IN THE NAME OF GOD

A case of adrenal mass and hypokalemia

A 54-year-old woman was referred for the evaluation of an adrenal tumor with a history of hypertension since age 29 years and hypokalemia during the past 7 to 8 years.

She was seen in the ED for abdominal pain . A CT scan with contrast identified a large ventral hernia as the cause of her pain and a 1.8 cm × 2.4 cm right adrenal nodule (Figure 1A).

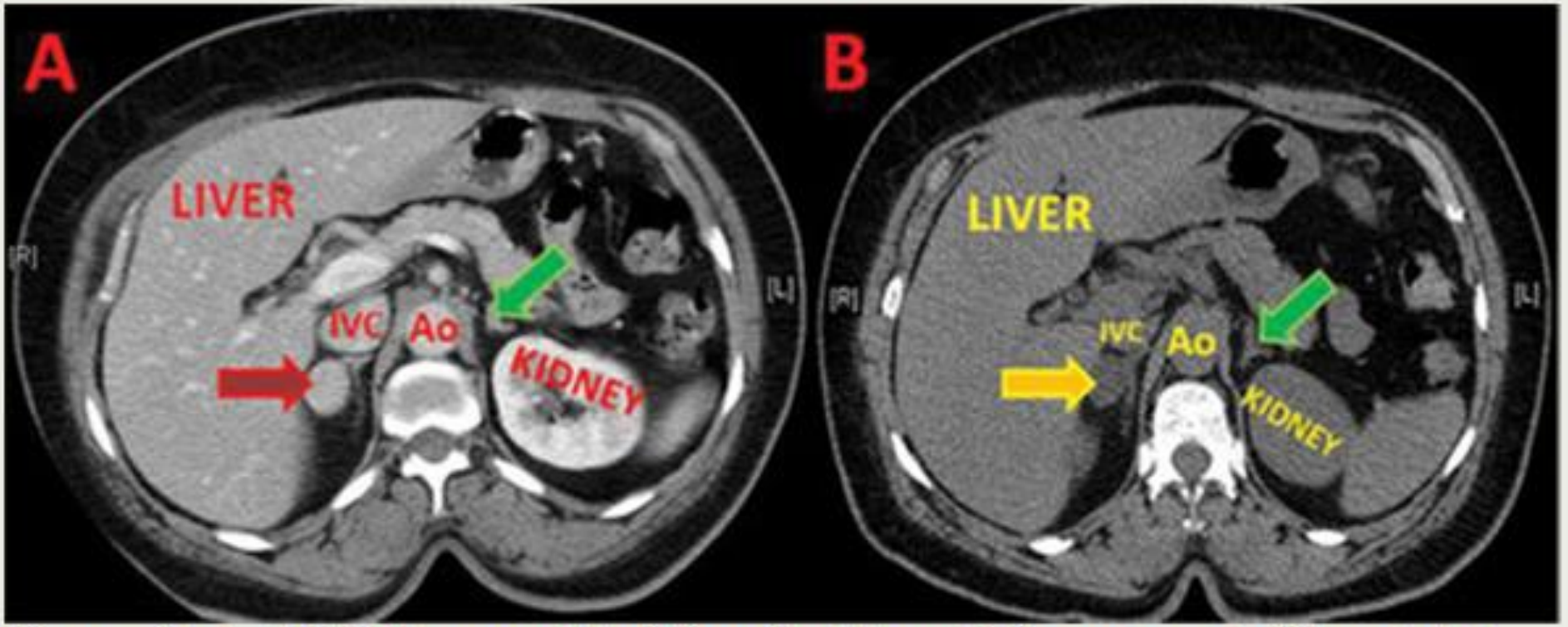


Figure 1. Axial CT scan with (A) and without (B) contrast of the right adrenal mass. A. Red and yellow arrows indicate the right adrenal mass. Green arrow indicates left adrenal.

Her blood pressure was 158/84 mm Hg with a pulse of 60 bpm while taking atenolol 50 mg twice daily, nifedipine 60 mg daily and potassium chloride 20 mEq twice daily .

Laboratory testing showed the followings: serum sodium 141 mmol/L; blood urea nitrogen 13 mg/dL; creatinine 0.66 mg/dL; potassium 3.6 mmol/L; chlorine 102 mmol/L; carbon dioxide 27.8 mmol/L; and aldosterone 42 ng/dL with a plasma renin activity (PRA) of 0.5 ng/mL/hour .

The serum aldosterone/PRA ratio was elevated at 84, consistent with primary aldosteronism. A repeat CT of the abdomen without contrast reported a normal-appearing left adrenal gland and a 2 cm × 1.9 cm right adrenal mass with low attenuation of 6.6 Hounsfield units (Figure 1B),

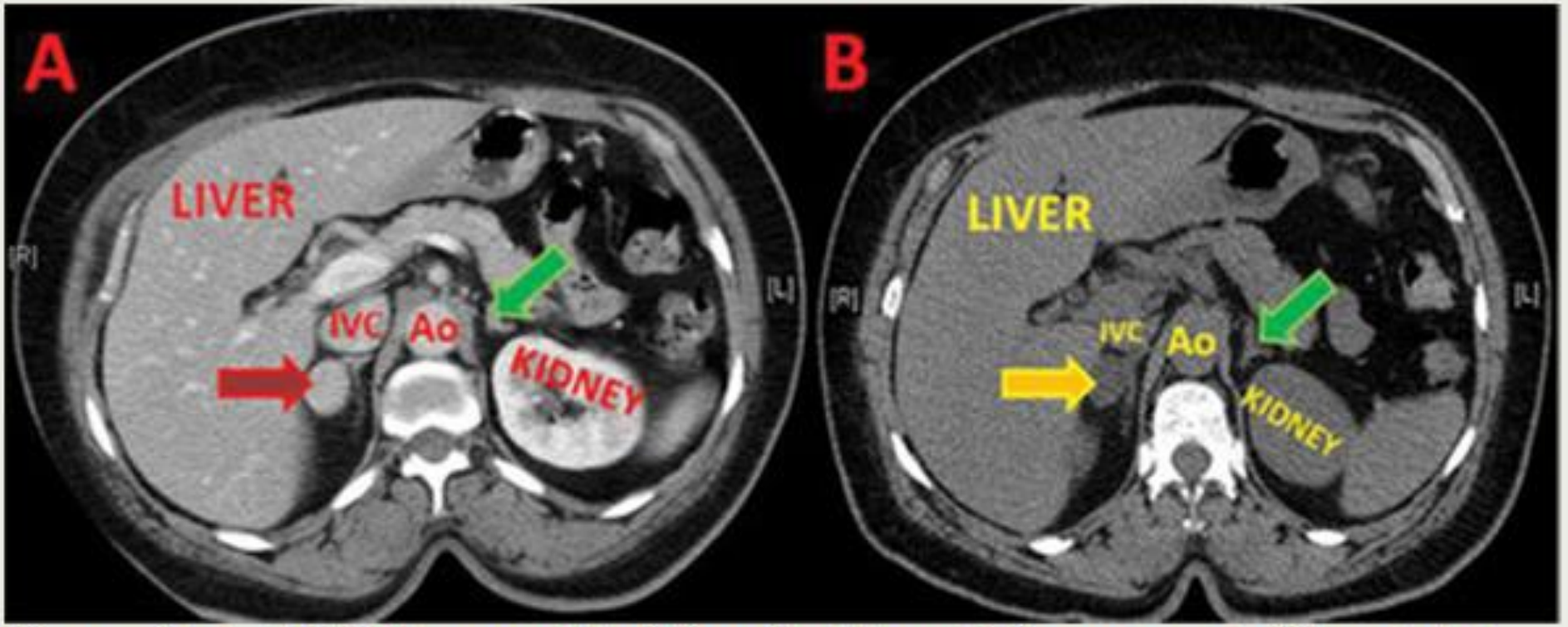


Figure 1. Axial CT scan with (A) and without (B) contrast of the right adrenal mass. A. Red and yellow arrows indicate the right adrenal mass. Green arrow indicates left adrenal.

Bilateral adrenal vein sampling was performed with continuous IV cosyntropin 50 mcg/hour started 30 minutes before the procedure.

Table. Bilateral Adrenal Vein Catheterization During Cosyntropin Infusion

	R AV	IVC	L AV	R AV/IVC	L AV/IVC
Cortisol mcg/dL	1235.7	42.8	1283.3	28.9	30
Aldosterone ng/dL	176	76	267	2.3	3.6
Aldosterone/Cortisol	0.14	1.78	0.21		
A/C Ratio R/L	0.67				
A/C Ratio L/R			1.5		

Venous blood samples were obtained from the right and left adrenal veins and the IVC and analyzed for aldosterone and cortisol. The cortisol ratio of the right adrenal vein to IVC (28.9) and the left adrenal vein to IVC (30) were identical The aldosterone/cortisol ratio from the right adrenal vein (0.14) was the same as the left adrenal vein (0.21; Table)

This nonlateralizing test result is consistent with bilateral aldosterone secretion and a nonsecreting adrenal adenoma. She was treated medically instead of surgically. After starting spironolactone 50 mg daily, an aldosterone receptor antagonist, her BP is well controlled on this single agent, and her potassium is stable in the low 4s without supplementation.

She had a repeat adrenal CT scan 2 years later showing the absence of growth of the low attenuation adrenal nodule consistent with a benign nonsecreting adrenal adenoma .

primary aldosteronism should be considered when hypertension is associated with hypokalemia and/or resistant to medical therapies. This patient has bilateral adrenal hyperplasia (BAH) with excess aldosterone secreted from both adrenal glands. She would not have benefited from adrenal surgery and should be treated medically with an aldosterone receptor blocker .

Initial radiologic investigation in the workup of primary hyperaldosteronism is high-resolution, thin-slice (2 mm-2.5 mm) adrenal CT scanning with contrast. Aldosteronomas tend to be small and may not always be seen on CT or MRI scans. .

In a systematic review, it has been estimated that CT and MRI scans would misdiagnose assigning unilateral vs. bilateral aldosterone secretion in 37.8% of patients. This error would lead to an inappropriate adrenalectomy in 14.6% of the patients, an inappropriate exclusion from adrenalectomy in 19.1% of patients and adrenalectomy on the wrong side in 3.9% of patients .

The accuracy of AVS is more than 95% when the procedure is technically successful. The procedure must be performed by an experienced and skilled radiologist.

Currently, adrenal vein sampling remains the gold standard to establish unilateral of primary aldosteronism that can be surgically cured. It is important to understand that CT/MRI imaging may misclassify as many as 37.8% of patients with primary aldosteronism.

