0-1/HPF, Protein neg, Glucose neg, Ketone neg

136 ปี ศิริราช

Investigation

Investigation

136 ปี ศิริราช

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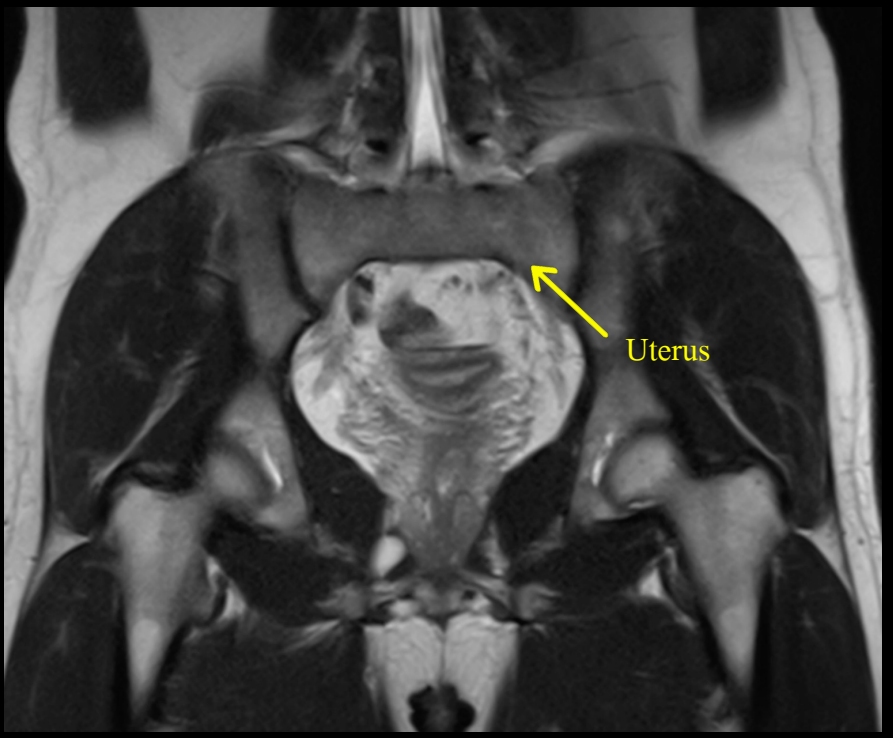
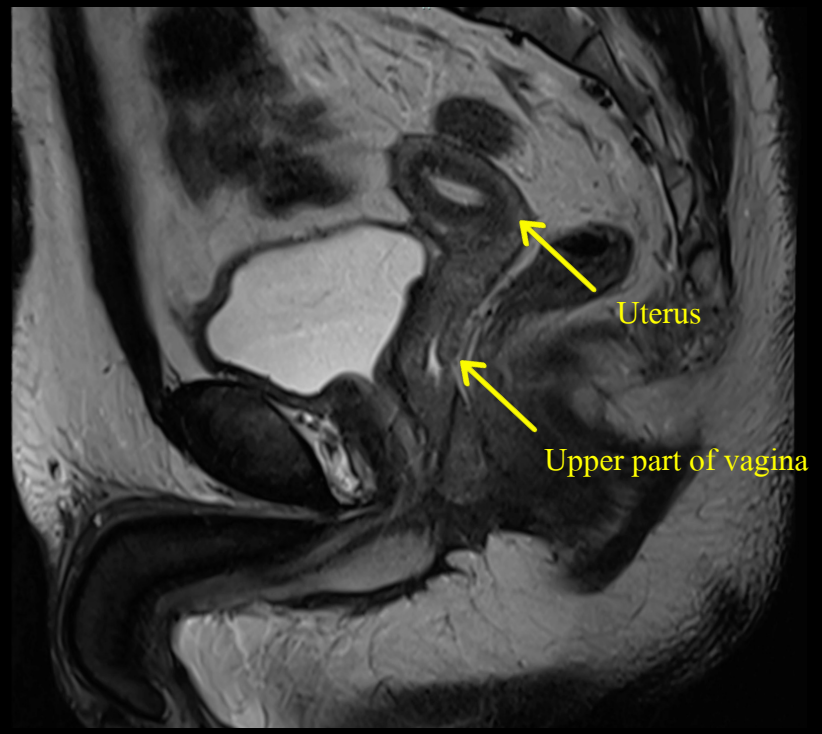
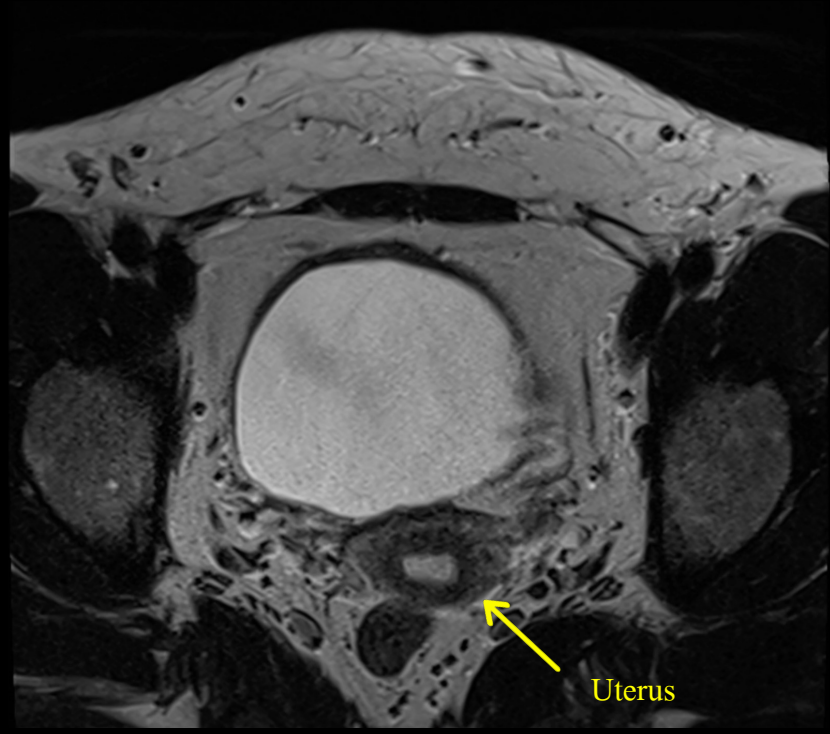
Present uterus, cervix and upper part of vagina

