Cushing's syndrome

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Outline

- Introduction
- Epidemiology
- Aetiology & Classification
- Pathophysiology
- Clinical presentation
- Diagnostic tests
- Management
- Conclusion

Introduction

- Syndrome of chronic exposure to inappropriately elevated levels of free plasma glucocorticoids.
- Cushing’s Syndrome vs Cushing’s Disease
- Harvey Cushing – 1912 “diabetes in bearded women”
- Walters et al – 1934 : Adrenalectomy is curative

Epidemiology

- Rare. True prevalence difficult to define
- 5 to 10 cases per million have CD
- Incidentalomas + hypercortisolaemia present in 1% of people > 70yrs
- 1-5% of obese type 2 DM pt have CS
- Few case reports from our climes.

Unilateral macronodular adrenal hyperplasia as an unusual cause Cushing's syndrome--a case study.

Agboola-Abu C Kuku SF. (West Afr J Med. 1999 Apr-Jun;18(2):124-9.)

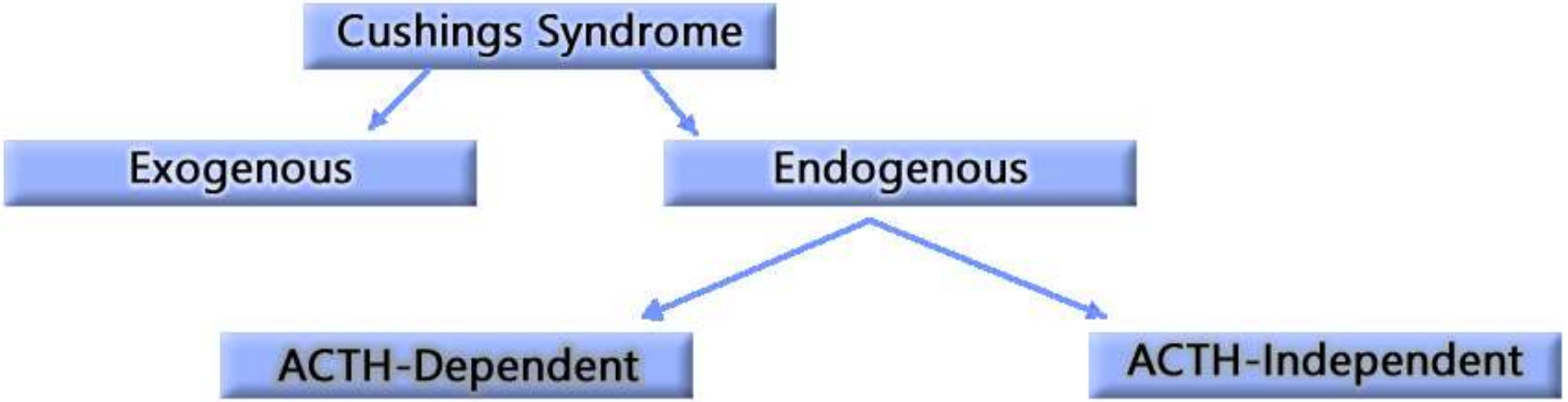
- A 20-year old female, who was admitted with a recently developed central obesity, amenorrhea, hirsutism, proximal myopathy and depression. She was found to have multiple striae, thin skin, elevated blood pressure glycosuria and hyperglycaemia.
- Morning and mid-night plasma cortisol concentrations revealed elevated levels, with a loss of diurnal variation. There was a failure of the normal suppressibility of cortisol secretion by low doses of dexamethasone, while a significant suppression of plasma cortisol concentration was observed with high doses of dexamethasone.
- There were no significant abnormalities observed in the pituitary fossa on skull radiograph and on the cranial computerised tomographic scan.

Unilateral macronodular adrenal hyperplasia as an unusual cause Cushing's syndrome--a case study.

After a period of stabilisation, she had a bilateral adrenalectomy done, with a histopathological finding of a left adrenal macronodular hyperplasia, while the right adrenal gland was small and friable.

There was an uneventful post-operative period, with a gradual return to normality of most of the presenting complaints. The hyperglycaemia and hypertension got controlled without medications, while her menstrual cycles resumed within three months of bilateral adrenalectomy.

This case report illustrates that an adrenal-dependent Cushing's syndrome may mimic a pituitary-dependent one, especially as regards the suppressibility of plasma cortisol secretion by high doses of dexamethasone.



Cushing's disease (pituitary-dependent) 68%

Ectopic ACTH syndrome 12%

Ectopic CRH syndrome

Iatrogenic (treatment with 1-24 ACTH)

Adrenal adenoma (10%) and carcinoma (8%)

Primary pigmented nodular adrenal hyperplasia and Carney's syndrome.