Endocrine Hypertension: Causes, Diagnosis and Management

FREQUENCY OF VARIOUS DIAGNOSiS IN HYPERTENSIVE SUBJECTS

Diagnoses	Berglund	Percentage Rudnick	Danielson
Essential hypertension	94	94	95.3
Chronic renal disease	4	5	2.4
Renovascular disease	1	0.2	1.0
Coarctation	0.1	0.2	
Primary aldosteronism	0.1		0.1
Cushing's syndrome		0.2	0.1
pheochromocytoma			0.2
Oral contraceptive induced		0.2	0.8
Number of patients	689	665	1000

Br Med J 1976; 2: 554

Can Med Assoc J 1977; 117: 492

Acta Med Scand 1981; 209: 451

Secondary Causes of Hypertension

renal Hypertension

renovascular

renal parenchymatous disease

primary reninism

primary hyperaldosteronism

unilateral adrenal adenoma

bilateral hyperplasia of the zona glomerulosa

rare causes of Hypertension

phaeochromocytoma

cushing's syndrome

coarctation of the aorta

The Secondary Causes of Hypertension. These can be classified as primary hyperaldosteronism, renal causes and rare causes of Hypertension.

Renal causes of hypertension

Renal parenchymatous	Renovascular
Acute and chronic glomerulonephritis	Coarctation of the aorta
Chronic pyelonephritis – especially if calculi or obstruction with hydronephrosis	Renal artery stenosis e. g. with fibromuscular hyperplasia, atheromatous plaque, congenital
Polycystic disease	Malignant or accelerated – phase hypertension
Interstitial nephritis, e. g. with gout, hypercalcemia, or excessive analgesics (analgesic nephropathy)	**Primary reninism**
Amyloidosis	Reninomas (juxlaglomerular tumors)
Connective tissue disease, e, g, with polyarteritis, systemic lupus erythematosus, and diabetes mellitus	Some Wilm's tumors
	Ectopic renin secretion

FEATURES OF "INAPPROPRIATE" HYPERTENSION

1. Onset before age 20 or after age 50 years
2. Markedly elevated pressures, particularly with grade 3 or 4 funduscopic changes
3. Organ damage
    a. Funduscopic findings of grade 2 or higher
    b. Serum creatinine > 1.5 mg/100 mL
    c. Cardiomegaly (on x-ray) or left ventricular hypertrophy (on electrocardiogram or echocardiogram)
4. Features indicative of secondary causes
    a. Unprovoked hypokalemia
    b. Abdominal diastolic bruit
    c. Variable pressures with tachycardia, sweating, termor
    d. Family history of renal or endocrine disease
    e. Hematuria, palpable kidneys
    f. Decreased femoral pulses
5. Poor response to therapy that is usually effective

ENDOCRINE HYPERTENSION (1)

I. Primary (essential) hypertension(?)

II. Renin-angiotensin mediated

- A. Renovascular
- B. Renin-secreting tumors
- C. Renal parenchymal diseases (?)
- D. Coarctation of theaorta
- E. Estrogen- induced (?)
- F. Pregnancy-induced (?)

ENDOCRINE HYPERTENSION (2)

III. Mineralocorticoid mediated

- A. Primary aldosteronism
- B. Cushing's syndrome
- C. Congenital adrenal hyperplasia
- D. Exogenous: licorice, adrenal steroids

IV. Volume mediated

- A. primary renal sodium retention (Liddle's, Gordon's syndromes)
- B. Inappropriate ADH secretion
- C. Acromegaly
- D. Increased intravascular volume (e.g., polycythemia)

ENDOCRINE HYPERTENSION (3)

V. Catecholamine mediated

- A. Pheochromocytoma and chromaffin tumors
- B. Acute stress
  1. Postoperative
  2. Hypoglycemia
  3. Alcohol withdrawal
  4. Miscellaneous: e.g., burns, pancreatitis, sickle cell crises
- C. Neurological diseases
  1. Increased intracranial pressure
  2. Quadriplegia
  3. Porphyria
  4. Familial dysautonomia
  5. Miscellaneous: lead poisoning, Guillain-Barre syndrome
- D. Exogenous
  1. Sympathomimetics
  2. MAO Inhibitors and tyramine-containing foods

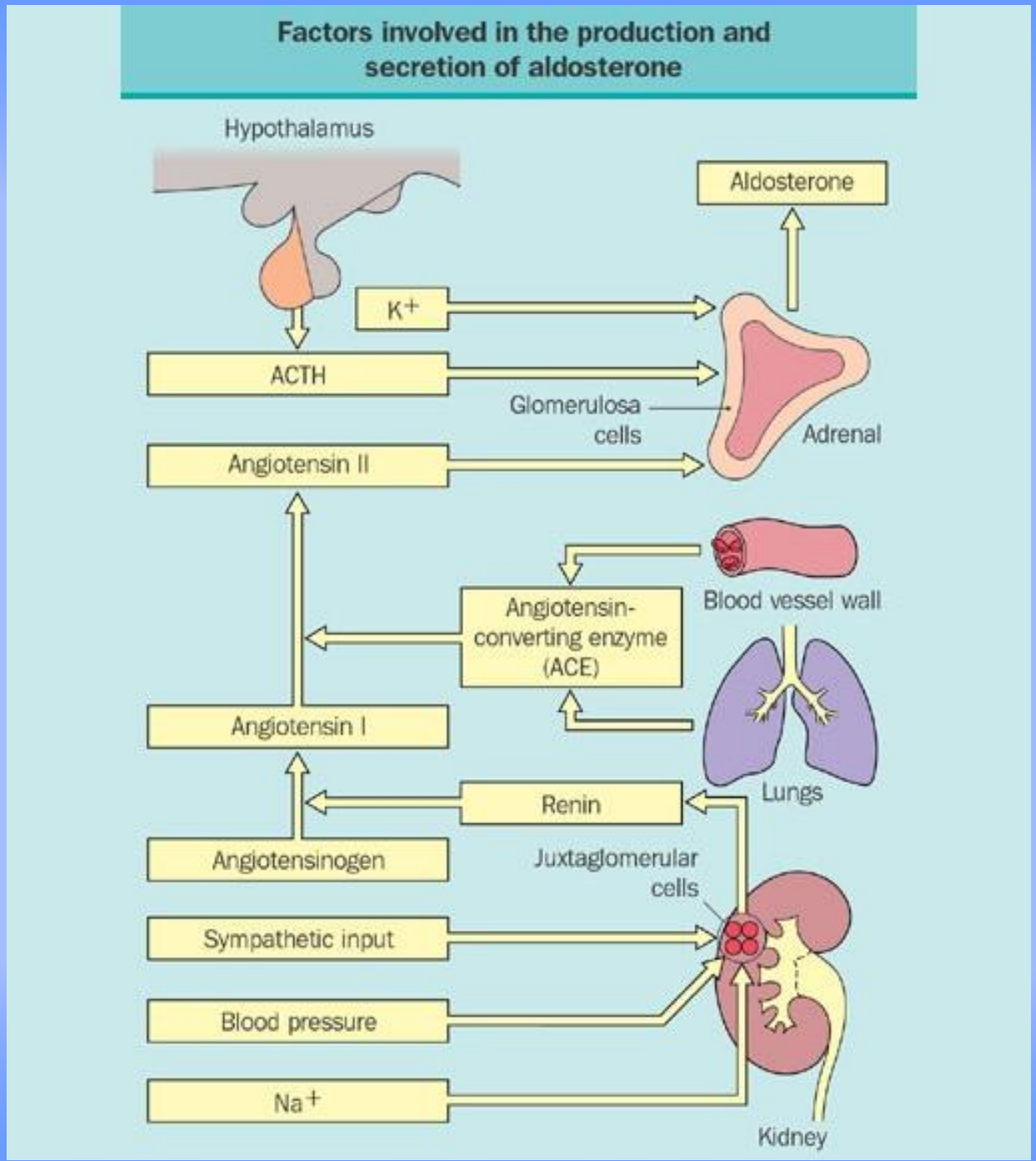
ENDOCRINE HYPERTENSION (4)

VI. Unknown mechanisms

- A. Pregnancy-induced (? prostaglandin deficiency)
- B. Renoprival (? renal depressor deficiency)
- C. Hypercalcaemia
  1. Hyperparathyroidism
  2. Other Hypercalcaemc states
- D. Hypothyroidism


پرورنین
رنین
آنژیوتانسینوژن
آنژیوتانسین ۱
آنزیم تبدیل کننده آنژیوتانسین
آندوپپتیداز
آنژیوتانسین ۷ – ۱
آنژیوتانسین II
آمینوپپتیداز
آنژیوتانسین III
آنژیوتانسین IV
فراگمانهای غیر فعال
گیرنده‌های آنژیوتانسین II
پیام آور ثانوی
رسپانس سلولی

اجزای سیستم رنین – آنژیوتانسین – آلدوسترون (الف) و فعال شدن سیستم به وسیله کاهش حجم در گردش و اثر فیدبک بعدی برگشت مجدد حجم به وضعیت طبیعی در جلوگیری از آزاد شدن بیشتر رنین(ب)


Factors involved in the production and secretion of aldosterone
Hypothalamus
Aldosterone
K+
ACTH
Glomerulosa cells
Adrenal
Angiotensin II
Blood vessel wall
Angiotensin-converting enzyme (ACE)
Angiotensin I
Lungs
Renin
Angiotensinogen
Juxtaglomerular cells
Sympathetic input
Blood pressure
Na+
Kidney