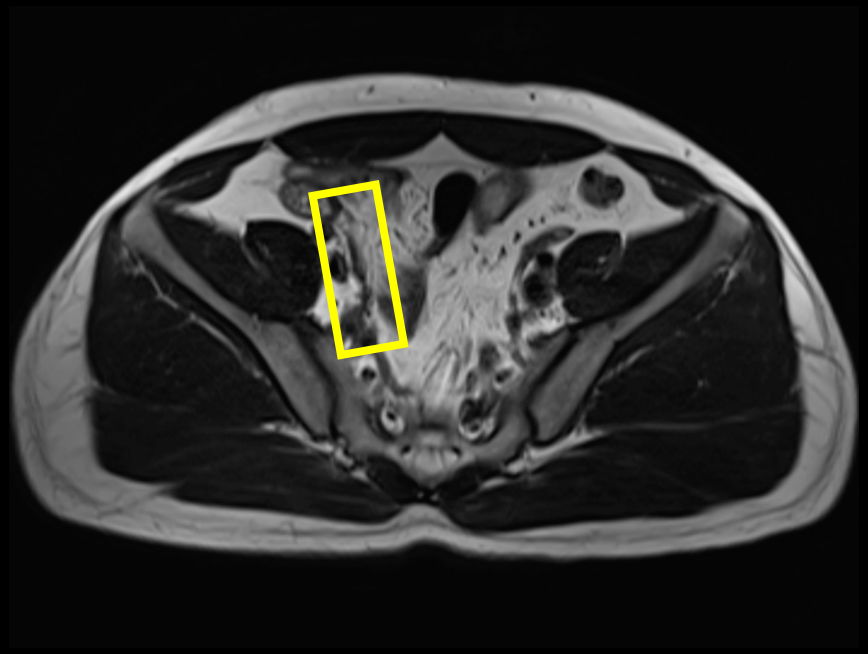




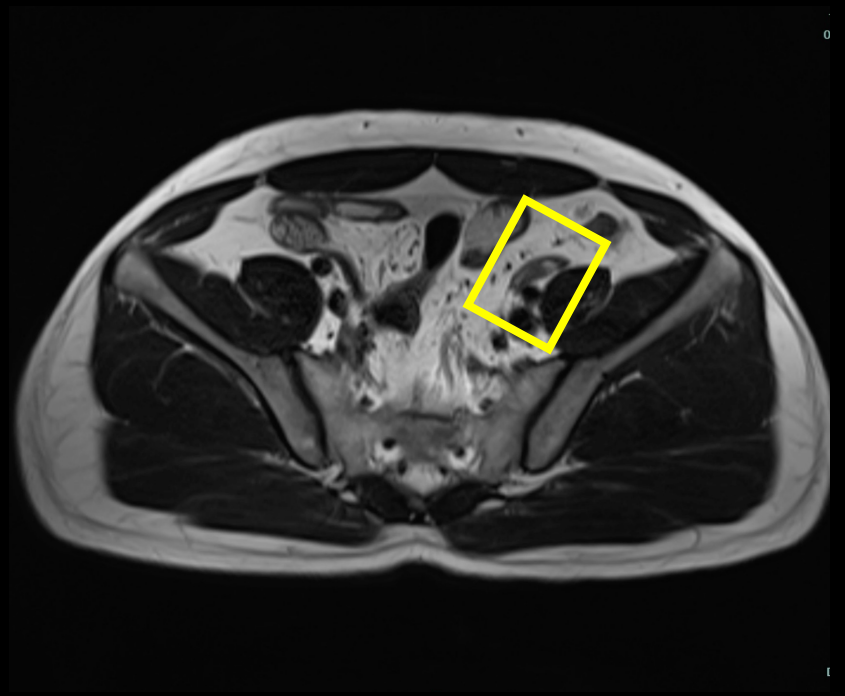


Uterus size 2.04 x 2.99 cm

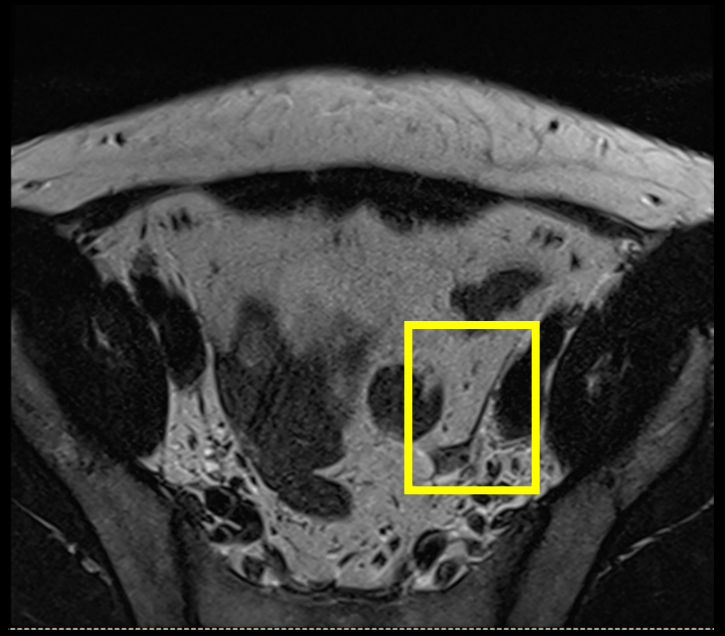
Present ovaries in normal position



Rt.ovary 1.4x2.5 cm

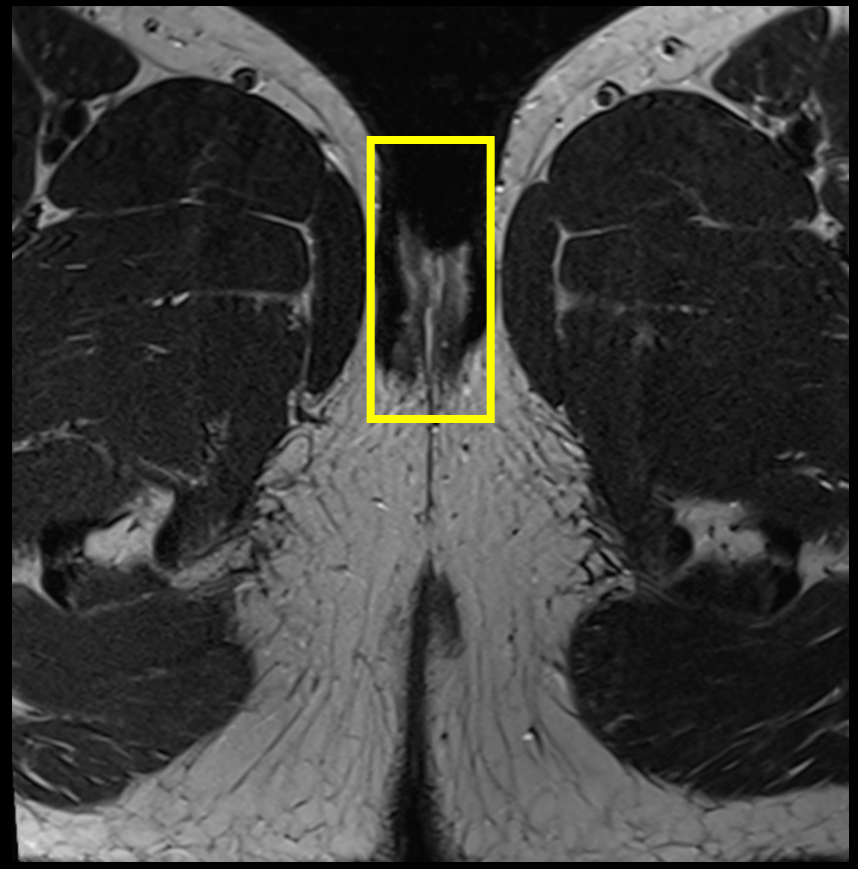


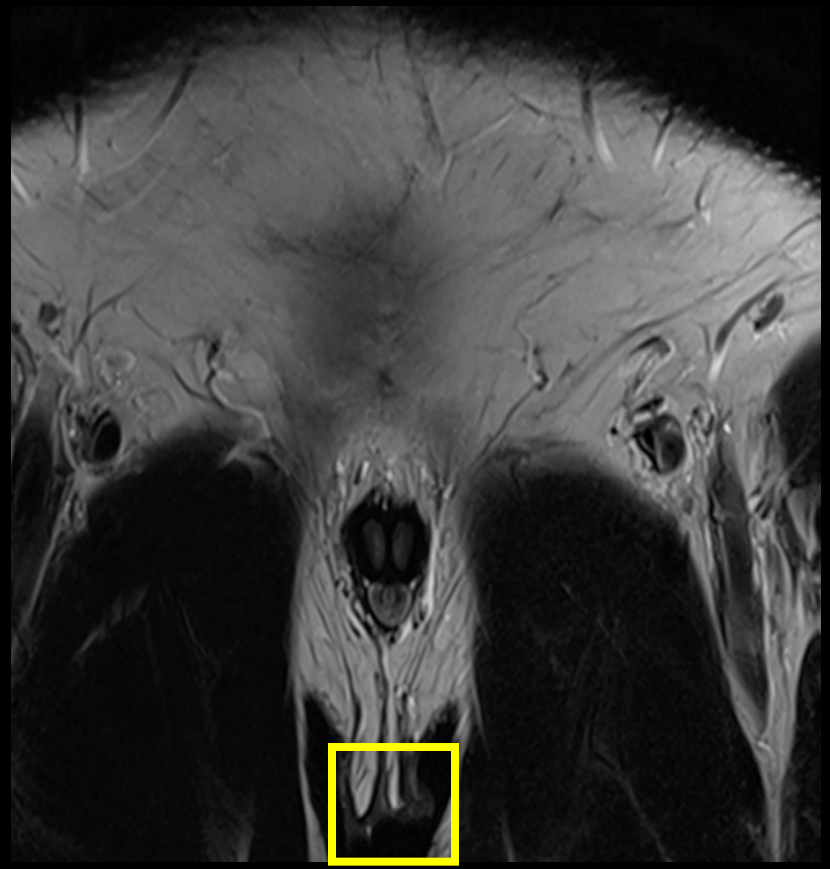
Lt.ovary 2.3x0.8 cm



Fallopian tube

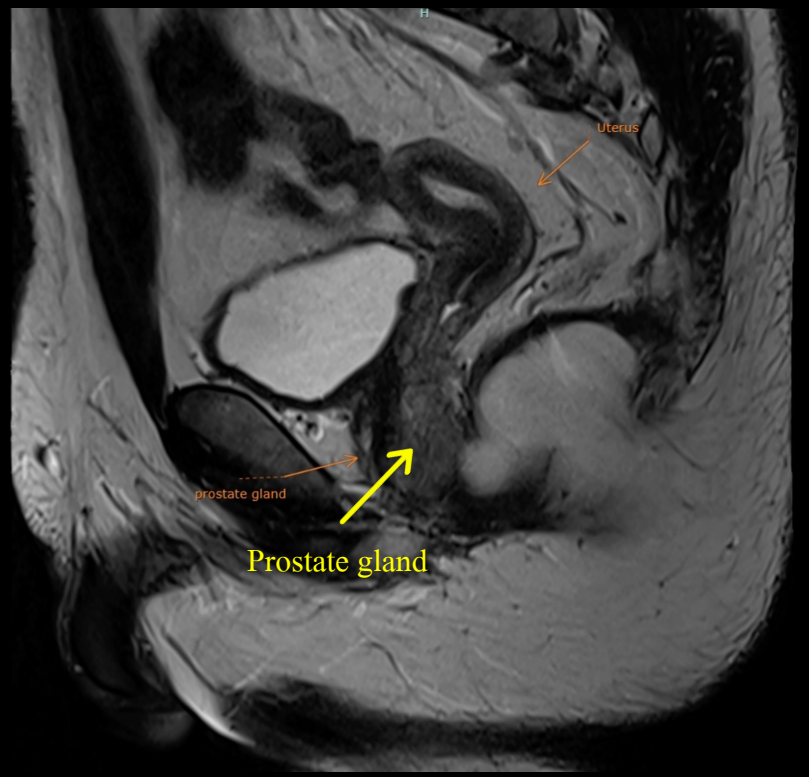
Empty scrotal sac

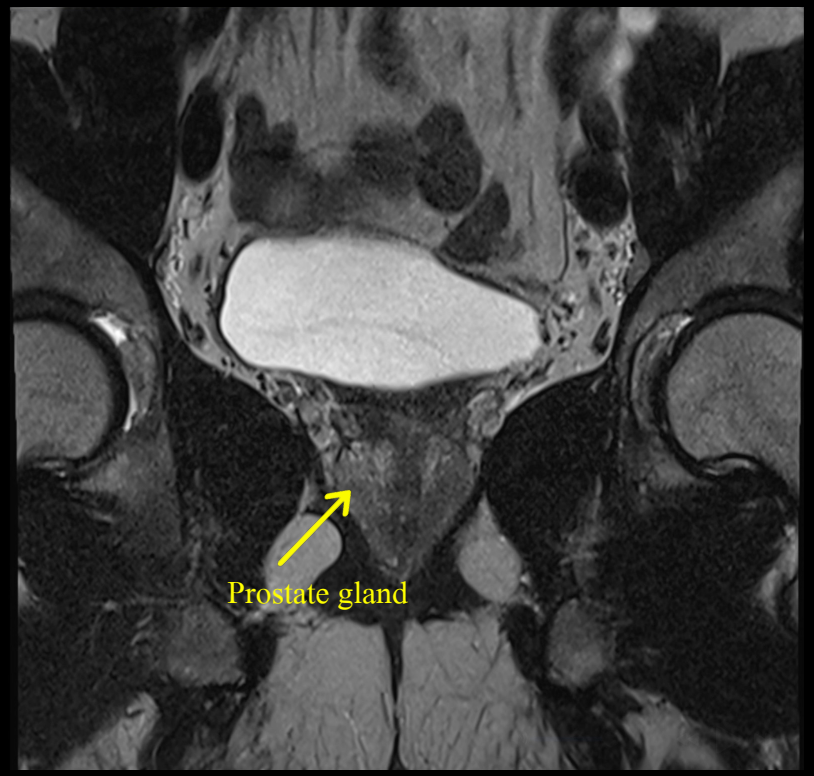


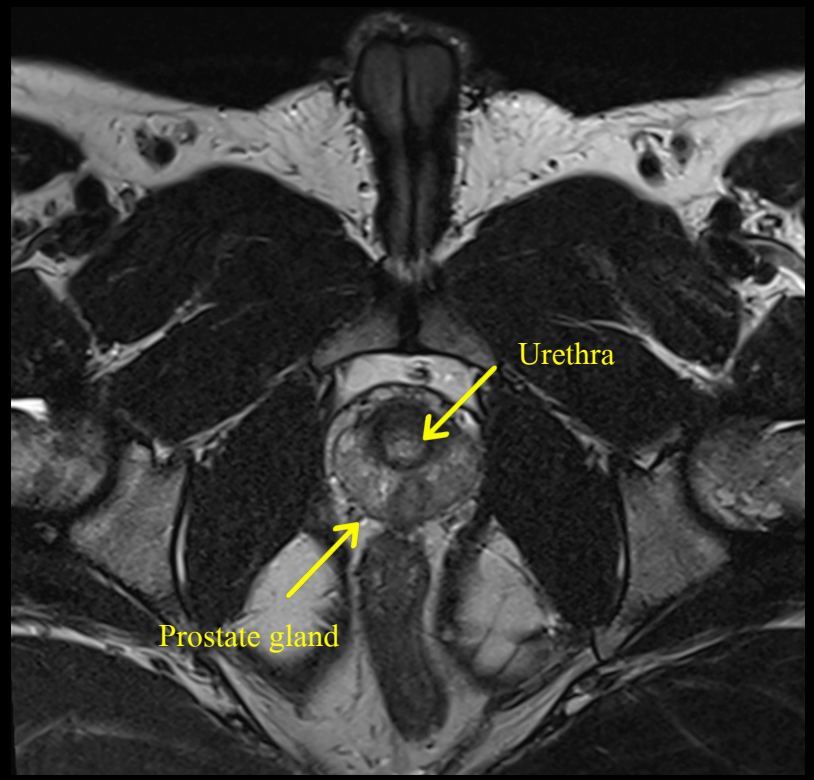


Can’t identify seminal vesicle, ejaculatory duct, vas deferens

Present prostate gland slightly below bladder neck