McCune-Albright syndrome

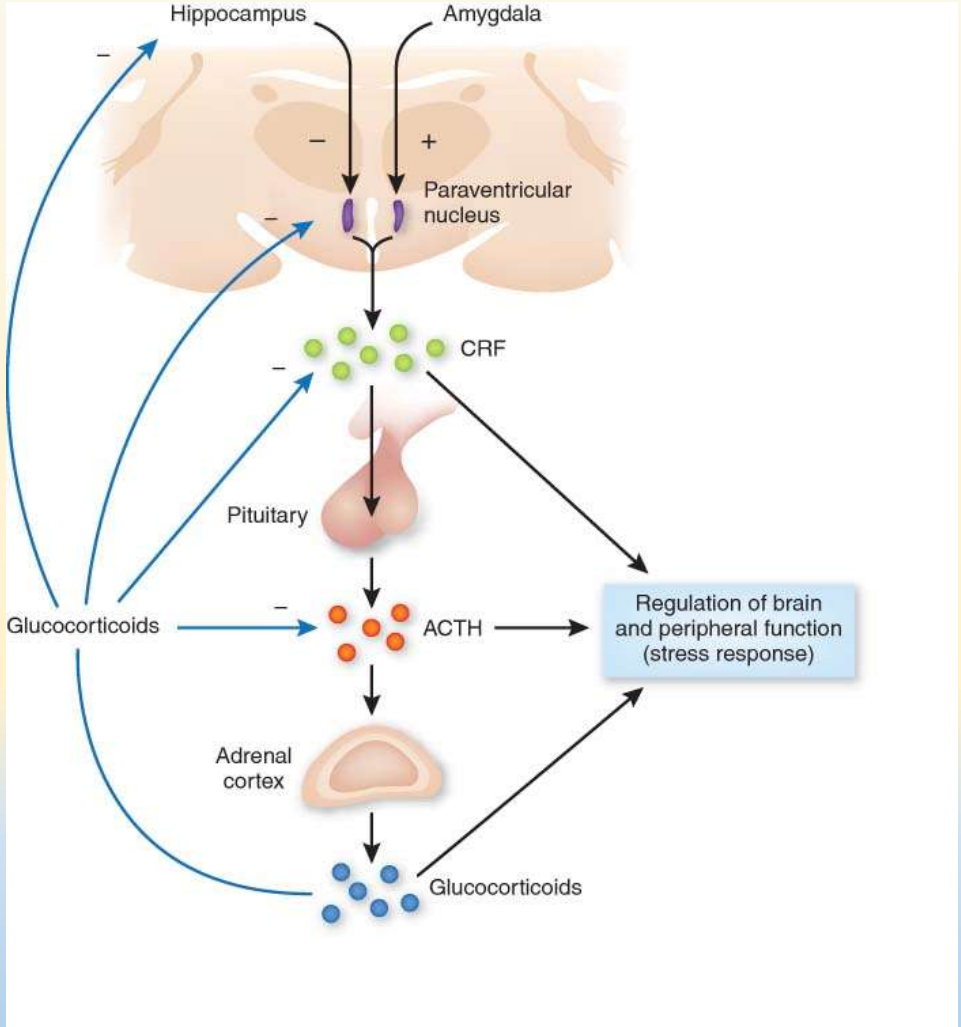
Macronodular adrenal hyperplasia

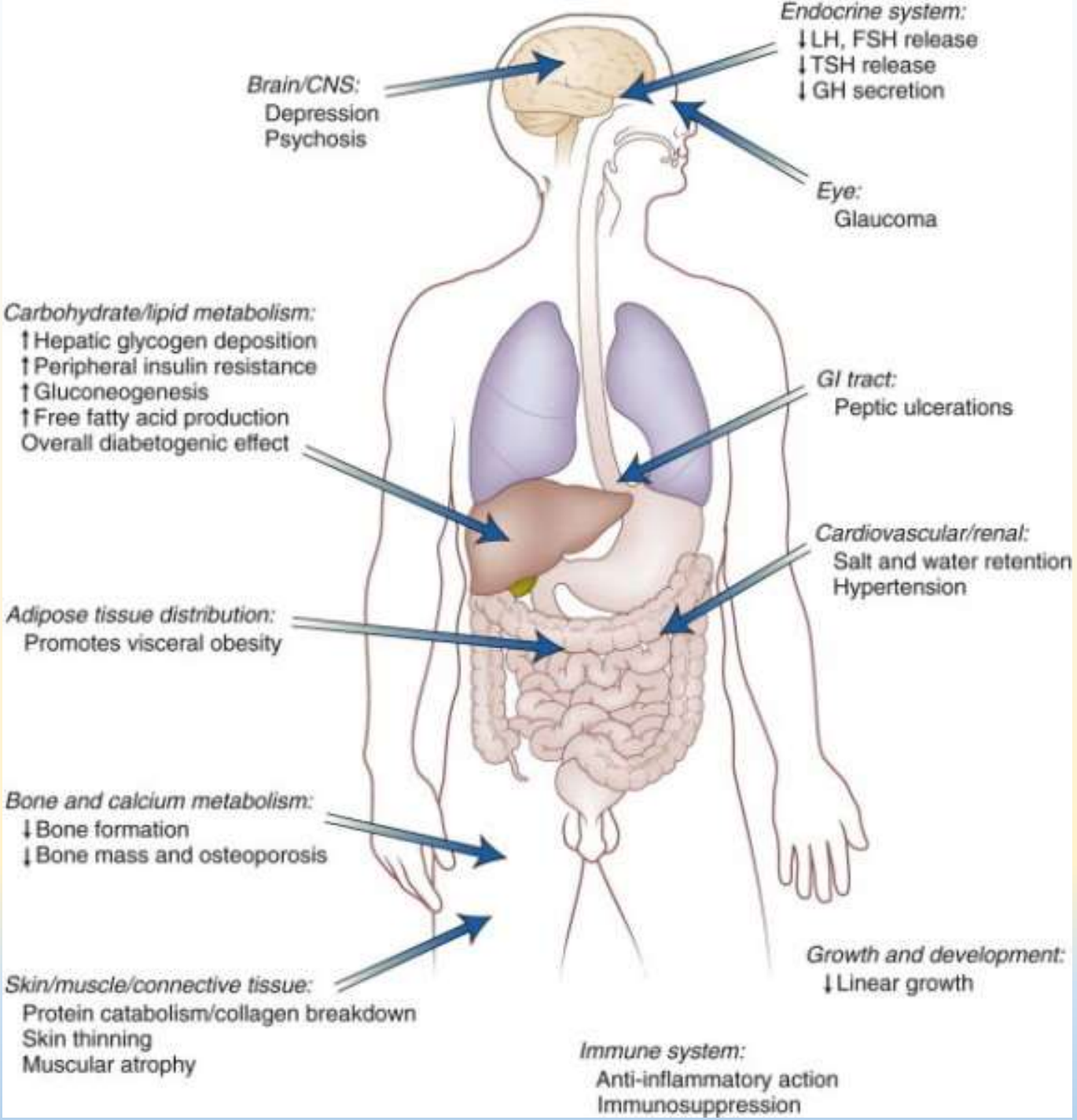
Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β, LH)

Tumours associated with ectopic ACTH

Tumor Type	Approximate Incidence (%)
Small-cell lung carcinoma	50
Non–small-cell lung carcinoma	5
Pancreatic tumors (including carcinoids)	10
Thymic tumors (including carcinoids)	5
Lung carcinoids	10
Other carcinoids	2
Medullary carcinoma of thyroid	5
Pheochromocytoma and related tumors	3
Rare carcinomas of prostate, breast, ovary, gallbladder, colon	10

Pathophysiology





Aetiology of CD: Hypothalamic or Pituitary ?