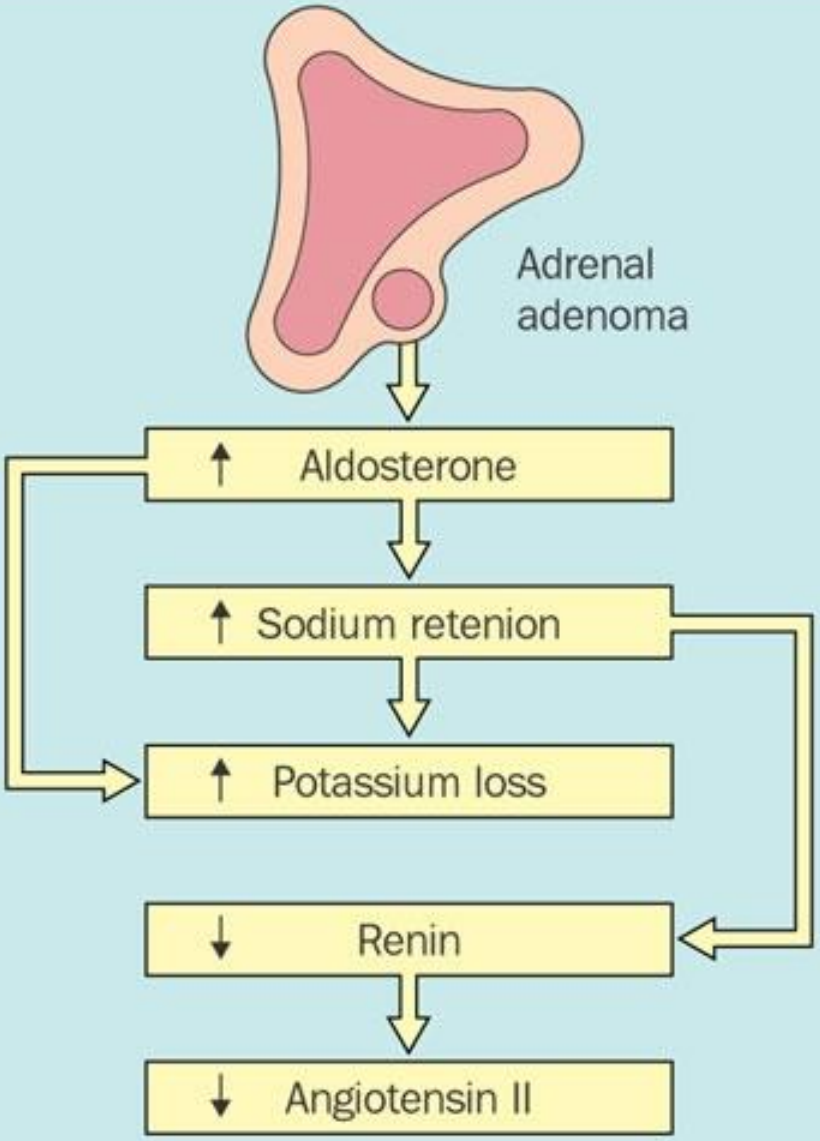
ADRENOCORTICAL CAUSES OF HYPERTENSION

LOW RENIN AND HIGH ALDOSTERONE

Primary Aldosteronism

- Aldosterone-producing adenoma (APA)—65% of cases
- Bilateral idiopathic hyperplasia (IHA)—30% of cases
- Primary (unilateral) adrenal hyperplasia—2% of cases
- Aldosterone - producing adrenocortical carcinoma—<1% of cases
- Familial Hyperaldosteronism (FH)
  - Glucocorticoid-remediable aldosteronism (FH type I)—<1% of cases
  - FH type II (APA or IHA)—<2% of cases
- Ectopic aldosterone-producing tumors — < 0.1% of cases

Mechanism of pathophysiologic changes in primary hyperaldosteronism

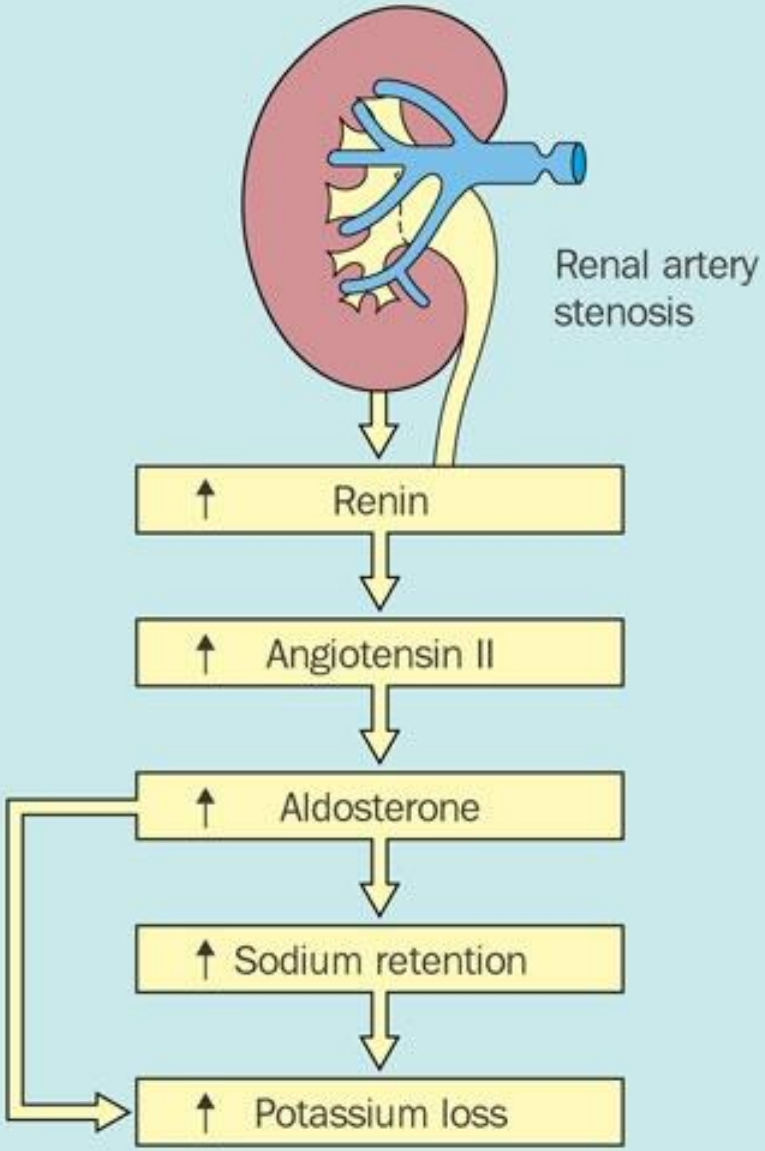


Causes of Hypertension Associated With Minerocorticoid Excess

Aldosterone excess with high plasma renin activity (secondary hyperaldosteronism)

- Benzothiadiazine diuretics
- Renal Artery stenosis or unilateral renal disease
- Malignant-phase hypertension
- Chronic bilateral renal disease
- Renin-secreting renal tumor
- “Congenital” hyperaldosteronism
- Hypertensive disease of pregnancy

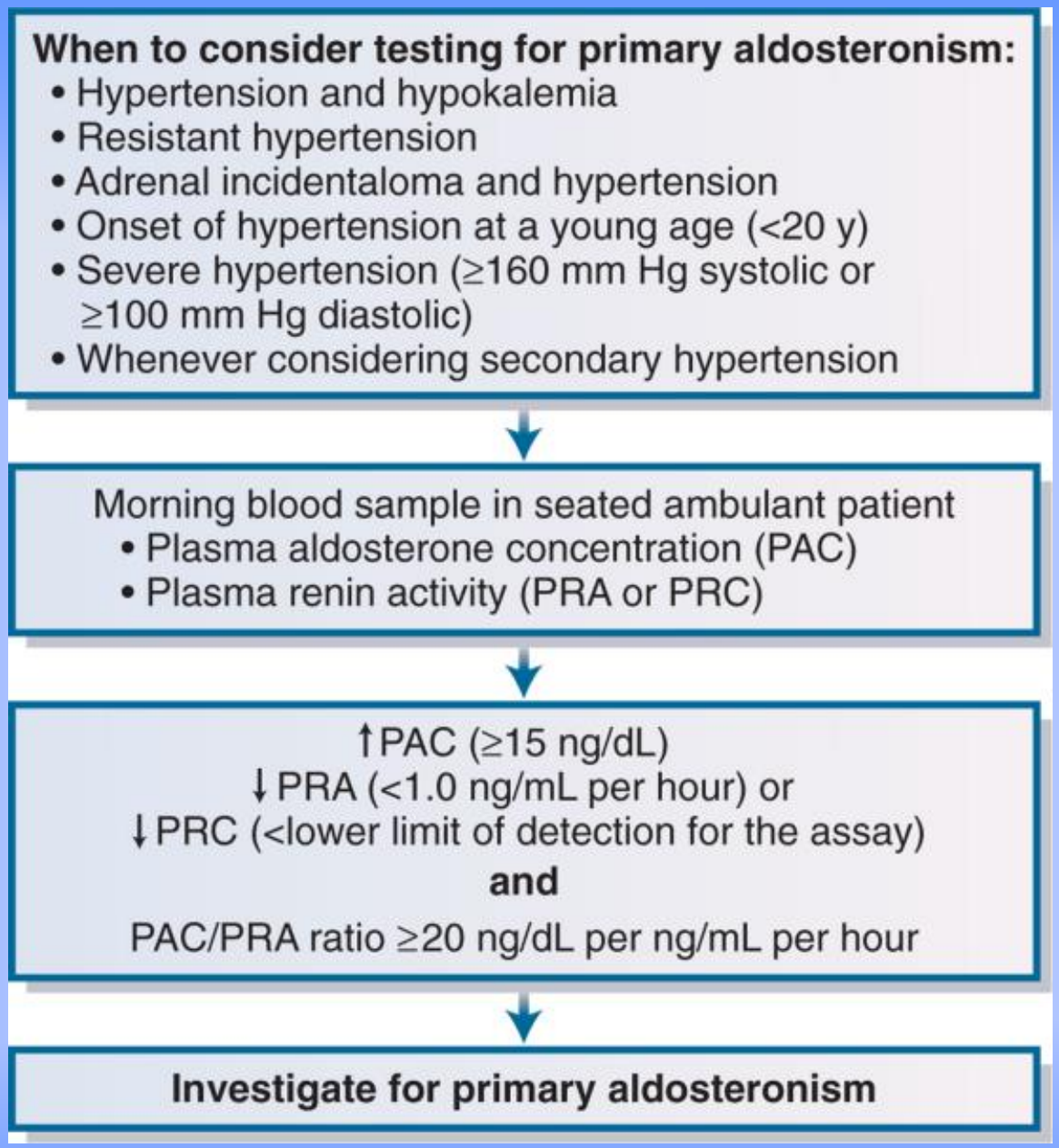
Sequence of events in secondary hyperaldosteronism