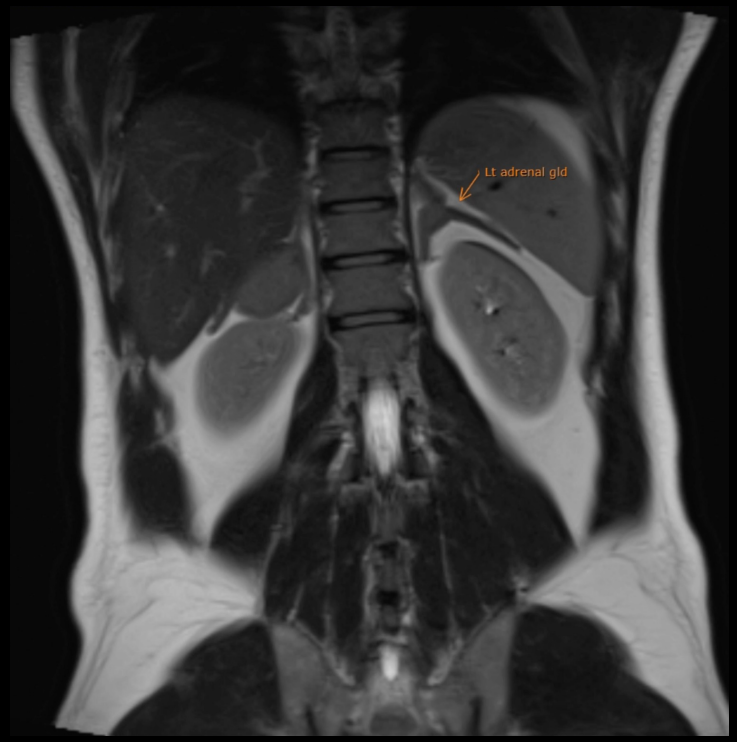


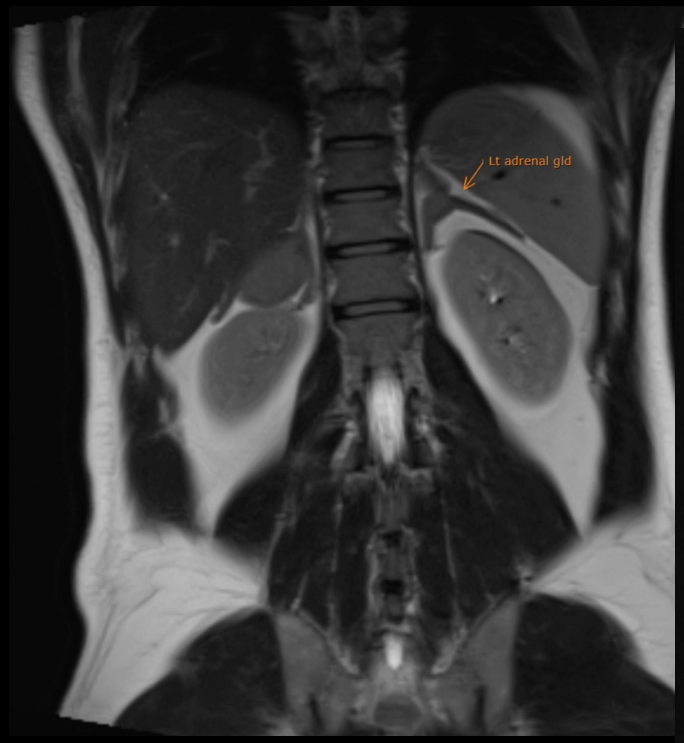


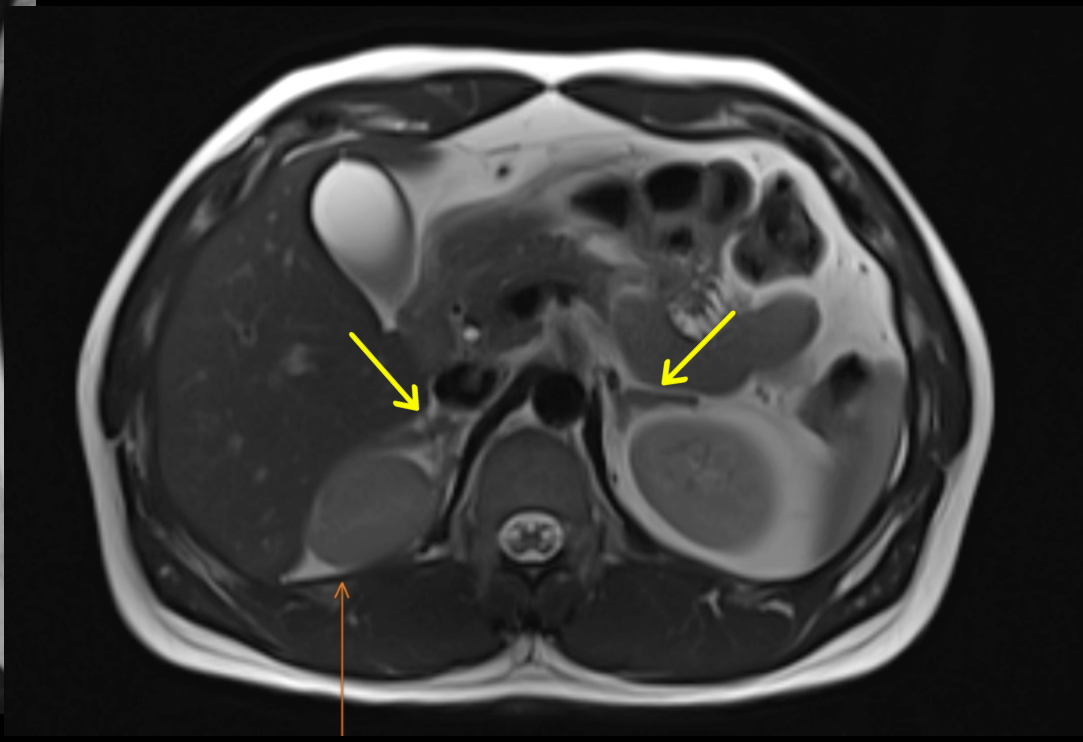
T2 Hyposignal intensity of peripheral zone of prostate gland

Volume of prostate gland 3.2x2.6x2.6x0.5 = 10.8 ml

Adrenal glands: Bilateral adrenal thickening

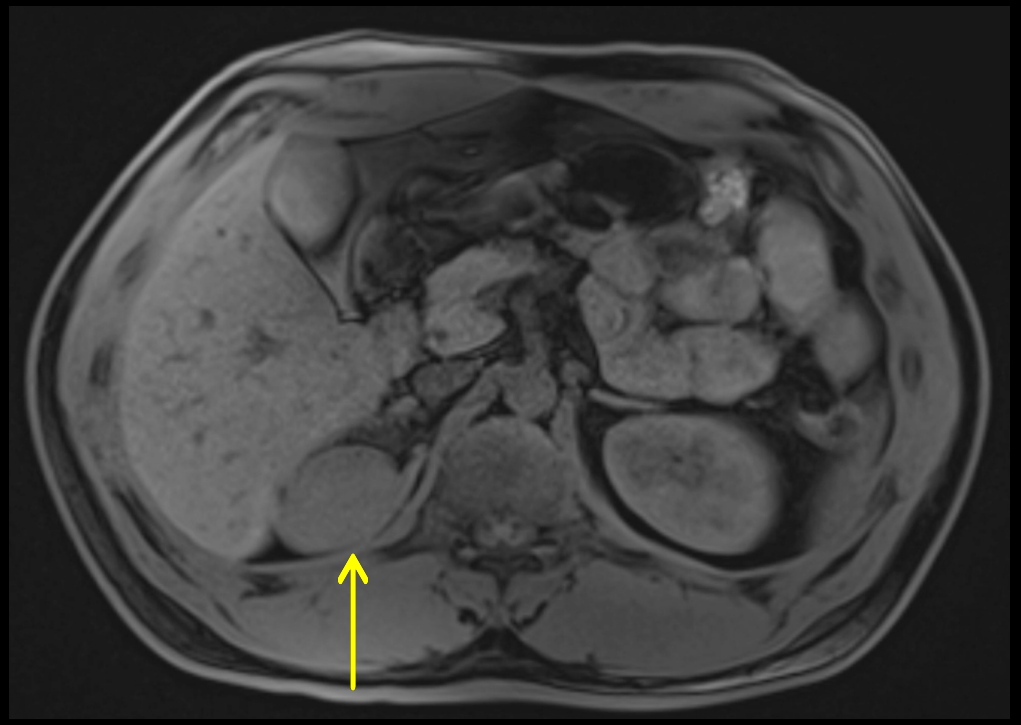


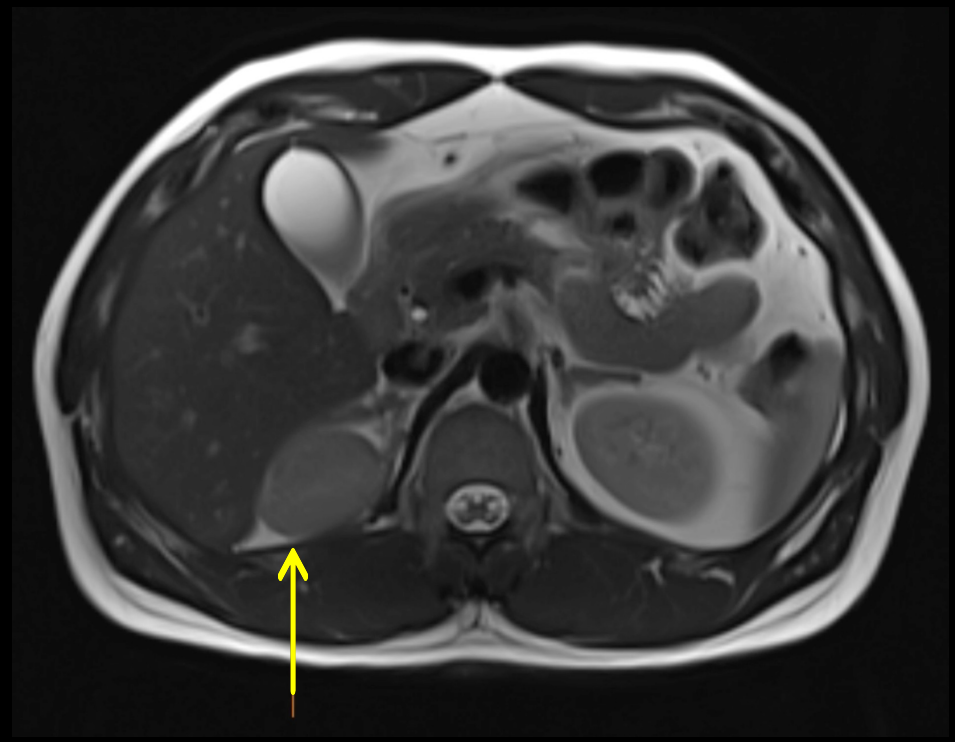




Bilateral adrenal thickening

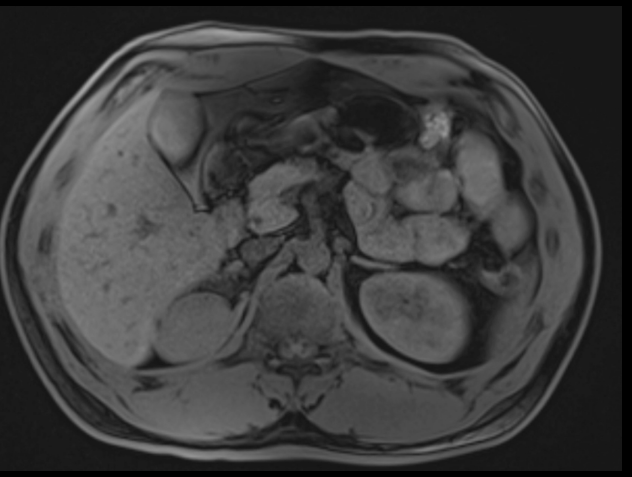
Adrenal tumor



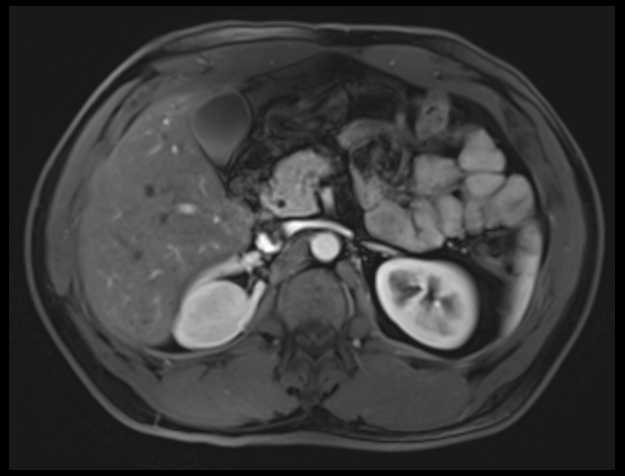


Rt.adrenal tumor : well-defined homogeneous density size 4.1x3.0x3.6 cm, hypo SI in T1, intermediate in T2