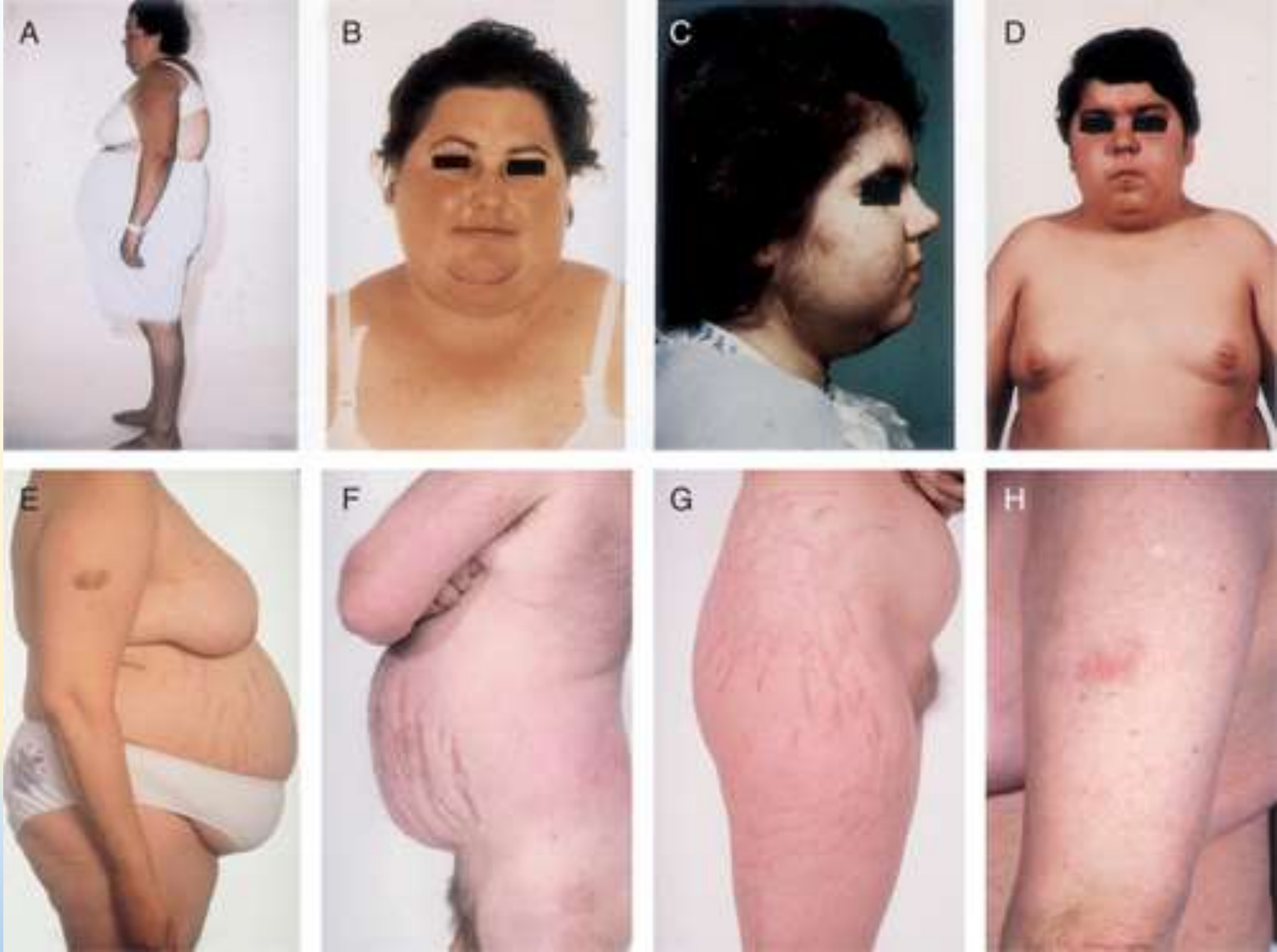
Hypothalamic	Pituitary
Presence of Neuroendocrine abnormalities	No cure after pituitary stalk section
Loss of circadian rhythm, sleep disturbance	Circulating and CSF CRH levels are suppressed
Other “hypothalamic defects” (TSH, LH/FSH secretion)	Reversal of “hypothalamic defects” on correction of hypercortisolism
Efficacy of centrally acting drugs (bromocriptine, cyproheptadine, sodium valproate)	High surgical cure rate
Recurrences after pituitary surgery	Pituitary ACTH-secreting adenoma in almost 90% of cases are monoclonal in origin.[291,292]
Ectopic CRH-secreting tumours cause Cushing's disease.	