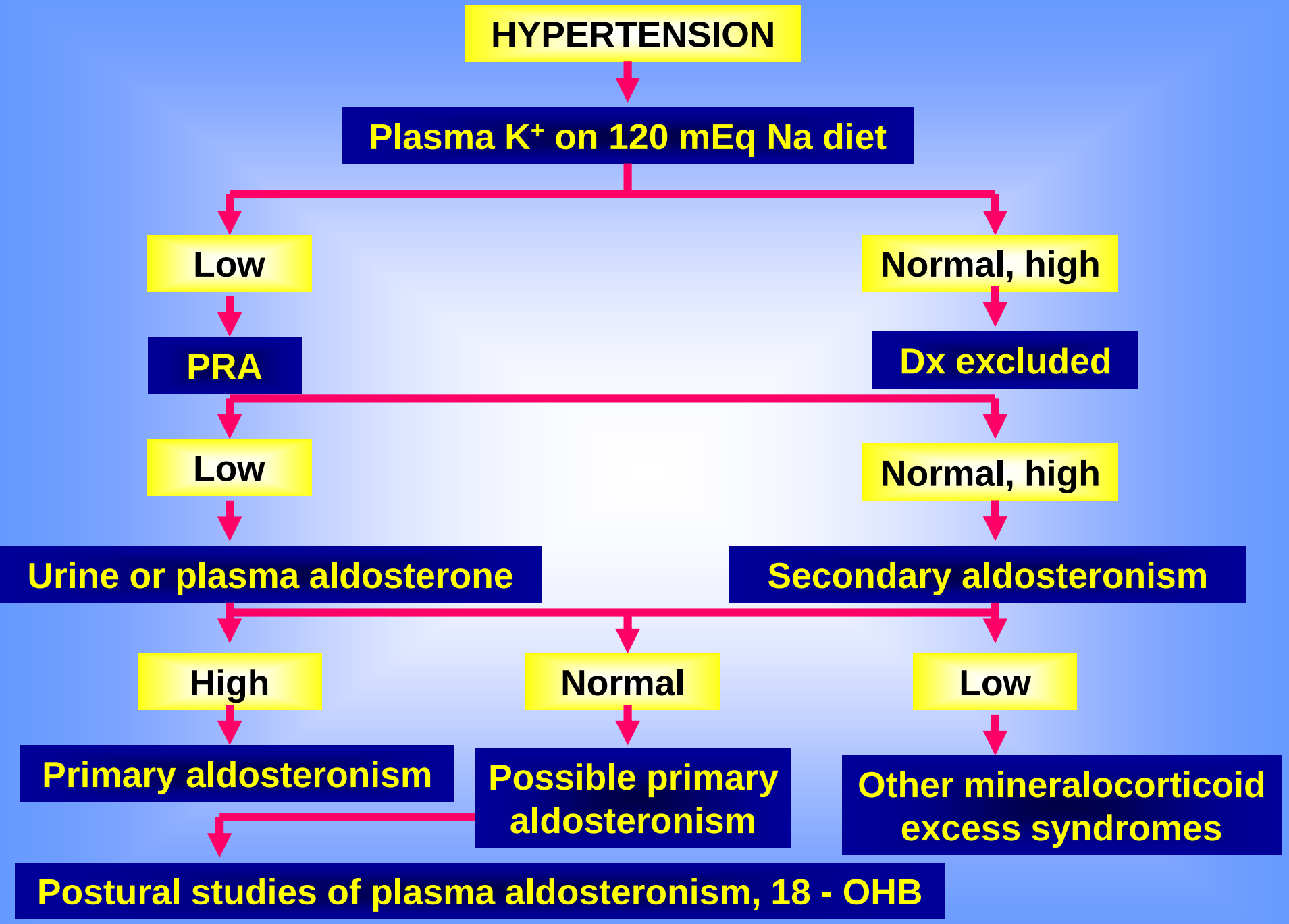
ADRENOCORTICAL CAUSES OF HYPERTENSION

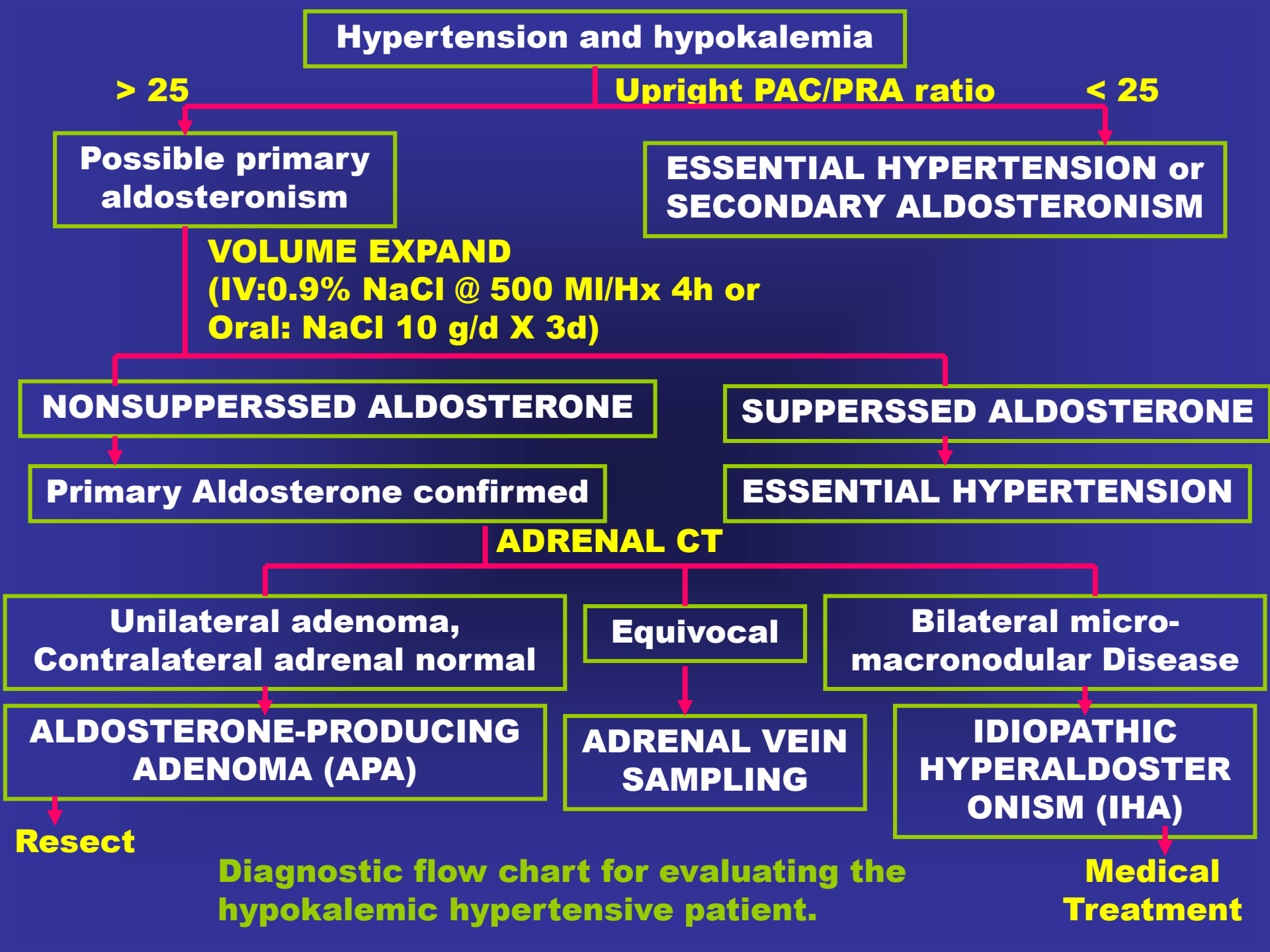
LOW RENIN AND LOW ALDOSTERONE

- Hyperdeoxycorticosteronism
- Congenital adrenal hyperplasia
  - 11β-Hydroxylase deficiency
  - 17α-Hydroxylase deficiency
- Deoxycorticosterone-producing tumor
- Primary cortisol resistance
- Apparent Mineralocorticoid Excess (AME)/11β-Hydroxysteroid Dehydrogenase Deficiency
  - Genetic
    - Type 1 AME
    - Type 2 AME
  - Acquired
    - Licorice or carbenoxolone ingestion (type 1 AME)
    - Cushing's syndrome (type 2 AME)

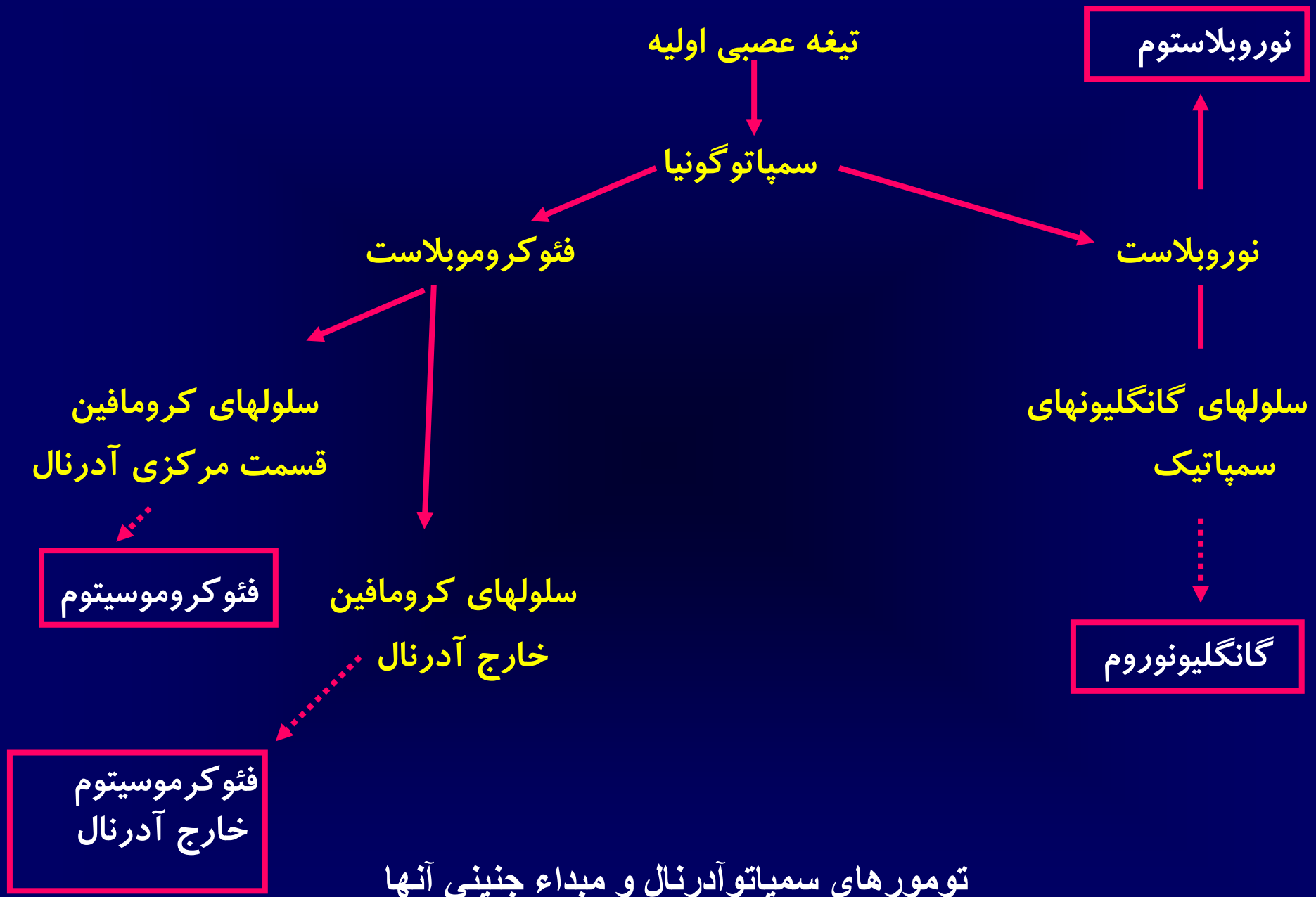


When to consider testing for primary aldosteronism and use of the plasma aldosterone concentration-to-plasma renin activity ratio as a case-finding tool .*PAC* ,Plasma aldosterone concentration ;*PRA* , plasma renin activity ,*PRC* ,plasma renin concentration .