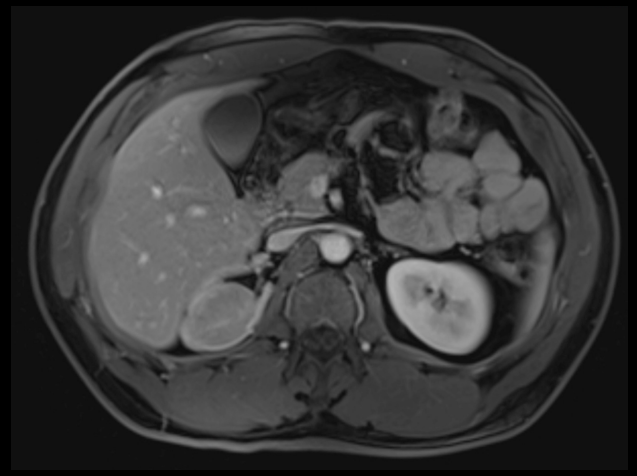
Adrenal tumor



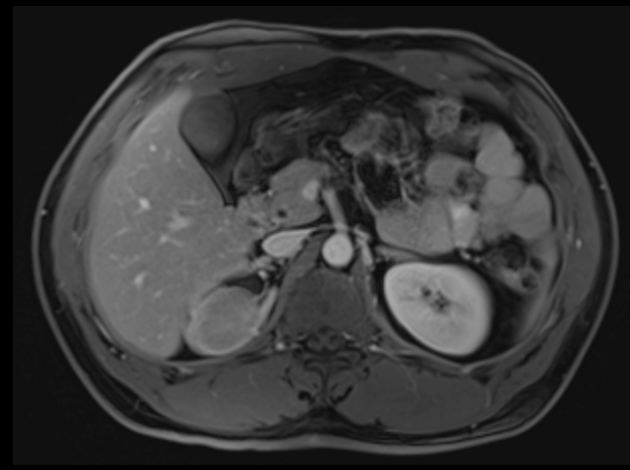
Pre Gd



A phase



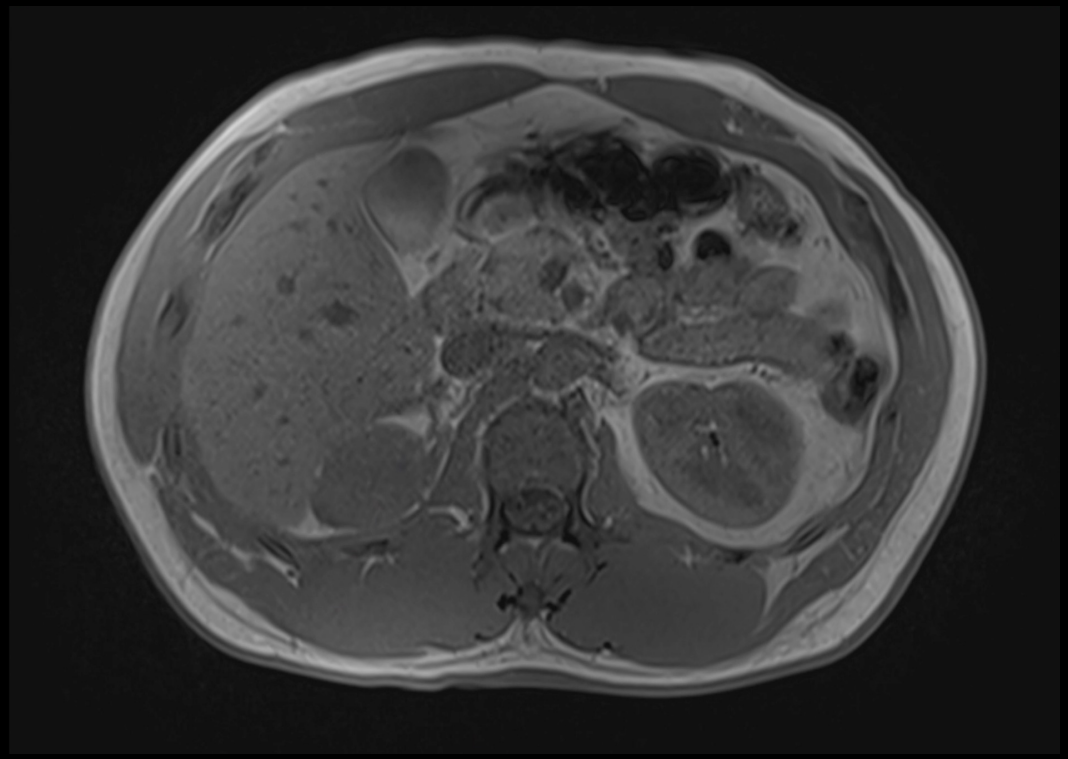
Delay 70 s

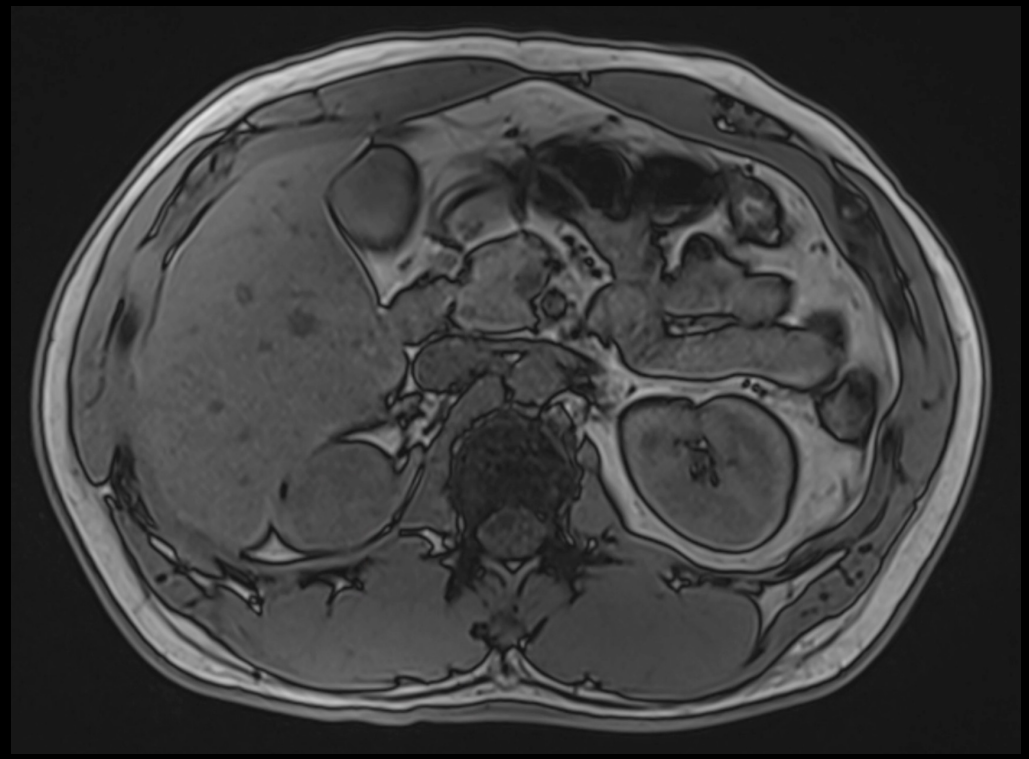


Delay 120 s

Rt.adrenal tumor: well-defined 4.1x3.0x3.6 cm hypervascular mass, no vascular invasion

Adrenal tumor





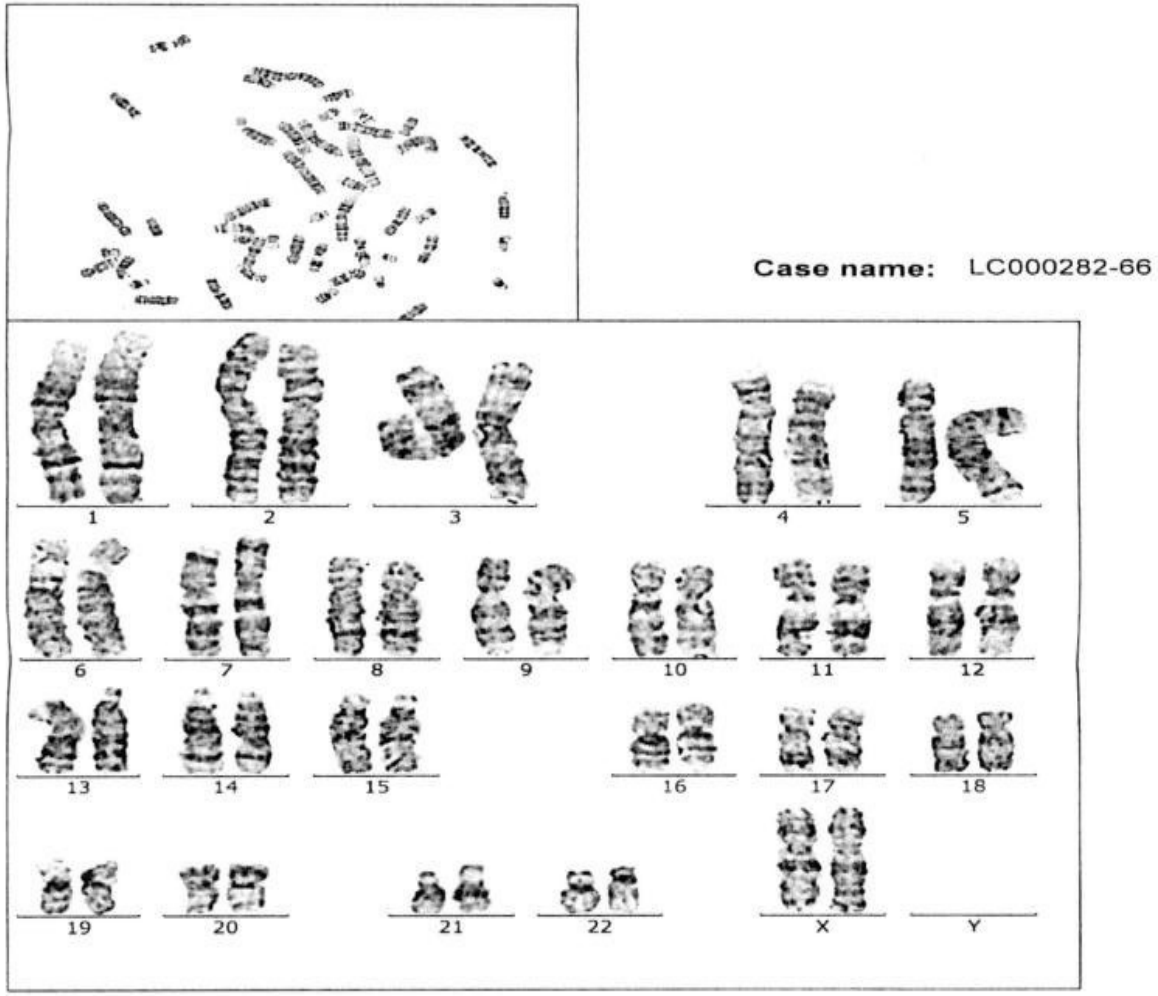
No signal dropout on opposed-phase

Rt.adrenal tumor: A hypervascular mass DDx adenoma, hyperplastic nodule, less likely pheochromocytoma or malignancy