Clinical presentation

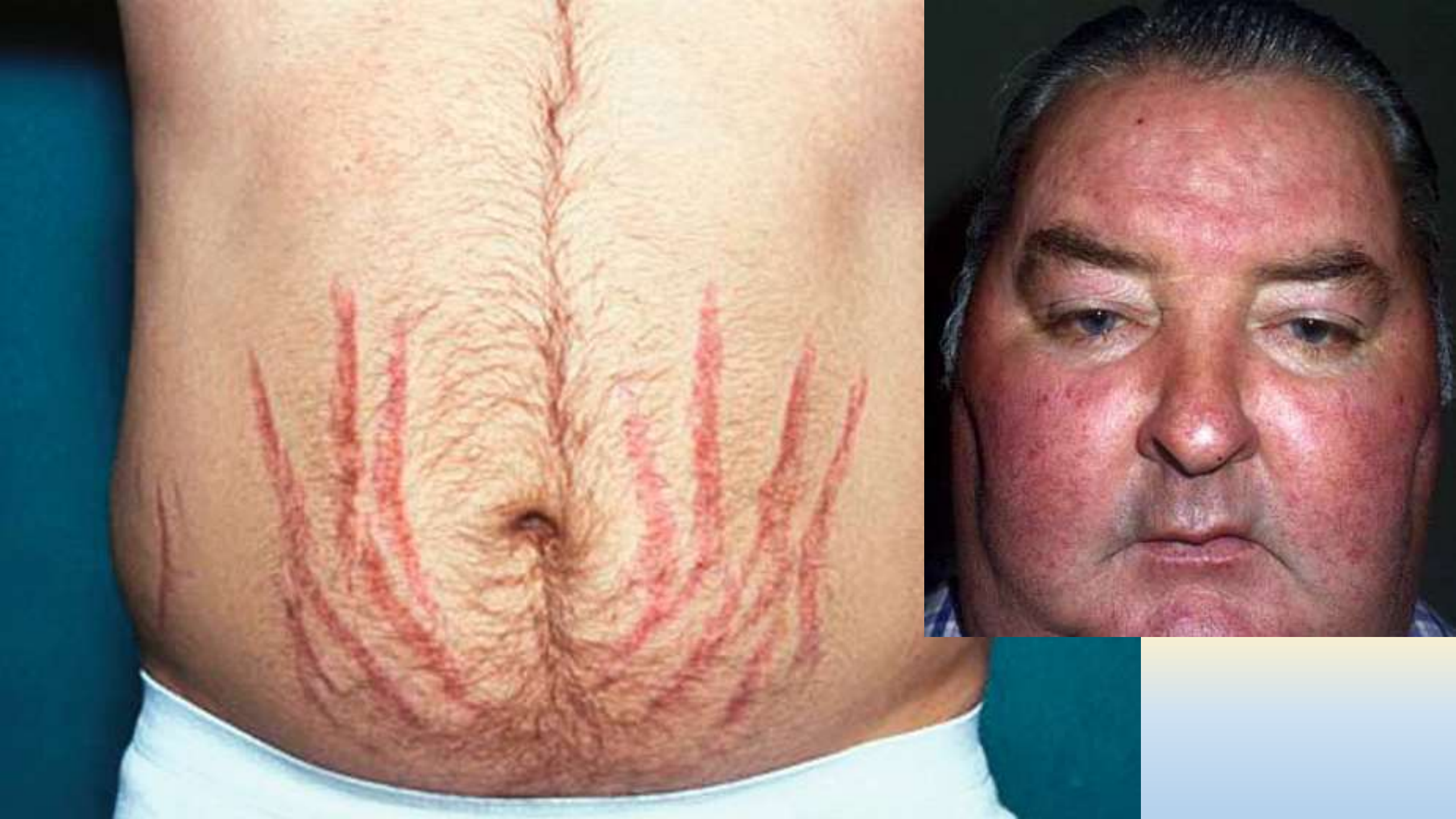
- Obesity
- Gonadal dysfunction
- Psychiatric abnormalities
- Bone abnormalities
- Dermatological changes
- Myopathy (proximal)
- Cardiovascular abnormalities: HTN, DVT-TE
- Metabolic and Endocrine changes
- Infections
- Ocular changes

Special situations of hypercortisolism

- Pseudo-Cushing’s
- Cyclic Cushing’s Syndrome
- Children
- Pregnancy
- Glucocorticoid resistance states


A
B
C
D
E
F
G
H

Symptoms		***Signs***	
Weight gain	91	Obesity	97
Menstrual irregularity	84	Truncal	46
Hirsutism	81	Generalized	55
Psychiatric dysfunction	62	Plethora	94
Backache	43	Moon facies	88
Muscle weakness	29	Hypertension	74
Fractures	19	Bruising	62
Loss of scalp hair	13	Red-purple striae	56
		Muscle weakness	56
Other Findings		Ankle edema	50
Hypertension	74	Pigmentation	4
Diabetes	50		
Overt	13	Osteoporosis	50
Impaired glucose tolerance test	37	Renal calculi	15



Differential diagnosis

- Obesity & its secondary causes
- Pseudo-Cushings
- NETs which?
- Polycystic Ovarian Syndrome.

Diagnostic tests

- Does this patient has Cushing’s syndrome
- If yes, what's the cause?