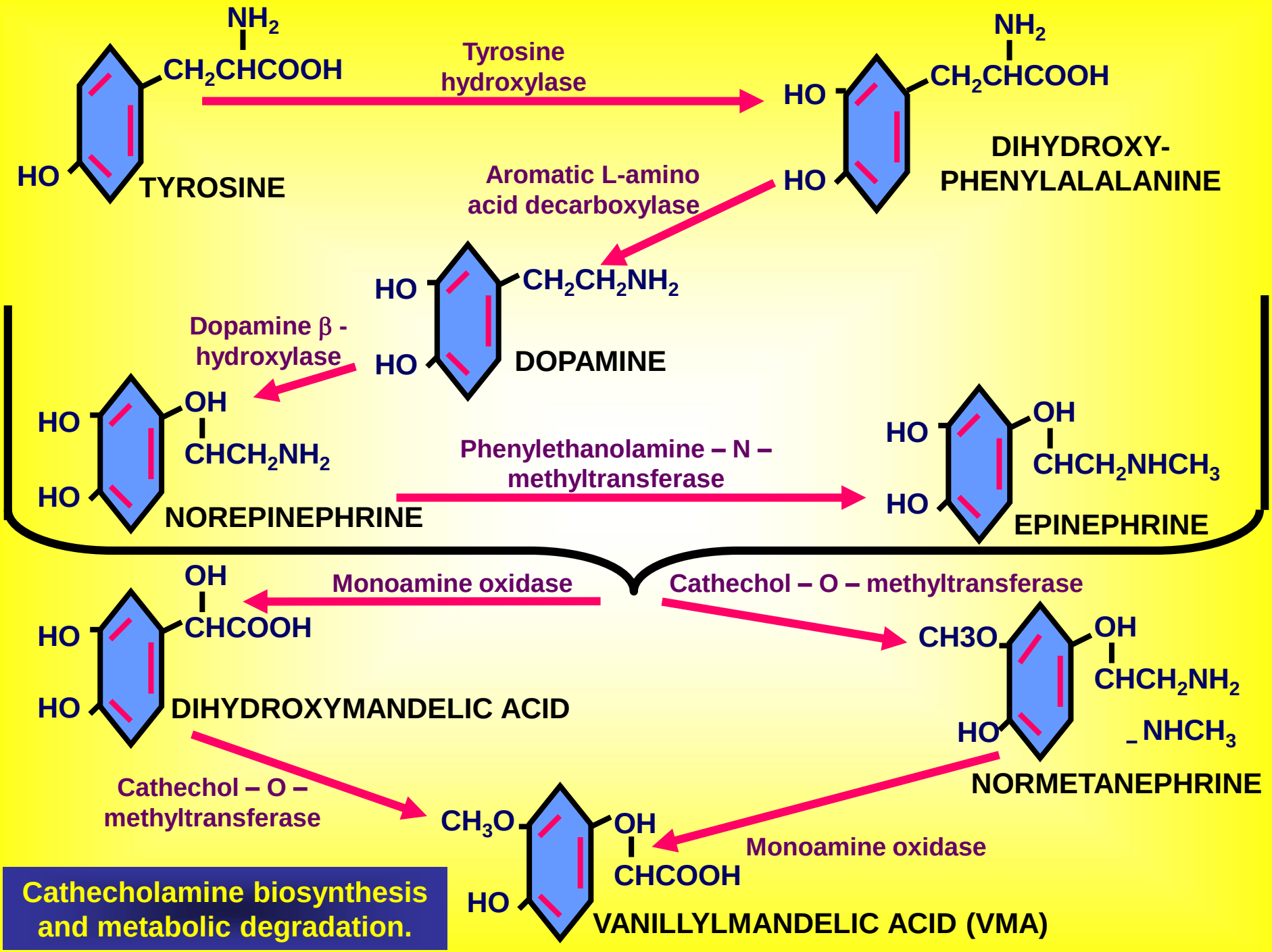

HYPERTENSION
Plasma K+ on 120 mEq Na diet
Low
Normal, high
PRA
Dx excluded
Low
Normal, high
Urine or plasma aldosterone
Secondary aldosteronism
High
Normal
Low
Primary aldosteronism
Possible primary aldosteronism
Other mineralocorticoid excess syndromes
Postural studies of plasma aldosteronism, 18 - OHB



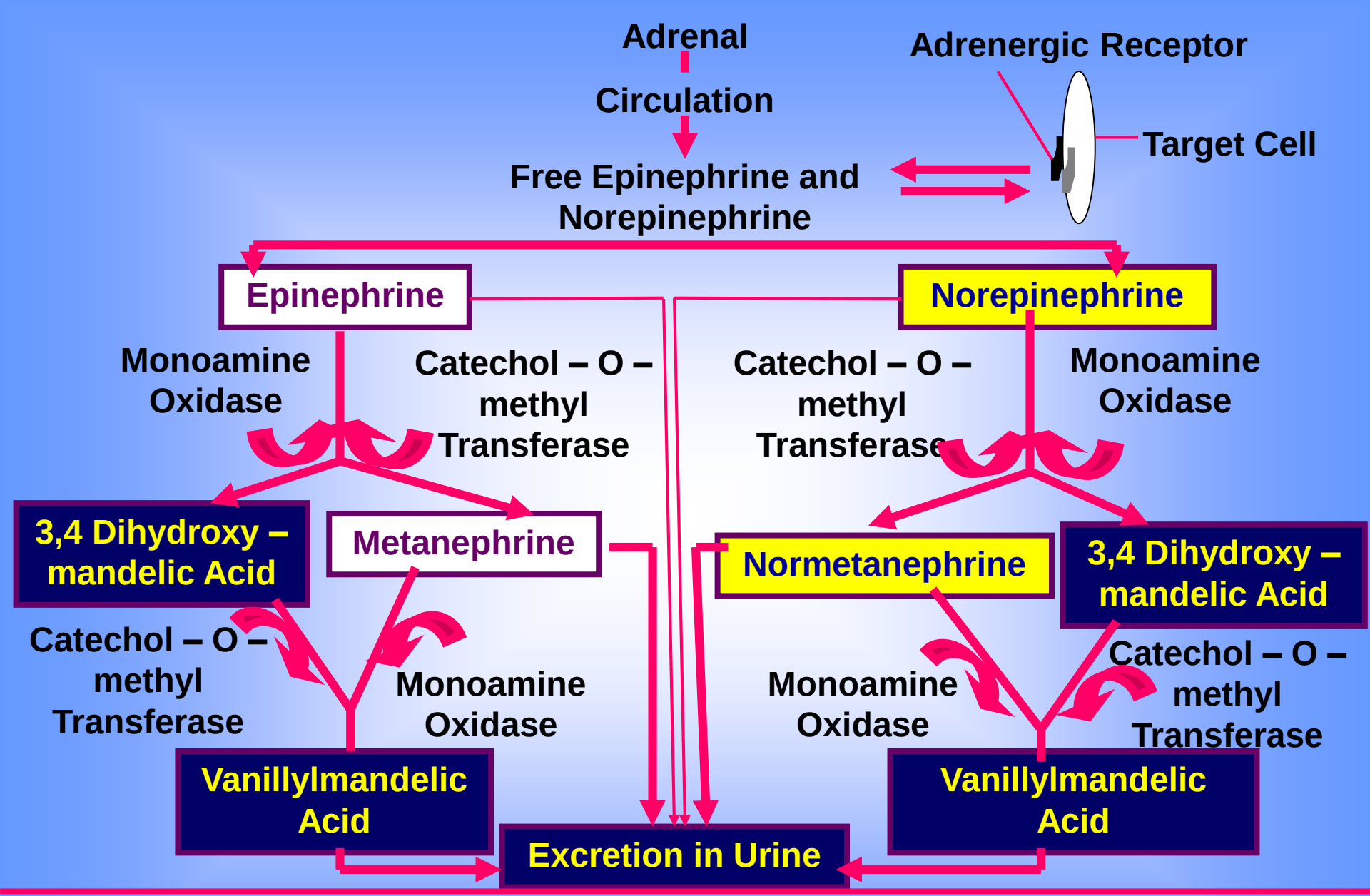
Diagnostic flow chart for evaluating the hypokalemic hypertensive patient.



تومورهاي سمپاتوآدرنال و مبداء جنيني آنها



Catecholamine biosynthesis and metabolic degradation.



Scheme of catecholamine metabolism shows slightly different pathways for epinephrine and norepinephrine. Main sites of metabolism for both are the liver, kidneys, and red blood cells.

Target cells include smooth muscle myocardial, and glandular cells. Catecholamines are excreted as 5% unchanged; 20% metanephrine and normetanephrine; and 75% VMA.

گیرنده های کاتکولامین ها

نوع گیرنده	مکانیسم اثر اصلی	نمونه های پراکندگی نسجی	قدرت نسبی آگونیست های مختلف در تحریک گیرنده
آلفا – ۱	DAG ، ↑ IP3	انتهاهای عصبی بعد سیناپسی آدرنرژیک	اپی نفرین اندکی بیشتر از نوراپی نفرین
آلفا – ۲	↓ cAMP	انتهاهای عصبی قبل سیناپسی آدرنرژیک	اپی نفرین اندکی بیشتر از نوراپی نفرین
بتا – ۱	↑ cAMP	قلب	اپی نفرین و نوراپی نفرین هر دو به یک اندازه
بتا – ۲	↑ cAMP	کبد	اپی نفرین خیلی بیشتر از نوراپی نفرین

IP3, Inositol triphosphate ; DAG, Diacylglycerol ; cAMP, cyclic aldenosine monophosphate.

اساس پاتوفیزیولوژیک تظاهرات بالینی فئوکروموسیتوم در رابطه با اثرات فیزیولژیک کاتکولامین ها در روی پروسه های وابسته به گیرنده های آدرنرژیک آلفا و بتا

اختلال پاتوفیزیولژیک و تظاهر بالینی در اثر تحریک گیرنده آدرنرژیک

گیرنده	اثر	پاتوفیزیولژی	تظاهر بالینی
بتا آدرنرژیک	افزایش تعداد ضربانات قلب	تاکیکاردی، تاکی آریتمی ها	• طپش قلب ، آنژین صدری، مرگ ناگهانی
آنتاگونیستها: (پروپرانولول،	افزایش قدرت انقباضی قلب	میوکاردیت، کاردیومیوپاتی	• نارسایی قلب، مرگ ناگهانی
متوپرولول،		افزایش مصرف اکسیژن	• آنژین صدری
آتنولول		میوکارد	
اسمولول)	افزایش تولید گلوکز توسط کبد	اختلال تحمل گلوکز	• هیپرگلیسمی، گلوکزوری
	لیپولیز	افزایش اسید های چرب آزاد در پلاسما	• کاهش وزن
	افزایش میزان سوخت و ساز	افزایش تولید حرارت	• تب، تعریق، کاهش وزن، کاهش تحمل گرما
	شلی دیواره روده ها	اختلال حرکتی روده ها	• ایلئوس، یبوست

اساس پاتوفیزیولوژیک تظاهرات بالینی فئوکروموسیتوم در رابطه با اثرات فیزیولژیک کاتکولامین ها در روی پروسه های وابسته به گیرنده های آدرنرژیک آلفا و بتا