MRI whole abdomen with Gd

- Bilateral diffuse adrenal enlargement with presence of a uterus in a phenotypic male
- No undescended testes could be identified
- Cervix and upper vagina are observed, normal appearance of penis is observed
- Left ovary 2.5x0.7 cm. Possible atrophic right ovary at right side of pelvic cavity is seen
- Presence of prostate gland 2.4x3.1x2.9 cm
- A hypervascular right adrenal mass (4.1x3.0x3.6 cm) with no signal dropout on opposed phase, mild hyperintense on T2WI, mild restricted diffusion on high b-value DWI

Karyotype


Case name: LC000282-66
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FISH Study

- 46 XX

REPORT

CHROMOSOME ANALYSIS :

Date of culture	Number of cells counted & chromosomal complement						
	< 45	45	46	47	48	> 48	Total
02 Aug 2023							20

KARYOTYPE ANALYSIS :

In situ hybridization with probe specific to DXZ1 locating on the centromere of chromosome X and SRY gene on Yp11.3, was performed on the cells prepared from peripheral blood. The 20 hybridized metaphases showed two signals on centromere of chromosome X. There was no signal of SRY gene on the metaphases.

Lab Investigation

- Total Testosterone 7.53 ng/mL (2.49-8.36)
- SHBG 13.3 nmol/L (18.3-54.1)
- Estradiol 33 pg/mL
- LH < 0.09 mIU/mL
- FSH 0.11 mIU/mL

Lab Investigation

- Total Testosterone 7.53 ng/mL (2.49-8.36)
- Free testosterone = 24.7 ng/dL = 247 pg/mL = 3.28 %
- Free androgen index = total testosterone/ SHBG x 100

  = 26.1/13.3 x 100 = 196.24%

Testosterone	
Healthy non obese men	66-309 pg/mL
Women	0.86- 10.67 pg/ml

Lab Investigation

Female E2 range		
Follicular	30.9-90.4	pg/mL
Ovulation	60.4-533	pg/mL
Luteal	60.4-232	pg/mL
Postmenopausal	< 5-138	pg/mL

Female LH range		
Follicular	2.4-12.6	mIU/mL
Ovulation	14.0-95.6	mIU/mL
Luteal	1.0-11.4.	mIU/mL
Postmenopausal	7.7 - 58.5	mIU/mL

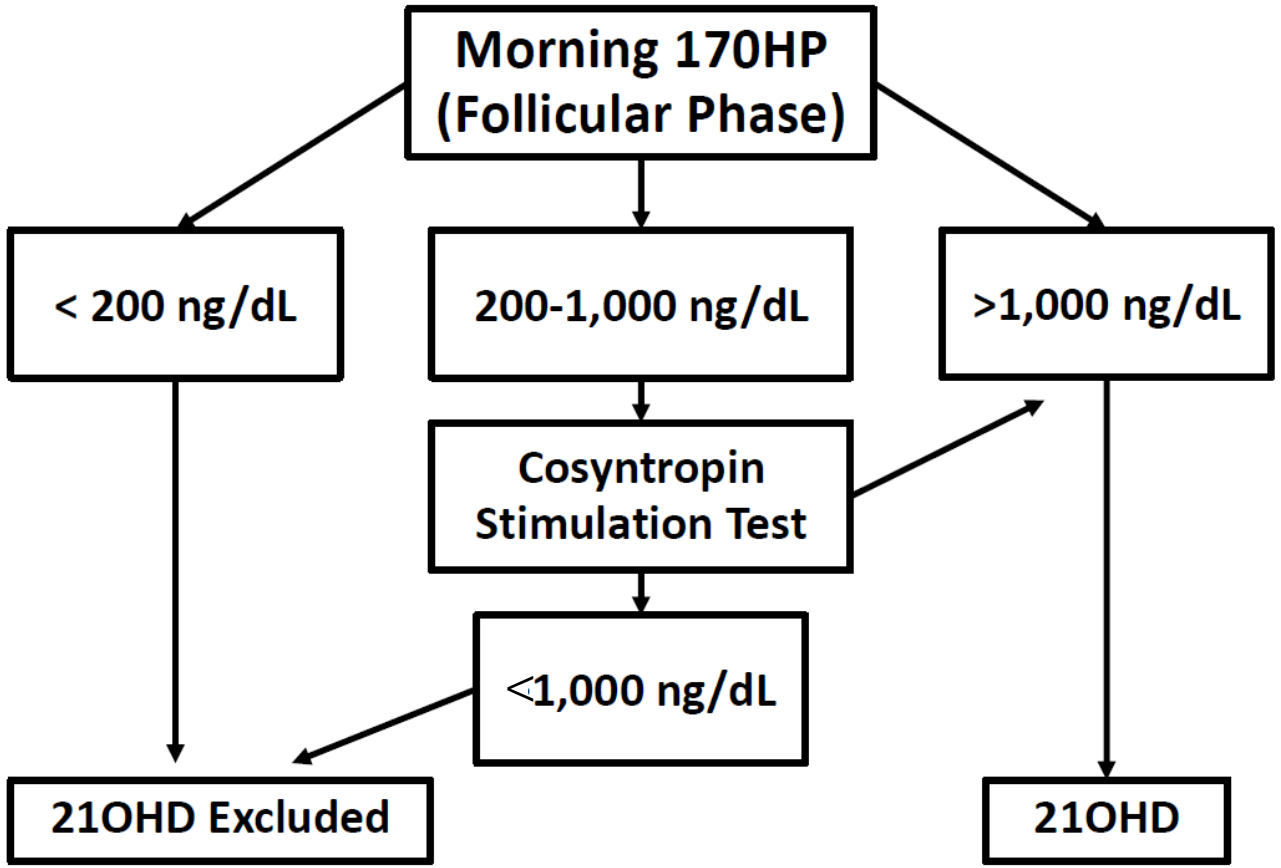
Female FSH range		
Follicular	3.5-12.5	mIU/mL
Ovulation	4.7-21.5	mIU/mL
Luteal	1.7-7.7	mIU/mL
Postmenopausal	25.8-134.8	mIU/mL

17 OH progesterone range		
Males	0.37-2.38	ng/mL
Females		
Follicular	0.32-0.82	ng/mL
Luteal	0.79-3.29	ng/mL

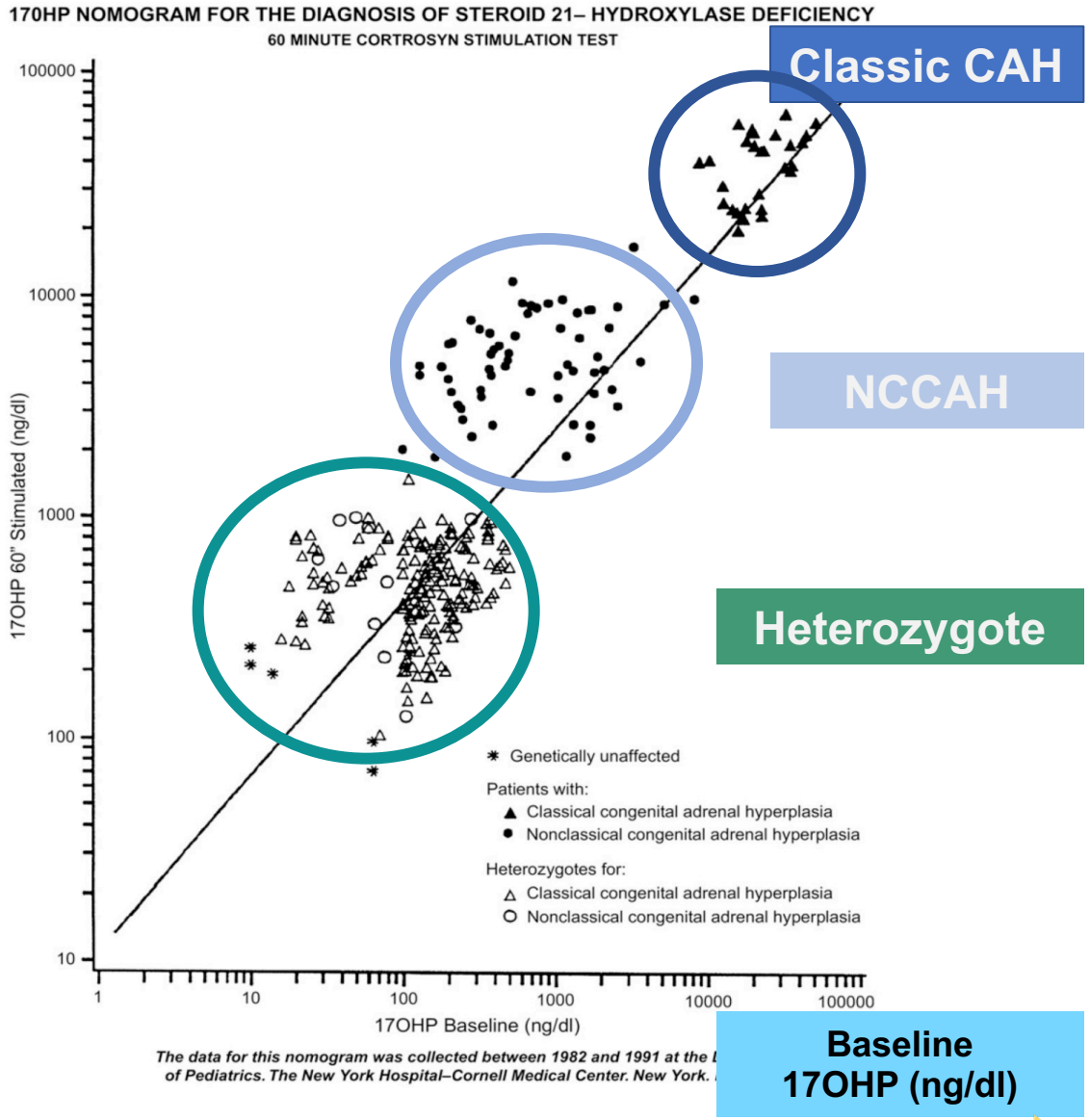
Lab Investigation

- 17 OH Progesterone >12,632 ng/dL

Diagnosis of 21OHD



Stimulated 17OHP (ng/dl)



Classic CAH

NCCAH

Heterozygote

Baseline 17OHP (ng/dl)

Speiser PW. J Clin Endocrinol Metab 2018.