Diagnosis—Does the Patient Have Cushing's Syndrome?
Circadian rhythm of plasma cortisol
Urinary free cortisol excretion
Low-dose dexamethasone suppression test*
Salivary Cortisol
Differential Diagnosis—What Is the Cause of the Cushing's Syndrome?
Plasma ACTH
Plasma potassium, bicarbonate
High-dose dexamethasone suppression test
Metyrapone test
Corticotropin-releasing hormone
Inferior petrosal sinus sampling
CT, MRI scanning of pituitary, adrenals
Scintigraphy
Tumor markers

Urinary Free Cortisol Excretion

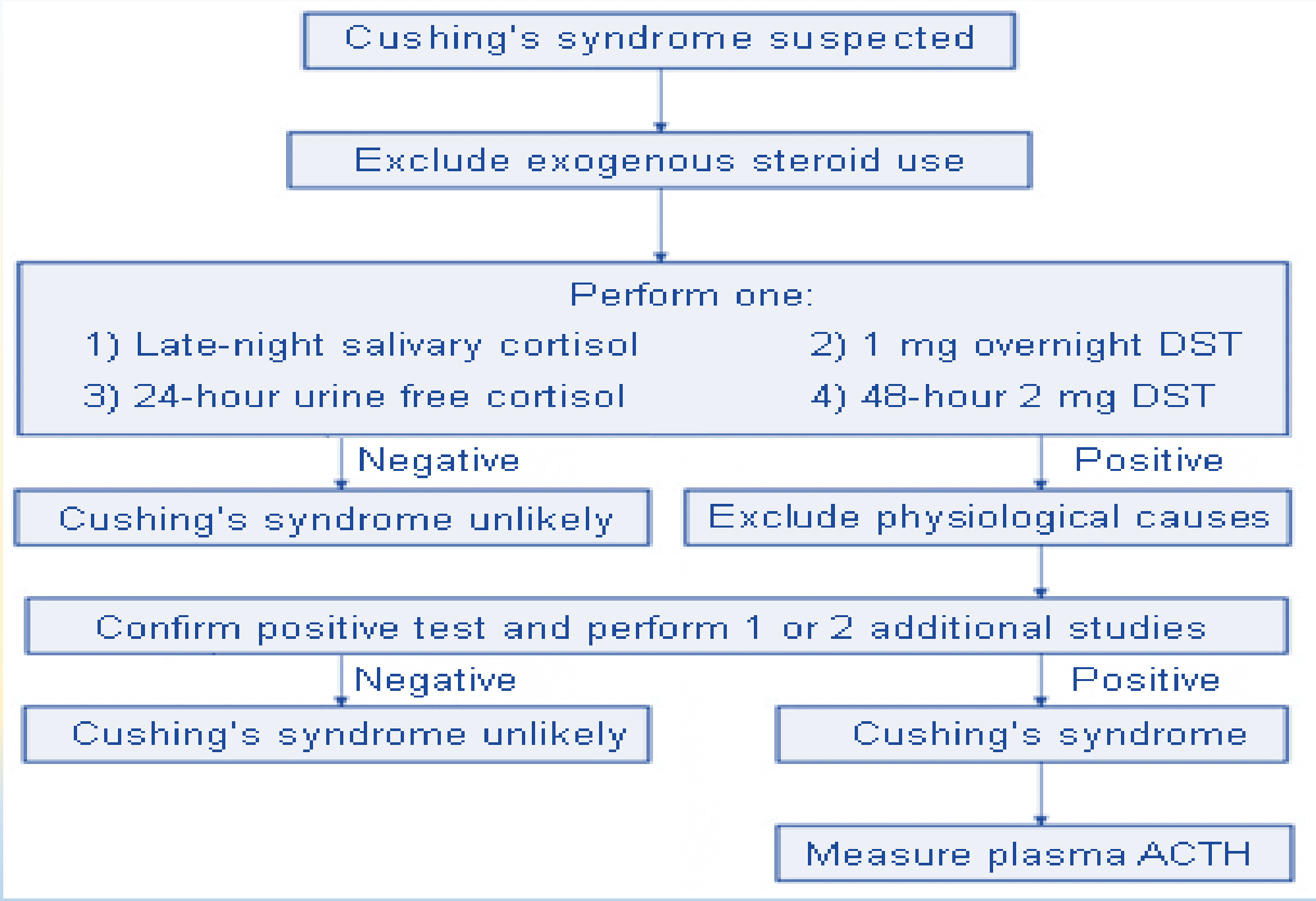
- Excess cortisol is excreted in urine as free cortisol.
- 24 hour collection gives integrated estimation of the level of hypercortisolaemia
- 2 or 3 24 hour collections should be done
- False +ve : digoxin and carbamazepine
- False –ve : incomplete collection, renal impairment (GFR< 30ml/min)

Midnight Salivary Cortisol

- Loss of normal circadian rhythm of cortisol secretion.
- A single sleeping midnight plasma cortisol of less than 50 nmol/l effectively excludes CS at the time of the test.
- Useful, esp when on drugs that alter dexamethasone metabolism.
- Values above 50 nmol/l when asleep or above 207 nmol/l when awake are found in Cushing's syndrome