اختلال پاتوفیزیولژیک و تظاهر بالینی در اثر تحریک گیرنده آدرنرژیک

گیرنده	اثر	پاتوفیزیولژی	تظاهر بالینی
آلفا آدرنرژیک	انقباض آرتریولها	هیپرتانسیون	• سردرد، آنژین صدری، نارسایی احتقانی قلب، رنگ پریدگی
آنتاگونیستها : (فن اکسی بنزامین، فنتولامین، پرازوسین، ترازوسین، دوکسازوسین)	انقباض وریدی	کاهش حجم پلاسما	• هیپوتانسیون اورتواستاتیک، شوک و کلاپس عروقی
	مهار ترشح انسولین	اختلال تحمل گلوکز،	• هیپرگلیسمی، گلوکزوری
	شل شدن دیواره روده ها	کاهش حرکات روده	• ایلئوس، یبوست
	تحریک فعالیت غدد عرق	تعریق فراوان	• تعریق آدرنرژیک
	گردن مثانه	ازدیاد فشار مجرای ادرار	• رتانسیون ادراری
	اتساع مردمک ها		• میدریاز

شیوع هیپرتانسیون و حملات در ۵۰۷ بیمار با فئوکرموسیتوم

علامت	شیوع (٪)
هیپرتانسیون مداوم	۵/۶۰
همراه با کریز	۲۷
بدون کریز	۵/۳۳
هیپرتانسیون حمله ای (پاروکسیسمال)	۴/۲۶
هیپرتانسیون حاملگی	۵/۳
فقدان هیپرتانسیون	۵/۹
علائم حمله ای	۸/۲
علائم مداوم	۲/۱
فقدان هر گونه علامتی (کشف تصادفی)	۳/۴
نشانه های موضعی	۲/۱
علائم حمله ای یا کریزهایی از انواع مختلف	۲/۵۶

CLINICAL FEATURES ASSOCIATED WITH PHEOCHROMOCYTOMA

- Headaches
- Sweating attacks
- Palpitation and tachycardia
- Hypertension, sustained or paroxysmal
- Anxiety and panic attacks
- Pallor
- Nausea
- Abdominal pain
- Weakness
- Weight loss
- Paradoxical response to antihypertensive drugs
- Polyuria and polydipsia
- Constipation
- Orthostatic hypotension
- Dilated cardiomyopathy
- Erythrocytosis
- Elevated blood sugar
- Hypercalcemia

اشکال مختلف تظاهر فئوکروموسیتوم

شکل تظاهر	علائم
حملات پاروگسیسمال	هیپرتانسیون، سردرد، تعریق، رنگ پریدگی، طپش قلب، تهوع، دردهای شکمی و سینه ای، ترمور
هیپرتانسیون دائمی	علائم خفیف و غیر اختصاصی بوده و با هیپرتانسیون اولیه اشتباه می شود
افزایش متابولیسم	ترمور، تعریق، کاهش وزن، افزایش متابولیسم بازال که در این صورت با پرکاری تیروئید اشتباه می شود
افزایش قند خون	با دیابت تظاهر می نماید
کاهش حرکات گوارشی	ممکن است با انسداد روده ای یا بیماری Hirschsprung اشتباه شود
هیپرتانسیون در حاملگی	مسمومیت حاملگی (toxemia of pregnancy) را تقلید می نماید
سندرمهای اضطراب	سرگیجه وضعیتی، طپش قلب، پاراستزی و ترمور که در این صورت با پسیکونوروز (psychoneurosis) یا سندروم هیپرونتیلاسیون تشخیص افتراقی می شود
توده شکمی	درصورتی که تومور بزرگ باشد و کاتکولامین ها را بسرعت متابولیزه نماید ممکن است بیمار فاقد علائم باشد
هیپوتانسیون	در اینصورت اشکال شایعتر شوک را تقلید می نماید
نارسایی احتقانی قلب	کاردیومیوپاتی ناشی از کاتکولامین ها ممکن است علل شایعترنارسایی احتقانی قلب را تقلید نماید.

یافته هایی که احتمال وجود فئوکرموسیتوم را مطرح می کنند

تظاهرات بالینی

علائم حمله ای از هر نوعی

نشانه های تحریک بیش از حد آدرنرژیک

۱- تاکی کاردی

۲- تعریق فراوان

نشانه های افزایش متابولیسم

۱- تب

۲- کاهش وزن

هیپوتانسیون ارتواستاتیک

اضطراب – تحریک پذیری

نشانه های کاردیومیوپاتی

سردرد

درد سینه یا شکم

نشانه های بیماریهای جلدی عصبی (neurocutaneous)

۱- لکه های شیر قهوه ای (بیشتر از ۵ لکه)

۲- همانژیوم های شبکیه

۳- تغییر شکل مهره ها

افزایش غیر معمول فشار خون در حین عمل جراحی، دادن بیهوشی یا تروما

وجود توده شکمی

یافته های آزمایشگاهی

افزایش قند خون

بالا بودن هماتوکرین

بیماریهای همراه

کارسینوم مدولر تیروئید

سندرم نروم های مخاطی

نروفیبروماتوز

همانژیوبلاستوم های مخچه ای- شبکیه ای

هیپرپاراتیروئیدیسم

تومورهای از منشاء سلولهای بتای پانکراس (انسولینوما)

سابقه فامیلی

فئوکرموسیتوم

بیماریهای همراه

Indication for Screening

Because pheochromocytomas do not occur frequently, physicians must appreciate when screening for the disorder is appropriate. The following are reasonable indications for screening:

1. **Hypertension with episodic features suggesting pheochromocytoma (the classic triad of headaches, palpitations, and diaphoresis)**
2. **Refractory hypertension**
3. **Prominent lability of blood pressure**
4. **Severe pressor response during anesthesia, surgery, or angiography**
5. **Unexplained hypotension during anesthesia, surgery, or pregnancy**
6. **Family history of pheochromocytoma or a familial disorder such as MEN-2, VHL disease, neurofibromatosis, or glomus tumors**
7. **Incidentally discovered adrenal masses**
8. **Idiopathic dilated cardiomyopathy**

DIAGNOSIS OF PHEOCHROMOCYTOMA (1)

Clinical Suspicion

1. Paroxysmal symptoms (especially headache, palpitations, and diaphoresis
2. Intermittent or unusually labile hypertension or hypertension refractory to therapy
3. Incidental adrenal mass (rarely a pheochromocytoma in the absence of one or more of the above)
4. Family history of pheochromocytoma, MEN2, or MEN3

DIAGNOSIS OF PHEOCHROMOCYTOMA (2)

Biochemical Confirmation

1. Plasma norepinephrine and epinephrine (± dopamine)

Patient sampled in the basal state (and supine position) and, if possible, during a paroxysm

Radioenzymatic or HPLC method

Note blood pressure, heart rate, and any symptoms

2. Urinary catecholamines or metanephrines (or VMA)

If plasma values are normal or equivocal but clinical suspicion is high, repeated plasma measurements are an alternative

Can be used as the initial test

DIAGNOSIS OF PHEOCHROMOCYTOMA (3)