Lab Investigation

- Progesterone 17.70 ng/ml

Progesterone range	
Males	<0.05-0.149 ng/mL
Females	
Follicular	<0.05-0.193 ng/mL
Ovulation	0.055-4.14. ng/mL
Luteal	4.11-14.5 ng/mL

Lab Investigation

- 8 AM Cortisol 5.1 ug/dL
- ACTH 247.6 pg/ml

Cortisol	
Morning hrs.(6-10 a.m.)	6.02-18.4 ug/dl
Afternoon hrs.(4-8 p.m.)	2.68-10.5 ug/dl
ACTH	4.7 - 48.8 pg/ml

250 mcg ACTH stimulation test

Time	0 min at 08.30	30 min	60 min
Cortisol(mcg/dL)	4.3	3.4	4.1
17-OH progresterone(ng/dL)	>12,656	-	>12,656
DHEAs(mcg/dl)	990	-	>5,000
Testosterone(ng/ml)	7.97	-	8.3
Progesterone(ng/ml)	7.71	-	17.70

Lab Investigation

- DHEAS > 990 ug/dl (160-449)

Lab Investigation

- AMH 2.29 ng/mL (0.77-14.5)
- PSA 0.251 ng/mL

AMH range		
Males	0.37-2.38	ng/mL
Females		ng/mL

PSA	0-4 ng/mL

Lab Investigation

- TSH 3.073 uIU/mL
- Prolactin 14.68 ng/mL

TSH	0.35-4.94 uIU/mL
Prolactin	3.46-19.40 ng/mL

Lab Investigation

- Beta hCG < 1.20 mIU/mL (0-3)
- AFP 1.59 ng/mL (0-8.78)
- LDH 168 U/L (125-220)

PAC/DRC (Supine)

- PAC 11.90 ng/dl (1.17-23.6)
- DRC 25.77 uIU/mL (2.8-39.9)

Urine metanephrine/normetanephrine

24 Hr Urine	Day 1	Day 2
Metanephrine (<350 ug/day)	177.38	219.91
normetanephrine (<600 ug/day)	102.59	114.28
Volume (mL)	3400	3100
Creatinine (mg/kgIBW)	23.99 Adequate	31.05 Adequate

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Discussion

Problem List

A 33-year-old phenotypic male

1. 46,XX DSD with male type external genitalia and presence of uterus, cervix, upper vagina, left ovary and prostate gland
2. History of precocious male puberty
3. Proportionate short stature, skin hyperpigmentation, male-pattern hair loss, non-palpable testes and hypospadias
4. Elevated 17 OH Progesterone level and ACTH level with low cortisol level
5. Bilateral adrenal gland enlargement with right adrenal mass 4.1x3.0x3.6 cm

Phenotypic male with nonpalpable testis

Present Müllerian structures

- 46,XX DSD
  - 21-hydroxylase deficiency (CYP21A2)
  - 11-hydroxylase deficiency (CYP11B1)
  - 3β-HSD2 deficiency (HSD3B2)
  - POR deficiency (POR)
  - Androgen-secreting tumors of the ovary or adrenal gland
  - Aromatase deficiency (CYP19A1)
- Ovotesticular DSD
- 45,X/46,XY mosaicism

Absent Müllerian structures

- 46,XY
  - Bilateral Cryptorchidism with hypospadias
  - Vanishing Testis
- 46,XY DSD
  - 17βHSD type 3 deficiency
  - 5α reductase type 2 deficiency
  - Partial androgen insensitivity syndrome
  - Partial gonadal dysgenesis
  - Ovotesticular DSD
  - 45,X/46,XY mosaicism

Presence of 3 pathogenic variants in CYP21A2 supporting the diagnosis of CAH

Method	This patient 's genotype	Zygosity
Common mutation screening by ASA	Intron2 genotype ☑ Intron2 (656) A/C>G [Pathogenic]	Homozygous
	Exon 1 genotype ☑ P30L [Pathogenic]	Heterozygous
	Exon 3 genotype ☑ G110Δ8nt [Pathogenic]	Heterozygous

Common mutations in 21-hydroxylase deficiency.

Mutation	Location	Alteration	Phenotype
Partial or Complete Deletion	Variable	Deletion	SW
P30L	Exon 1	Missense	NC
656A/C-G	Intron 2	Aberrant splicing	SW, SV
G110Δ8nt	Exon 3	Deletion 8 bases	SW
I172N	Exon 4	Missense	SV
I236N + V237E + M239K	Exon 6	Missense x3	SW
V281L	Exon 7	Missense	NC
Q318X	Exon 8	Nonsense	SW
R339H	Exon 8	Missense	NC
R356W	Exon 8	Missense	SW, SV
P453S	Exon 10	Missense	NC
R483P	Exon 10	Missense	SW

SW, salt wasting; SV, simple virilizing; NC, nonclassical.

R.J. Auchus, A.Y. Chang / Best Practice & Research Clinical Endocrinology & Metabolism 24 (2010) 219–242

Definite Diagnosis

46,XX 21-hydroxylase deficiency

Congenital adrenal hyperplasia (Simple virilizing form) with Right adrenal mass with prostate gland

Forms of 21-hydroxylase deficiency CAH

Forms of 21-Hydroxylase Deficiency

Phenotype	Classic Salt Wasting	Simple Virilizing	Nonclassic
Age at diagnosis	Newborn to 6 mo	*Female:* Newborn to 2 yr *Male:* 2-4 yr	Child to adult
Genitalia	*Female:* Ambiguous *Male:* Normal	*Female:* Ambiguous *Male:* Normal	*Female:* Virilized *Male:* Normal
Incidence	1:20,000	1:60,000	1:1000
Hormones			
Aldosterone	Reduced	Normal	Normal
Renin	Increased	Normal or increased	Normal
Cortisol	Reduced	Reduced	Normal
17-OHP	>5000 ng/dL	2500-5000 ng/dL	500-2500 ng/dL (ACTH stimulation)
Testosterone	Increased	Increased	Variable, increased
Growth	–2 to –3 SD	–1 to –2 SD	Probably normal
21-Hydroxylase activity (% of wild type)	0	1-5	20-50
Typical *CYP21A2* mutations	Deletions, conversions, nt656g G110Δ8nt, R356W I236N, V237E, M239K, Q318X	I172N Intron 2 splice site (nt656g)	V281L P30L

ACTH, adrenocorticotropic hormone; 17-OHP, 17-hydroxyprogesterone; SD, standard deviation.

Enzyme activity **0%** **1-2%** **30-50%**

William textbook of endocrinology, 13th edition

Severity of CAH due to 21-hydroxylase deficiency

Genotype	C	B	A	0
Enzyme activity	30-50%	1-2%	0%	
Phenotype	**Non-classic CAH:**	**Classic CAH:**		
		Simple virilizing:	**Salt-wasting:**	
	cortisol (=)	cortisol ↓	cortisol ↓	
	aldosterone =	aldosterone =	aldosterone ↓	
	androgens ↑	androgens ↑↑	androgens ↑↑	

Clinical Characteristics of 46,XX Males with CAH

The 46,XX CAH patients raised as males were diagnosed late, and included cases of advanced virilization.

Table 2. Clinical follow-up characteristics of 46,XX congenital adrenal hyperplasia patients raised male

	Clinical characteristics
Age of diagnosis, median (range) in years	3 (0.1-18.3)
Age of last follow-up mean ± SD (range) in years	14.9 ± 5.7 (1-24.9)
Duration of follow-up mean ± SD (range) in years	10 ± 6.1 (0.1-24)
Distribution of patients by age of diagnosis	Newborn (n = 8)
	< 2 years (n = 7)
	Pre-schooler (n = 18)
	School-aged (n = 5)
	Adolescents (n = 5)
	Adult (≥18 years) (n = 1)
Virilization Prader stage in diagnosis	Stage 3 (n = 2) (4.5 %)
	Stage 4 (n = 13) (29.5 %)
	Stage 5 (n = 29) (65.9 %)

Table 2. Clinical follow-up characteristics of 46,XX congenital adrenal hyperplasia patients raised male

	Clinical characteristics
Median (range) age of hysterectomy and bilateral salpingoopherectomy (years) (n = 34)	7.25 (2.4-25.3)
Number of patients who had more than one operation	n = 13 (38.2 %)
Median (range) testicular prosthesis placement age (n = 11) (years)	14 (2.8-17)
Steroid treatment compliance	Good (n = 19) (42.2 %)
	Poor (n = 26) (57.7 %)
Testosterone treatment start age, mean ± SD (range) (years) (n = 21)	14 ± 1.85 (10-17)
Testosterone treatment compliance	Good (n = 18) (85.7 %)
	Poor (n = 3) (14.2 %)
Median Final height (cm) (n = 38)	149.2 (132.8-172)

SD: standard deviation

J Clin Res,*Pediatr Endocrinol*. 2021;13(2):180-186

Glucocorticoid replacement

- Lowest possible doses: Minimize risk of adrenal crises and control androgen excess
- HC: Better BMD and metabolic and CV outcome than Dex in both sexes
- Adverse effect profiles intermediate between HC and Dex

Drug	Recommended total daily dose	Divided dosing frequency (times daily)
Children		
Hydrocortisone	10-15 mg/m^2	3-4
Fludrocortisone	0.05-0.2 mg	1-2
Sodium chloride supplements	1-2 g (17-24 mEq/day) in infancy	Several
Adults		
Glucocorticoids		
Hydrocortisone	15-25 mg	2-3
Prednisone	5-7.5 mg	2
Prednisolone	4-6 mg	2
Methylprednisolone	4-6 mg	2
Modified-release hydrocortisone (Plenadren®)	15-25 mg	No published data in CAH patients, clinical experience shows that in addition to the morning dose a second GC dose is required in the evening
Modified- and delayed-release hydrocortisone (Chronocort®)[a]	15-25 mg	2 (2/3 of dose at 2300 and 1/3 of dose at 0700)[a]
Dexamethasone[b]	0.25-0.5 mg	1
Fludrocortisone	0.05-0.2 mg	1

Endocrine Reviews, 2022, Vol. 43, No. 1

Monitoring Glucocorticoid replacement

Table 6. Monitoring glucocorticoid replacement by history and clinical/technical examination (generally every 4-6 months in adults, every 3-4 months in children >18 months old)

Parameter	Goals and Comments
History	
Symptoms of adrenal insufficiency (fatigue, headache, nausea, abdominal pain, postural dizziness, frequent stress dosing)	No signs of adrenal insufficiency
Adrenal crisis prevention	Well-educated and equipped patient with knowledge of sick day rules, and possession of steroid emergency card and injection kit; medical alert identification worn at all time
Menstrual cycle	Regular menstrual cycles
Libido, erections (males)	Normal
Sexual health (females)	Pain-free intercourse
Physical examination	
Height (children)	Linear growth within target range
Pubertal development/Tanner stage (children and adolescents)	Normal pubertal development
Blood pressure	Within age- and sex-dependent reference range
BMI	Within age- and sex-dependent reference range
Cushingoid features, Striae distensae	No clinical signs of hypercortisolism
Gynecological assessment only if indicated	
Imaging	
Bone age yearly (children >2 years old/adolescents)	Bone age within 2 SD
Scrotal ultrasound every 2-5 years	No gonadal masses
Ovarian ultrasound only indicated in unexplained hyperandrogenism	
Bone mineral density every 3-5 years (adults treated with high GC doses)	Within age- and sex-dependent reference range
Others	
Semen analysis if indicated, ie, presence of TARTs (males)	Normal results (WHO guideline)
Genetic assessment and counselling	Confirmation diagnosis CAH; counselling for family planning