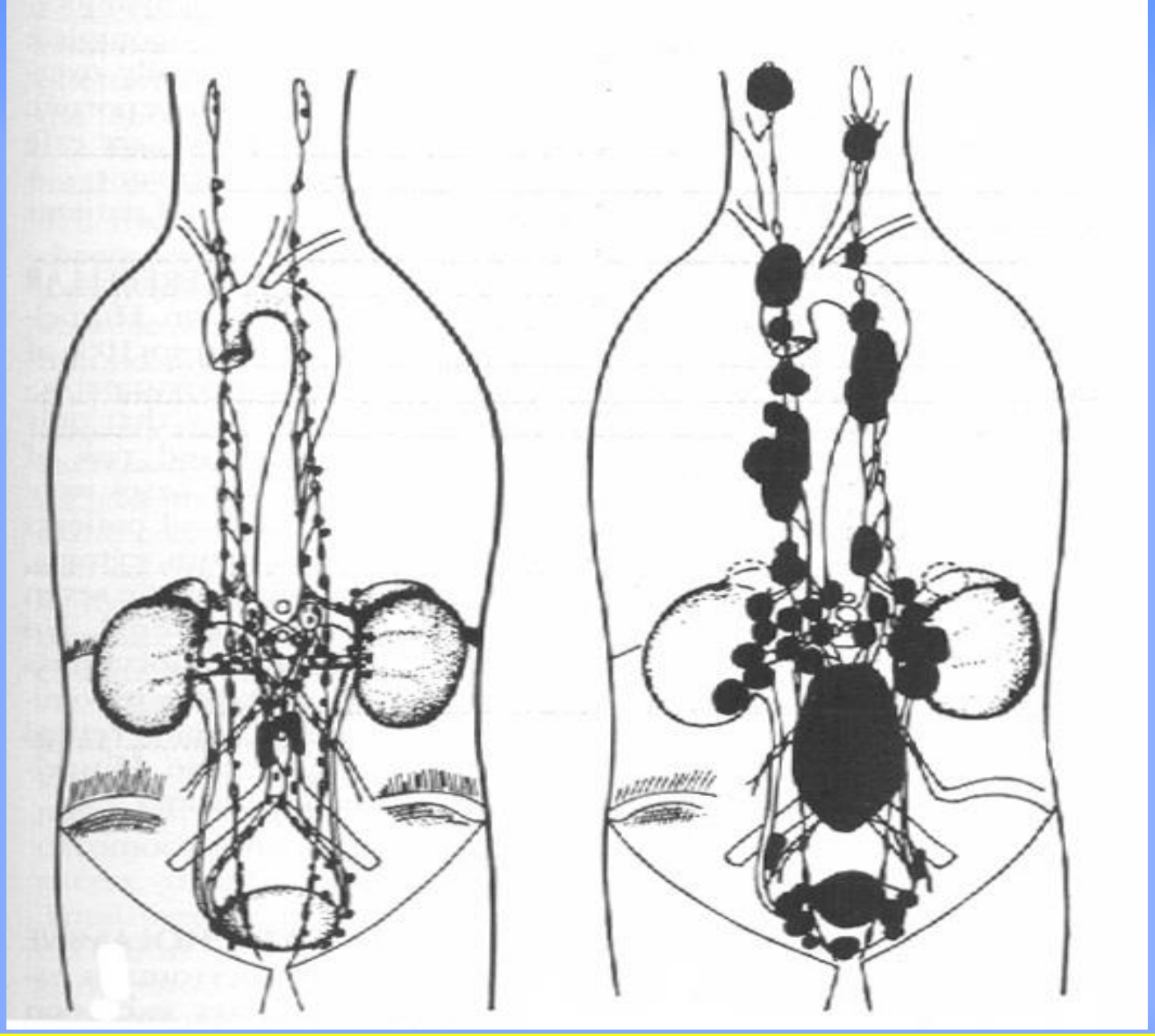
Anatomic Localization

1. Computed tomography

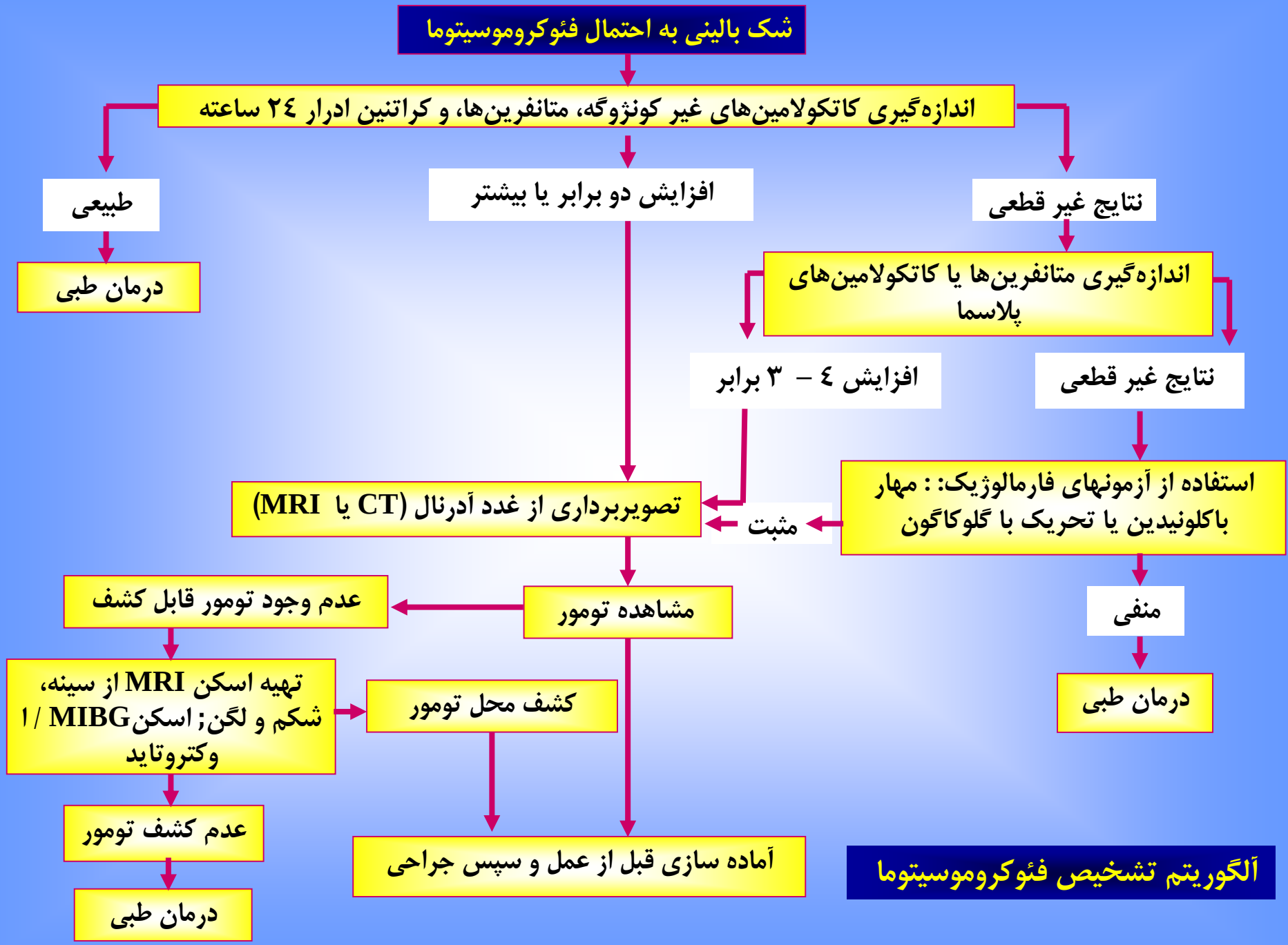
Of the abdomen, including the adrenals, initially; of the pelvis and thorax if the abdomen is negative

Indicated in the absence of biochemical evidence only if clinical suspicion is very high (e.g., positive family history)

2. Iodobenzylguanidine scan



پراکندگی آناتومیک بافت کرومافین در خارج از آدرنال در نوزاد (چپ). محلهای قرارگیری فئوکروموسیتومهای خارج آدرنال (راست)


شک بالینی به احتمال فئوکروموسیتوما
اندازه‌گیری کاتکولامین‌های غیر کونژوگه، متانفرین‌ها، و کراتنین ادرار ۲۴ ساعته
طبیعی
درمان طبی
افزایش دو برابر یا بیشتر
نتایج غیر قطعی
اندازه‌گیری متانفرین‌ها یا کاتکولامین‌های پلاسما
افزایش ۴ – ۳ برابر
نتایج غیر قطعی
استفاده از آزمونهای فارمالوژیک: : مهار باکلونیدین یا تحریک با گلوکاگون
مثبت
تصویربرداری از غدد آدرنال (CT یا MRI)
منفی
درمان طبی
مشاهده تومور
عدم وجود تومور قابل کشف
تهیه اسکن MRI از سینه، شکم و لگن؛ اسکنMIBG / ا وکتروتاید
کشف محل تومور
عدم کشف تومور
درمان طبی
آماده سازی قبل از عمل و سپس جراحی
آلگوریتم تشخیص فئوکروموسیتوما

Sensitivity and specificity of common biochemical tests in the diagnosis of catecholamine-secreting tumors

measurement	Normal range	If measurement greater than:	Sensitivity (%)	Specificity (%)
Urinary metanephrines	< 5 μmol/24 h	9 μmol/24 h	79	93
Urinary VMA	< 35 μmol/24 h	55 μmol/24 h	42	100
Urinary free norepinephrine	< 290 nmol/24 h	720 nmol/24 h	95	95
Urinary free epinephrine	< 90 nmol/24 h	200 nmol/24 h	95	95
Plasma norepinephrine	0.3 – 2.8 nmol/L	5 nmol/L	94	97
Plasma epinephrine	0.1 – 0.52 nmol/L	1.5 nmol/L	90	90

Test characteristics of plasma free and urinary fractionated metanephrines[a]

	Plasma Free Metanephrines		Urinary Metanephrines	
Study	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**
Perry et al[42]	—	—	97.1	91.1
Hickman et al[38]	100	97.6	85.7	95.1
Grouzmann et al[43]	96	89	95	86
Peaston et al[40]	100	96	—	—

Medications that increase catecholamine levels and/or their metabolites

Tricyclic antidepressants

Monoamine-oxidase-inhibitor therapy and concomitant consumption of cheese, or wine; or concomitant monoamine-oxidase inhibitor and sympathomimetic-amine therapy (episodic hypertension)

Labetalol

Levodopa

Drugs containing catecholamines (decongestants)

Amphetamines, buspirone, and most psychoactive agents (mainly tricyclic antidepressants)

Sotalol

Methyldopa

Withdrawal from clonidine

Ethanol

Benzodiazepines

Medical management of pheochromocytoma

Therapeutic	Medical therapy
Control of blood pressure	Alpha-blockers (phenoxybenzamine, terazocin) Calcium channel blockers Metyrosine
Treatment of hypertensive crisis	Phentolamine Sodium nitroprusside
Management of arrhythmias	Beta-blockers (propranolol, esmolol)
Prevention of postsurgical hypotension	Adequately long preoperative alpha- and beta-blocker Volume replacement Pressor agents (norepinephrine, phenylephrine)

Medical management of pheochromocytoma

Physical Examination

A 58-year-old previously healthy man presented to the clinic with an 8-week history of swelling involving his face and both knees, ankles, and hands. He reported a 4.5-kg weight gain over the same time period. He also noted persistent flushing of his face and a sensation of pressure behind his eyes with no headache or visual changes.

Physical Examination

On examination, the patient was alert and had obvious facial plethora. Vital signs were as follows: blood pressure (BP), 194/108 mm Hg, pulse rate, 92 beats/min and regular; and body mass index, 25.2 kg/m2. Of note, the patient was normotensive at a clinic visit 10 months previously. Cardiac examination revealed normal rate and rhythm, normal heart sounds

Physical Examination

Pulses were symmetric with no radioradial or radiofemoral delay.

Examination of the abdomen revealed no organomegaly, masses, audible bruits.

Moderate pitting edema of the lower extremities was present to the midshin.

Funduscopic examination demonstrated a normal optic disc.

Initial laboratory evaluation yielded the following results:

hemoglobin, 16.2 g/dL potassium, 3.9 mmol/LFBS, 99 mg/dL

creatinine, 1.0 mg/dL and thyrotropin, 2.1 mIU/L

Urinalysis was negative for protein and hemoglobin. Electrocardiography revealed normal sinus rhythm with no ST-, T-, or Q-wave changes. Chest radiography demonstrated a normal cardiac shadow and clear lungs.

1. Which one of the following terms best classifies the patient's presentation?

a. Normal BP

b. Prehypertension

c. Stage 1 hypertension

d. Stage 2 hypertension

e. Hypertensive emergency

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)1 classified hypertension as follows: normal BP, systolic less than 120 mm Hg and diastolic less than 80 mm Hg; prehypertension, systolic BP of 120 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg; stage 1 hypertension, systolic BP of 140 to 159 mm Hg or diastolic BP of 90 to 99 mm Hg; and stage 2 hypertension, systolic BP of 160 mm Hg or higher or diastolic BP of 100 mm Hg or higher. Of note, our patient had been advised to purchase an automated home BP cuff and reported systolic BPs above 180 mm Hg over several weeks, confirming the diagnosis of stage 2 hypertension in the absence of evidence for end-organ damage. Hypertensive emergency is defined as a systolic pressure of 180 mm Hg or higher and/or a diastolic pressure of 120 mm Hg or higher with evidence of end-organ dysfunction (such as encephalopathy, papilledema, or myocardial ischemia) requiring immediate BP reduction with parenteral agents.

Patients with stage 2 hypertension rarely respond to a single antihypertensive agent, and the JNC 7 recommends starting combination therapy in this population.1 This approach is controversial among clinicians who may argue that starting 2 drugs simultaneously could lead to an unpredictable BP response with possible confounding in the event of intolerance or allergy. For our patient, chlorthalidone, a potent yet well-tolerated thiazide diuretic with a long half-life, and lisinopril, an angiotensin-converting enzyme inhibitor with nephroprotective benefits, were chosen as a 2-agent combination for stage 2 hypertension. Calcium channel blockers were initially avoided because of the potential for worsening peripheral edema. The patient remained very active, and b-blockers were also not chosen because of concern regarding poor tolerability. After 2 weeks, the patient's edema improved in the setting of diuretic use, but his BP remained elevated at 166/92 mm Hg with a heart rate of 72 beats/min. Initiation of amlodipine, a calcium channel blocker, resulted in improved BP control at 139/82 mm Hg.

2. In addition to the evaluation obtained thus far, further investigation should be performed next for which one of the following conditions?

a. Essential or primary hypertension

b. Renovascular and endocrine disease

c. Primary intrinsic renal disease

d. Coarctation of the aorta

e. “White coat” hypertension

Any patient with severe hypertension or an acute increase in BP who has had previously normal values should undergo investigation for secondary causes of hypertension. Therefore, stopping the work-up at the diagnosis of essential hypertension would not be appropriate. Renovascular disease and endocrinopathies including hypercortisolemia, pheochromocytoma, and primary hyperaldosteronism are all causes of secondary hypertension and need to be further evaluated. The history, physical examination findings, and laboratory results thus far are not sufficient to exclude these conditions. Primary renal disease is unlikely given the patient's normal creatinine concentration and unremarkable urinalysis results. The patient's age at presentation and symmetric BP readings with no pulse delays make coarctation of the aorta an improbable scenario. White coat hypertension is a diagnosis that applies to patients who exhibit modestly elevated BPs in health care settings but normal home and ambulatory BP recordings. Our patient had markedly elevated in-office as well as home BP readings.