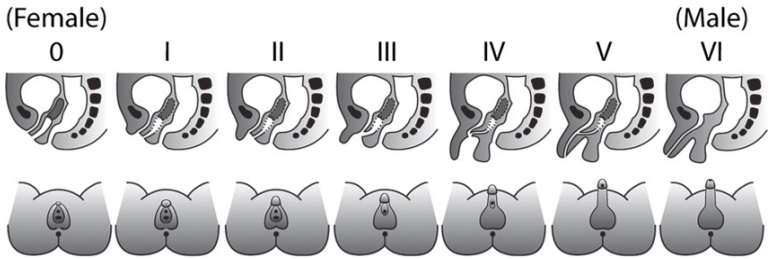
Endocrine Reviews, 2022, Vol. 43, No. 1

Monitoring Glucocorticoid replacement

Sample	Variable	Goals and Comments[a]
Serum	Androstenedione	Normal values for sex and age *(often useful to assess together with testosterone in males)*
	Testosterone	Normal values for sex and age *(assess in the context of gonadotropins and androstenedione)*
	Sex hormone–binding globulin	For calculation of free and bioavailable testosterone
	DHEAS	Low to suppressed, not a good marker of disease control, but can be used to check for compliance/adherence
	17OHP	Normal values indicate overtreatment, aim at ULN to 400-1200 ng/dL (12-36 nmol/L)
	ACTH	Not a useful parameter for disease control; normal values indicate overtreatment
	Androstenedione/Testosterone ratio	Healthy woman: <2 Women with CAH: >4 indicates testosterone mainly of adrenal origin Healthy males: <0.2 Men with CAH: >0.5 indicates testosterone mainly of adrenal origin Men with CAH: >1.0 + LH, FSH suppressed indicates testosterone only of adrenal origin due to poor disease control

Management for Severely virilized 46,XX CAH

- Treatment of Glucocorticoid Deficiency : Hydrocortisone 15-25 mg/d, Prednisolone 5-7.5 mg/d (Adult)
- Sex assignment
  - Genital appearance
    - Depend on Prader stage of virilization
      - I–III Prader Stage patients are usually assigned female
      - IV–V Prader Stages can be associated with worse feminizing surgical outcomes
  - Psychosexual considerations : genital virilization mostly develop a gender identity corresponding to sex assignment at birth
  - Potential for future fertility
  - Surgical options
- Sex hormone replacement therapy

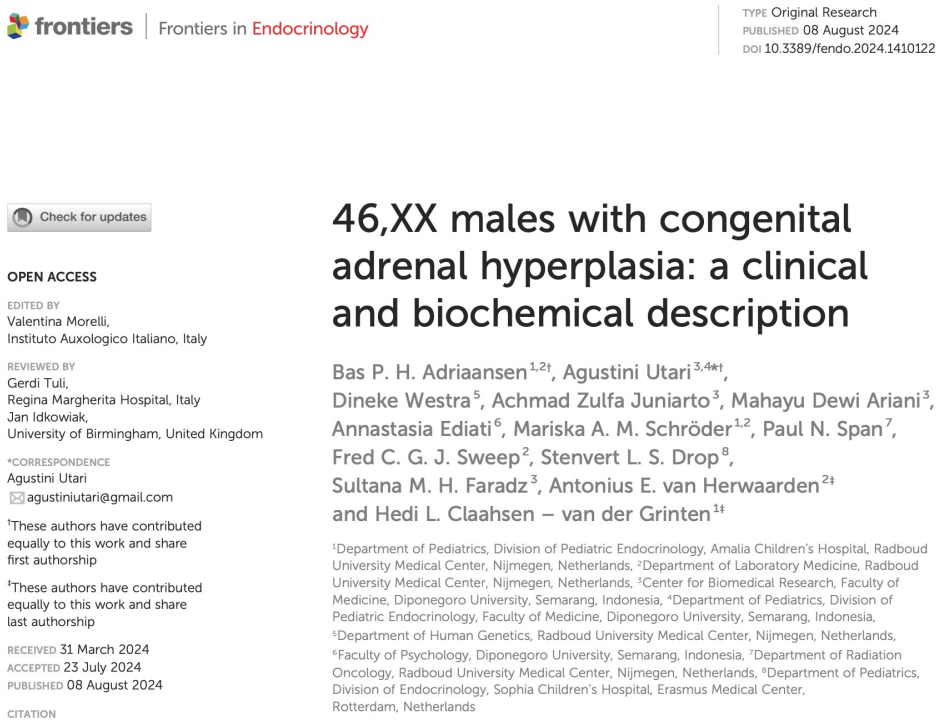


Pediatric Radiology 2022

Cera, et al.Severe hyperandrogenism in 46,XX CAH. *Int J Mol Sci*.2024,25,11779

Challenges in Treatment of 46,XX CAH Patients with Male Sex of Rearing

- Managing 46,XX male-reared CAH patients requires balancing androgen maintenance and adrenal crisis prevention, emphasizing personalized approaches and careful counseling.
- **Androgen Levels and Male Identity:** Glucocorticoid therapy, whil essential to prevent adrenal crises, reduces ACTH-driven androgen production, which is undesirable for male-reared 46,XX CAH patients.
- **Testosterone Treatment:** In some cases, testosterone is used alongside glucocorticoids to maintain male androgen levels while addressing cortisol deficiency.
- **Patient Decisions:** Patients often opt out of glucocorticoid treatment due to its feminizing effects and the lack of immediate health complaints, though they are counseled on risks and stress dosing during illness.



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46,XX males with congenital adrenal hyperplasia: a clinical and biochemical description

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The study describes nine untreated 46,XX male classic CAH patients.
Despite low cortisol levels, they survived without glucocorticoids, though the sample may be biased as other patients could have died undiagnosed.

https://doi.org/10.3389/fendo.2024.1410122

Challenges in Treatment of 46,XX CAH Patients with Male Sex of Rearing

	Glucocorticoid Treatment	No Glucocorticoid Treatment
Benefits	Maintenance and adrenal crisis prevention	Maintenance of Masculinizing effect
Disadvantage	Feminizing effect	Risk of Adrenal Crisis Adrenal size and tumor progression(?)
Further Treatment	Salpingo-oophorectomy Testosterone treatment	No further surgery

Front. Endocrinol. 15:1410122.
Senay Savas-Erdeve.J clin Res Pediatr Endocrinol 2021.
A.Khattab.Journal of steroid biochemistry&molecular biology 2017.

Management

- **Multidisciplinary Team Care:** Endocrinologist, Urologist, Psychiatrist, Geneticist
- **Glucocorticoid replacement:** Hydrocortisone 15 mg/day
- **Operation:** Laparoscopic right adrenalectomy with hysterectomy and bilateral salpingo-oophorectomy
- **Postoperative:** Testosterone replacement: Testosterone enanthate 250 mg IM q 4 weeks

Adrenal Oncocytic Neoplasms

Linn-Weiss-Bisceglia Criteria for Assessing The malignant potential of oncocytic

Criteria	Appearance
Major criteria	• Mitotic rate >5/50high power fields • Atypical mitotic figures • Venous invasion
Minor criteria	• Size > 10 cm and/or weight > 200 g • Microscopic necrosis • Capsular invasion • Sinusoidal invasion
Evaluation	• Presence of any major criteria = Oncocytic carcinoma (AOC) • Presence of any minor criteria = Oncocytic neoplasm of uncertain malignant potential (AONUMP) • Absence of all criteria = Oncocytoma (AO)

Thomas, Adrenocortical Oncocytoma, *AACE Clinical case Rep*. 2017;3(No.1)

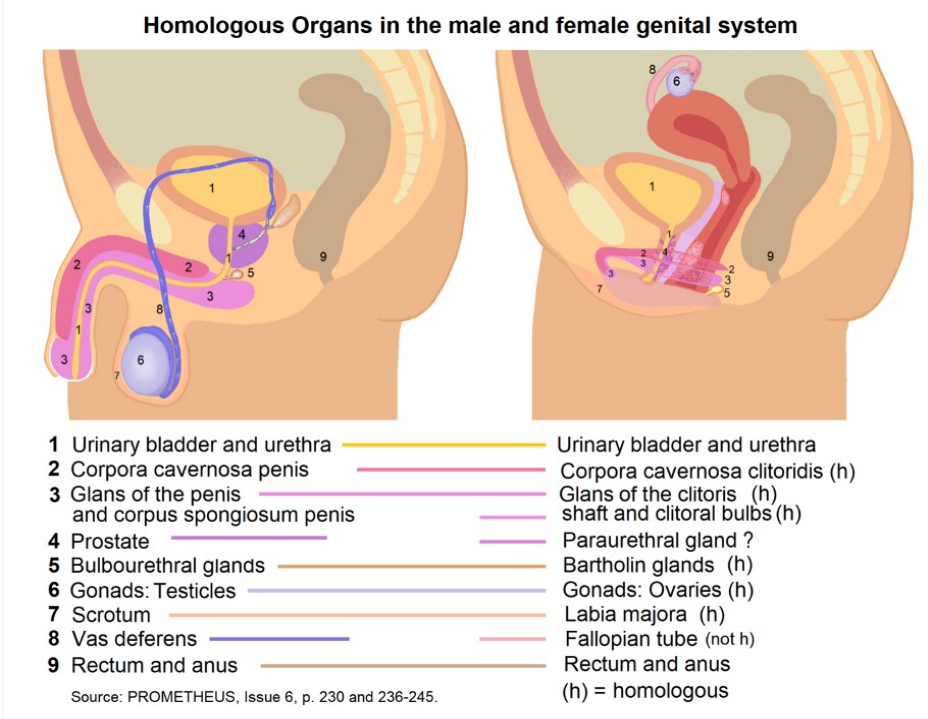
Adrenal Oncocytic Neoplasms

- These tumors are usually incidentalomas with an unpredictable malignant potential.
- Surgical resection remains the mainstay of treatment.
- Oncocytoma and Oncocytic neoplasm of uncertain malignant potential have an excellent prognosis and a low mortality rate, with only three cases of recurrence reported in the literature and one metastatic case four years after first adrenal surgery.
- Oncocytic carcinoma carries a high risk of local relapses, distant metastasis, and a significantly higher mortality rate (30%).

J. Clin. Med. 2023, 12, 6925.

Prostatic tissue in 46,XX CAH

- Rare
- Patients with Prader type III, IV, and V external genitalia or with excessive adrenal androgens stimulation before the 16th week of fetal development, the paraurethral gland may develop into identical male prostate tissue
- Reported 18 patients with 46,XX CAH having prostatic tissue.
- Diagnosis was confirmed by tissue in 7 cases
- Only one presented with adenocarcinoma of the prostate gland
- 17OHP level 1200 ng/dL to >24780 ng/dL.
- Total testosterone 2.59 to 9.51 ng/mL.



Clin Case Rep. 2021 Jan 27;9(3):1655–1662.