Additional evaluation yielded an undetectable aldosterone concentration, undetectable plasma renin activity, normal plasma fractionated metanephrine level, and a 24-hour urinary free cortisol level of 841 μg/24 h (3.5-45 μg/24 h). Renal artery Doppler ultrasonography revealed normal renal arteries and normal renal parenchyma but incidentally demonstrated a 7-cm irregular right-sided adrenal mass. Subsequent testing yielded a suppressed corticotropin level of 5.6 pg/mL (10-60 pg/mL), an elevated dehydroepiandrosterone sulfate concentration of 291 μg/dL (35-179 μg/dL), and an elevated 17 hydroxyprogesterone level of 244 ng/dL (<220 ng/dL). Androstenedione and estradiol levels were unremarkable.

3.On the basis of the results of these investigations, which one of the following is the most likely cause of this patient's hypertension?

a. Pheochromocytoma

b. Corticotropin-dependent Cushing syndrome

c. Corticotropin-independent Cushing syndrome

d. Primary hyperaldosteronism

e. Exogenous glucocorticoid intake

Plasma fractionated metanephrine levels are highly sensitive for the diagnosis of pheochromocytoma, and our patient's normal value makes this diagnosis unlikely. On the basis of the patient's clinical features, markedly elevated urinary free cortisol level, and the presence of an adrenal mass, Cushing syndrome was diagnosed. Corticotropindependent Cushing syndrome is heralded by an elevated corticotropin concentration, due either to pituitary or ectopic hyperproduction. The patient in this case had an appropriately suppressed corticotropin level and therefore has corticotropin-independent Cushing syndrome. A ratio of plasma aldosterone concentration to renin activity of greater than 20 is suggestive of primary hyperaldosteronism, most often caused by an aldosteroneproducing adrenal adenoma (Conn syndrome). Both values are low in this patient, suggesting an etiology for hypertension that is not associated with renin or aldosterone hypersecretion. Although exogenous intake of glucocorticoids such as hydrocortisone may result in excess urinary cortisol with a suppressed corticotropin concentration, the elevation of dehydroepiandrosterone sulfate and 17-hydroxyprogesterone in this case suggests endogenous hyperproduction of adrenocortical hormones. In view of the abnormal laboratory and ultrasonography findings, additional work-up of the adrenal mass was pursued.

4. Which one of the following is the best test to perform next to determine the nature of the patient's adrenal mass?

a. Computed tomography (CT) with intravenous contrast medium

b. Magnetic resonance imaging

c. [11C]-Metomidate positron emission tomography (PET)

d. Fine-needle aspiration biopsy

e. Surgical excision

An adrenal mass should be suspected in all patients with corticotropin-independent Cushing syndrome. In our patient, an adrenal mass was incidentally detected on ultrasonography; however, this testing modality cannot provide the information necessary to differentiate the common types of adrenal mass-benign adenoma, pheochromocytoma, adrenocortical carcinoma (ACC), and metastatic disease. Computed tomography adrenal protocol with intravenous contrast medium is well validated and the imaging test of choice for differentiating adrenal masses. In addition, CT allows operative planning and staging in the event that the mass represents a primary or metastatic neoplasm. Magnetic resonance imaging offers little additional information at a considerably increased cost and is not recommended as an initial imaging test. [^{11}C]-Metomidate is an agent with high affinity for adrenocortical enzymes. [^{11}C]-Metomidate PET is useful for imaging adrenocortical metastases but is unable to differentiate benign and malignant adrenocortical tumors. Fineneedle aspiration biopsy has utility in diagnosing metastatic disease, but the technique results in a specimen that lacks surrounding architecture and is unable to distinguish a benign cortical adenoma from ACC. The nature of the adrenal tumor must be elucidated before surgical excision because metastatic disease often requires systemic therapy, primary tumors may require open surgical exploration, and benign masses can often be removed with minimally invasive techniques.

Adrenal CT revealed a 6.15.87.4-cm nodular right adrenal mass partially compressing, but not invading, the inferior vena cava. The mass exhibited areas of calcification as well as central and peripheral contrast enhancement. Also noted was an unenhanced attenuation average of 30.2 Hounsfield units (HU) with 20% contrast washout at 10 minutes. The left adrenal gland appeared normal, and no other abdominal abnormalities were detected.

5. The imaging and laboratory characteristics are most consistent with which one of the following diagnoses?

a. Pheochromocytoma

b. Benign cortical adenoma

c. Adrenal metastasis

d. Adrenal cyst

e. ACC

The CT imaging characteristics of a pheochromocytoma include increased unenhanced attenuation (>20 HU), size greater than 4 cm, ncreased vascularity, cystic and hemorrhagic changes, and delay in contrast washout (<50% over 10 minutes). Many of these characteristics are met by this patient's mass, but pheochromocytoma tends to be well circumscribed and does not result in overproduction of adrenocortical hormones. Although benign adrenal adenomas may produce excess cortisol, these tumors are typically small (<4 cm), round, well encapsulated, and homogeneous with low unenhanced attenuation (<10 HU) and rapid contrast washout (>50% over 10 minutes). Lung, pancreatic, colorectal, and breast cancers have the potential to metastasize to the adrenal glands, and these metastatic lesions are more commonly diagnosed than primary adrenal tumors. These masses are identical to ACC on imaging but have a tendency to be bilateral and eventually result in adrenal hypofunction rather than hyperfunction. Adrenal cysts do not have a solid component, and the characteristic appearance allows them to be easily differentiated from other lesions. Our patient's adrenal mass and excess corticosteroid production are most consistent with a hyperfunctioning ACC: irregular shape, large size (>4 cm), unilateral, inhomogeneous density, calcification, locally invasive, high unenhanced attenuation (>20 HU), and delay in contrast washout (<50% over 10 minutes)

Staging CT of the chest yielded no evidence of metastatic disease. The patient underwent an uncomplicated open adrenalectomy and exploratory laparotomy. Histopathologic studies confirmed poorly differentiated ACC with clear resection margins. Adjuvant mitotane chemotherapy was initiated with a temporary corticosteroid course for expected adrenocortical insufficiency secondary to hypothalamic suppression. Antihypertensive medications were discontinued postoperatively. At outpatient follow-up 3 weeks later, the patient reported marked improvement in the diffuse swelling. He was taking no antihypertensive medications, and his BP was 118/72 mm Hg.

DISCUSSION

Adrenocortical carcinoma is a rare malignant tumor of the adrenal gland with an incidence of approximately 2 per million per year in the general population.3 Nonetheless, this diagnosis should be considered as part of the appropriate evaluation of secondary hypertension and incidental adrenal masses. Of all patients undergoing advanced imaging of the abdomen, an estimated 4% to 6% will have an adrenal incidentaloma. Between 2% and 5% of these masses will result in a diagnosis of ACC, with most being attributable to nonfunctioning cortical adenomas. The incidence of ACC appears to be increasing with the improved detection of incidental adrenal masses over the past decade. A slight female predominance (approximately 2:1) and a bimodal distribution in the age at diagnosis have been described, with peaks before the age of 5 years and again in the fourth to fifth decade of life. Most cases are sporadic, but several hereditary cancer syndromes including multiple endocrine neoplasia type 1, Beckwith-Wiedemann syndrome, and Li-Fraumeni syndrome are strongly associated with ACC

DISCUSSION

More than 60% of adults with ACC present with clinical symptoms of excess hormone production, with the remainder having nonfunctioning tumors producing compressive, metastatic, or constitutional symptoms. Cushing syndrome predominates as the most common presentation in patients with functioning masses (45%), followed by a combination effect of glucocorticoids and androgens (25%) and virilization alone (10%). Symptoms of glucocorticoid excess usually develop rapidly over 3 to 6 months and consist of weight gain, edema, weakness, or insomnia. The acuity may explain the occasional absence of classic features of chronic Cushing syndrome such as characteristic adipose tissue redistribution as well as skin and muscle atrophy.

DISCUSSION

History and physical examination should focus on excluding features of more common diagnoses including pituitary adenomas, pheochromocytoma, renovascular disease, and hyperaldosteronism. Even in patients with asymptomatic incidentalomas, determining secretory status is important with a laboratory evaluation for glucocorticoid excess, pheochromocytoma, hyperaldosteronism, and hyperandrogenism. Computed tomography with intravenous contrast medium remainsmthe most important first-line imaging modality for differentiating larger heterogeneously enhancing ACCs from smaller lipid-rich benign adenomas. Histopathologic examination is required to confirm the diagnosis; however, needle aspiration biopsy is unable to differentiate benign from malignant adrenocortical masses, and a surgical approach is recommended.

The TNM (tumor, node, metastasis) system is most widely used for staging, and CT of the chest, abdomen, and pelvis is generally sufficient for initial evaluation. Only 6% of ACCs are diagnosed at a size of 5 cm or less (stage I), with 42% of patients presenting with a tumor greater than 5 cm but localized to the adrenal gland (stage II). Local invasion into surrounding tissues, the inferior vena cava, renal veins, and lymph nodes (stage III) occurs in 16% of patients without distant metastases. The most common sites of distant spread for ACC are the liver, lungs, and bone and are present in 36% of patients at presentation (stage IV).

DISCUSSION

Prompt and complete surgical excision is the only potentially curative intervention for localized ACC. Open unilateral adrenalectomy is considered the criterion standard approach because some studies-although inconsistently so-have documented earlier and more frequent recurrence with laparoscopy. Functioning masses result in hypothalamic pituitary-adrenal axis suppression and require perioperative glucocorticoid support. Following resection, adjuvant therapy may be provided in those with a high risk of recurrence based on tumor stage, grade or proliferation, and completeness of resection. Mitotane is a drug that has a cytotoxic effect preferentially on adrenocortical tissue while inhibiting steroidogenesis and has been reported to reduce the rate of recurrence of ACC in randomized trials. Posttreatment surveillance is recommended with CT or PET at regular 3- to 6-month intervals. The 5-year survival for localized disease is 82%, 61%, and 50% for stage I, II, and III disease, respectively. In those with metastatic, unresectable, or recurrent ACC, mitotane may be combined with systemic chemotherapy (such as etoposide, doxorubicin, and cisplatin) to enhance cytotoxic activity in adrenocortical cells and has an overall response rate of 49%. Nonetheless, the prognosis for stage IV disease is poor, and 5-year survival is less than 15%. In conclusion, severe or resistant hypertension in a previously normotensive patient should prompt an evaluation for secondary causes. Adrenocortical carcinoma, although rare, is an important cause of Cushing syndrome and adrenal masses with a potential for disastrous outcomes if missed or neglected.