CAH with adrenal tumor

Table 3
Meta-Analysis of 59 Cases with 21-Hydroxylase Deficiency and Adrenal Tumors

First author and ratio of patients with tumor (REF)	Imaging modality	Age at tumor at diagnoses (years; median and range)	Gender N (%)	Size of adrenal tumor (mm) (median and range)	Bilateral N (%)	Adrenal side N (%)	Subtype of 21-OHD[a] N (%)
El-Maouche D, 19/88 (22)[c]	CT	38.0 (16-65)	12 in 41 male (29.3%) 7 in 47 female (14.9%)	15.0 (5-100)	7 (38%)	9 (47.4%) left 3 (15.8%) right	13 (68.4%) SW 6 (31.6%) SV
Nermoen I, 7/62 (10)[c]	CT with contrast	38.0 (27-58)	5 in 23 male (21.7%) 2 in 39 female (5.1%)	35.0 (12-165)	2 (28.6%)	3 (42.9%) left 2 (28.6%) right	5 (71.4%) SW 2 (28.6%) SV
Reisch N, 15/26 (24)	MRI	ND (age of total study population 33.0 years [18-48])	15 in 25 male (60.0%) (no female in study)	10.0 (6-37)	ND	ND	ND
Jaresch S, 16/20 (9)	CT with contrast	25.0 (12-60)	13 in 15 female (86.7%) 3 in 5 male (60.0%)	5-9 (5->50)	1 (6.3%)	12 (75.0%) left 3 (18.8%) right	11 (68.8%) SV 5 (31.3%) NC
Azziz R, 1/3 (23)	MRI	34.0	1 in 3 female (33.3%) (no male in study)	33.0	0 (0%)	1 (100%) left	1 (100%) NC
Falke TH, 1/11 (21)	CT with contrast	48.0	1 46 XX male with tumor (gender not stated in 6 cases)	55.0	0 (0%)	1 (100%) right	1 (100%) SV
Results		36.0 (12-60)[a]	36/95 male (37.9%)[b] 23/104 female (22.1%)[b] *P*<.05	24.0 (5-165)	10/44 (22.7%)[a]	left 25/44 (56.8%)[a] right 9/44 (20.1%)[a] *P*<.05	SW 18/44 (40.9%) SV 20/44 (45.5%) NC 6/44 (13.6%)

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; NC = nonclassic; ND = no data; 21-OHD = 21-hydroxylase deficiency; REF = reference; SV = simple virilizing; SW = salt wasting.
[a]Reisch not included.
[b]Falke not included.
[c]Some data obtained after contact with the corresponding author.

- Prevalence of adrenal tumors in patients with CAH was found to be up to 29.3%
- Myelolipoma in CAH 7.4%
- The median age at tumor diagnosis was 36.0 (12-60) years.

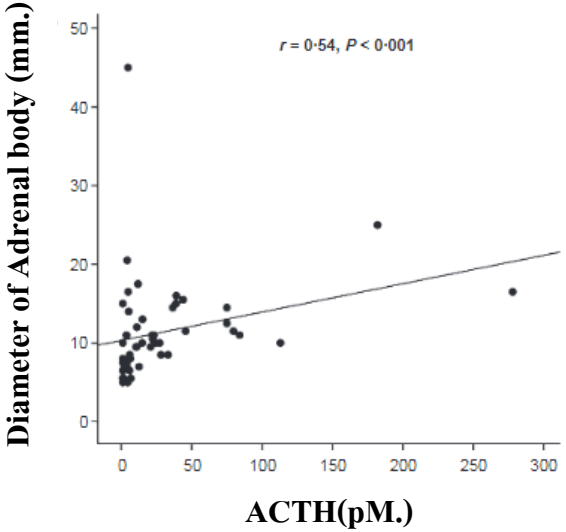
Adrenal tumors in CAH, *Endocr Pract.*2020;26(No.11);1361-1365

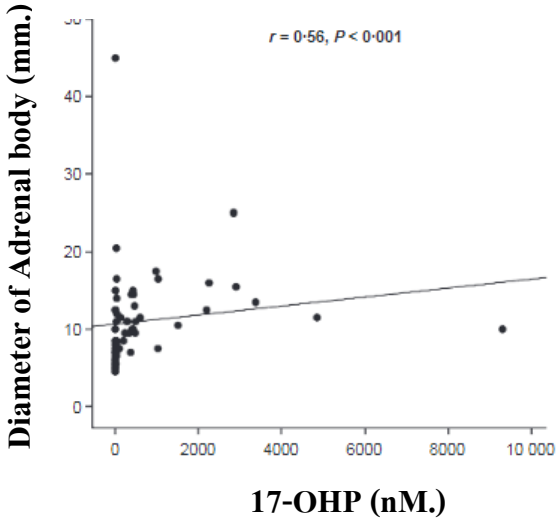
CAH with adrenal tumor

Prevalence of adrenal tumors in patients with CAH was found to be up to 29.3%

Table 1. Age, 17-hydroxyprogesterone levels, type of therapy and CT findings of the adrenal glands in the patients; median (range) or *n* (%)

	SW	SV	Men	Women	All
n	32	30	23	39	62
Age (year), median (range)	35 (19–55)	47 (19–72)*	38 (19–58)	39 (19–72)	39 (19–72)
17-hydroxyprogesterone (nmol/l), median (range)	164 (0·6–9300)	26 (0·6–4860)	33 (4·5–4860)	100 (0·6–9300)	36 (0·6–9300)
Treatment, *n* (%)					
Hydrocortisone	4 (13)	0	1 (4)	3 (8)	4 (6)
Cortisone acetate	10 (31)	2 (7)**	6 (26)	6 (15)	12 (19)
Prednisolone	10 (31)	13 (43)	6 (26)	17 (44)	23 (37)
Dexamethasone	4 (13)	8 (25)	3 (13)	9 (23)	12 (19)
Mix of two	4 (13)	5 (16)	6 (26)	3 (8)	9 (15)
Fludrocortisone	28 (88)	1 (3)**	12 (52)	17 (44)	29 (47)
Dose, median (range)					
GC-dose equivalent (mg/day)	30 (15–75)	30 (0–45)	30 (0–75)	30 (0–60)	30 (0–75)
FC-dose (mg/day)	0·1 (0–0·2)	0 (0–0·1)*	0·05 (0–0·2)	0 (0–0·2)	0·1 (0–0·2)
Adrenal measurements, *n* (%)					
Normal adrenals	5 (16)	12 (40)**	5 (22)	12 (31)	17 (27)
Tumour	5 (16)	2 (7)	5 (22)	2 (5)	7 (11)
Myelolipoma	3 (9)	1 (3)	4 (17)	0**	4 (6)
Adenoma	1 (3)	1 (3)	0	2 (5)	2 (3)
Pheochromocytoma	1 (3)	0	1 (4)	0	1 (2)
Hyperplasia	19 (58)	17 (57)	14 (61)	22 (55)	36 (58)
Hypoplasia	6 (19)	1 (3)	4 (17)	3 (8)	7 (11)
Adrenal width, median (range)					
Maximum width, right (mm)	9·0 (5–48)	9·0 (5–22)	10·0 (6–48)	8·5 (5–18)*	9·0 (5–48)
Maximum width, left (mm)	12·0 (4–42)	10·0 (5–17)	12·5 (5–42)	10·0 (4–18)	10·5 (4–42)
Tumour diameter, mm	35·0 (14–165)	35·0 (12–58)	40·0 (33–165)	13·0 (12–14)	35·0 (12–165)





If an adrenal tumor is found in any patient, including patients with CAH, exclusion of malignancy and hormone-production from the adrenal tumor should be done.

Adrenal tumors in CAH, *Endocr Pract.*2020;26(No.11);1361-1365

ACTH VS Tumor size

- Identified 11 reports
- ACTH was increased in 9/11 subjects:
  - 3 had tumors >10 cm.
  - 3 had adrenal tumors between 5-10 cm.
  - 3 had tumors <5 cm.
  - A mean ACTH 1830 pg/mL (27-10,445 pg/mL)
  - The mean ACTH levels in relationship with the tumour size.
    - tumors <5 cm: 1434 pg/mL
    - tumors: 5–10 cm: 3544 pg/mL
    - tumors >10 cm: 514.5 pg/mL

Table 4. Data regarding tumour size and hormonal findings at presentation in patients with genetically confirmed *CYP21A2* deficiency [50–67].

Reference	Hormonal Panel at Presentation for Adrenal Tumour			
	Tumour Size (cm)	ACTH (pg/mL)	17-hydroxyprogesterone (ng/mL or nmol/L)	Other Hormonal Assays or Observations
[50]	>10	1172	192 ng/mL	Testosterone = 949 ng/dL; Androstendione = 17 ng/mL
	>10	NA	120 ng/mL	Testosterone = 720 ng/dL; Androstendione = 39 ng/mL
[51]	5–10	NA	NA	Late diagnosis
	<5	NA	37 nmol/L	
	<5	NA	32 nmol/L	
	<5	NA	11.1 nmol/L	
	5–10	NA	338 nmol/L	
[52]	<5	NA	42 nmol/L	Late diagnosis
[53]	5–10	normal	51 nmol/L	Patient received diagnosis after incidentaloma was discovered
[54]	>10	214	28.6 ng/mL	DHEA-S = 29 (N:80-560) µg/dL
[55]	5–10	27	426 nmol/L	Testosterone = 13 nmol/L; Androstendione = 14 nmol/L
[56]	>10	NA	NA	Late diagnosis
[57]	5–10	NA	markedly raised	Testosterone normal (late diagnosis)
[58]	5–10	NA	17,900 ng/dL	Late diagnosis
[59]	<5	1820	9.4 ng/mL	Testosterone = 3.26 ng/mL; Androstendione = 1.15 ng/mL Late diagnosis, poor compliance with treatment
[61]	>10	157.6	27,500 ng/dL	Late diagnosis
[62]	5–10	10,445	2003 ng/dL	Late diagnosis
[63]	<5	1351	57 ng/mL	Testosterone = 0.7 ng/mL; Androstenedione = 4.5 µg/mL; late diagnosis
[64]	<5	NA	NA	
	<5	NA	NA	Irregular adherence to treatment during childhood
	<5	NA	NA	
[65]	>10	3	269 nmol/L	Androstenedione and 17-hydroxyprogesterone with fluctuant pattern
[66]	5–10	160	6078 ng/dL	Testosterone = 447.0 ng/dL; DHEA-S = 598 ug/dL; late diagnosis
[67]	<5	1131	485.20 nmol/L	Testosterone = 4.05 (normal: 1.75–7.81) ng/mL; DHEA = 7.99 ng/mL; late diagnosis
	>10	NA	NA	Late diagnosis

Biomedicines 2023, 11, 3081

Adrenal morphology and associated comorbidities in CAH,EL-MAOUCHE Et AL,Clinical Endocrinology. 2019;91:247–255

CAH with adrenal tumor

- Prolonged exposure to excess ACTH leads to bilateral adrenal gland hyperplasia and tumor formation.
- Patients with classic CAH have a higher prevalence of adrenal masses than the general population, including benign adrenocortical adenomas and myelolipomas.
- One aim of glucocorticoid therapy in CAH is to control excess stimulation of the HPA axis to prevent hyperandrogenism, adrenal enlargement and tumor formation, but supraphysiologic glucocorticoid therapy is needed to achieve this goal, placing patients at risk for iatrogenic Cushing syndrome and metabolic risk factors.
- As a result, patients are often maintained on glucocorticoid doses that fail to prevent adrenal enlargement and tumor formation.

CAH with adrenal tumor

- Only one case report described a 43-year-old female who was diagnosed at birth with non-salt-wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.
- MRI revealed a massive fibroid (30 cm), bilateral adrenal hyperplasia, and a left paraaortic retroperitoneal mass (5.9 cm).
- She underwent a hysterectomy and left adrenalectomy and removal of the left paraaortic mass
- Initially reported as an oncocytic adrenal cortical neoplasm.
- The revised report identified the paraaortic mass as a probable adrenal rest tumor.

Lee SJ, et al. CAH presenting as huge mass.*Endocrinol Metab* 2015;30;408-413

136 ปี ศิริราช

THANK YOU