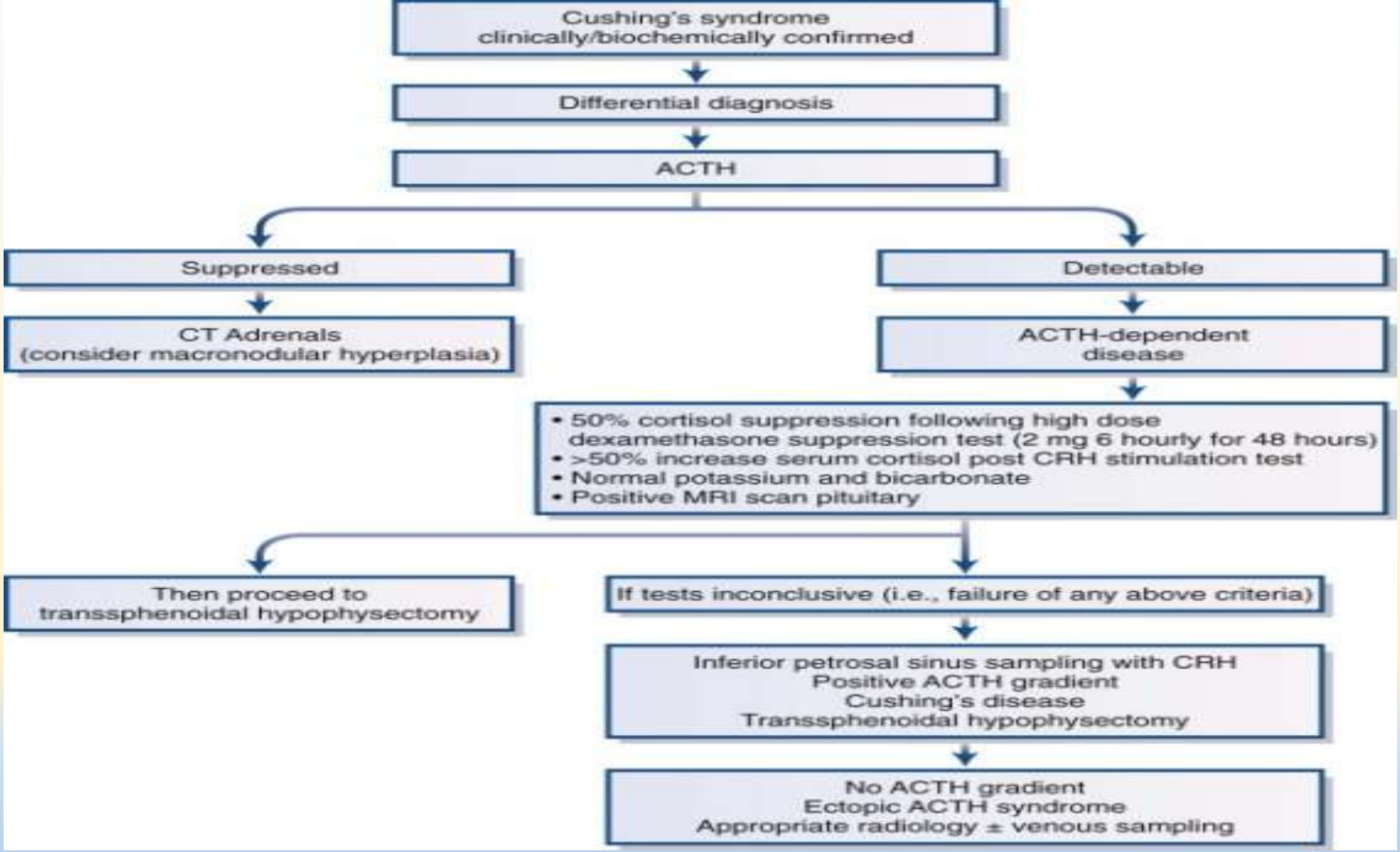
Low-Dose DST

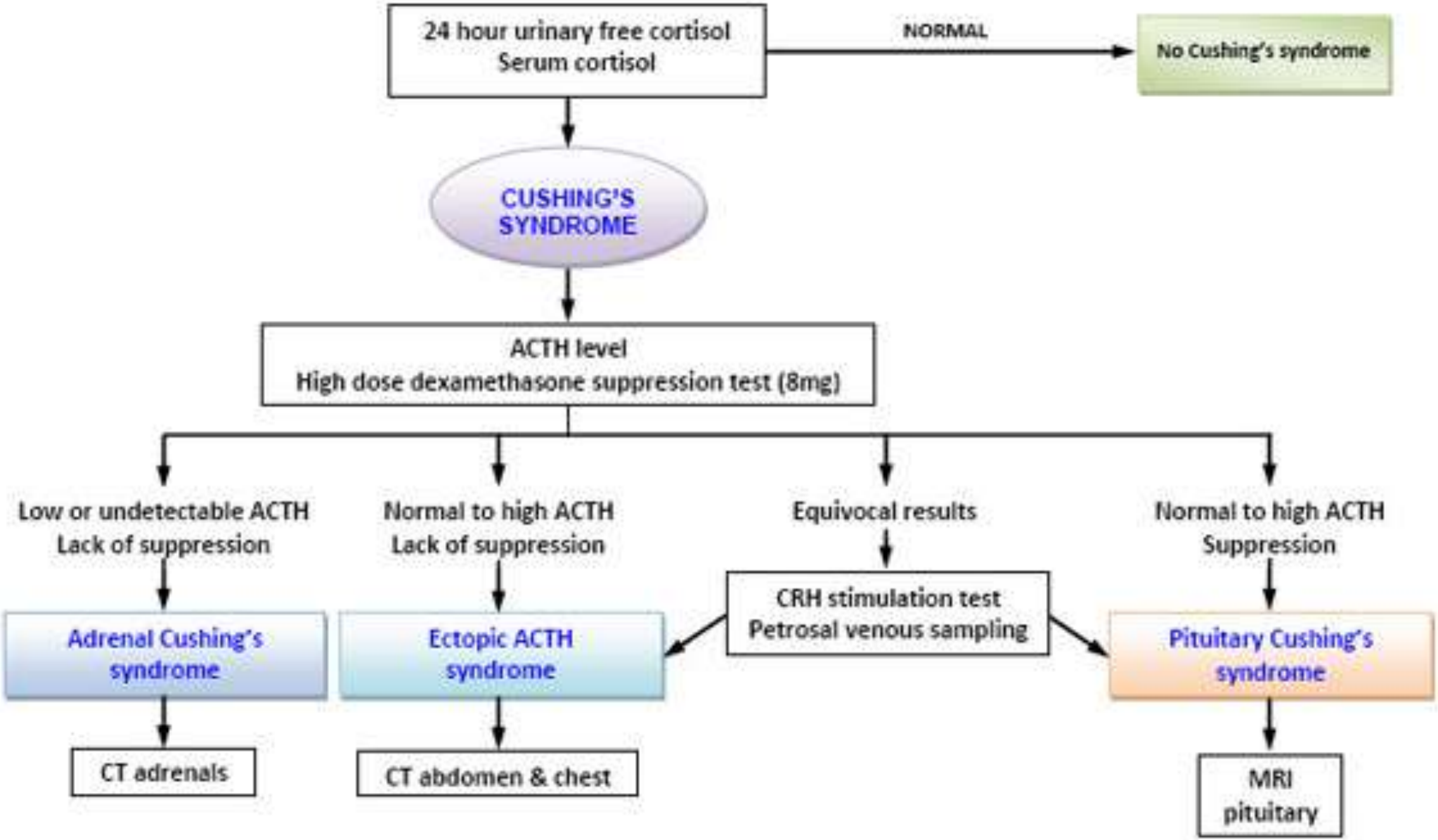
- Overnight: 1mg of Dexamethasone at 23:00hrs, take cortisol sample 08:00 – 09:00hrs.
- 48 hour LD-DST: 0.5 mg of Dexamethasone every 6 h for 2 days at 09.00, 15.00, 21.00, and 03.00 hours.
- Serum > 50 nmol/l excludes CS
- Consider interfering medications.
- 3–8% of patients with proven Cushing's disease supress.


Cushing's syndrome suspected
Exclude exogenous steroid use
Perform one:
1) Late-night salivary cortisol
2) 1 mg overnight DST
3) 24-hour urine free cortisol
4) 48-hour 2 mg DST
Negative
Positive
Cushing's syndrome unlikely
Exclude physiological causes
Confirm positive test and perform 1 or 2 additional studies
Negative
Positive
Cushing's syndrome unlikely
Cushing's syndrome
Measure plasma ACTH

Morning Plasma ACTH

- Take precautions. Follow local protocol.
- Suppressed ACTH levels (<1 picomol/L [<5 picograms/mL]) indicate ACTH-independent CS.
- Unsuppressed ACTH levels (>4 picomol/L [>20 picograms/mL]) indicate ACTH-dependent CS.
- Values in between require cautious interpretation.


Cushing's syndrome
clinically/biochemically confirmed
Differential diagnosis
ACTH
Suppressed
Detectable
CT Adrenals
(consider macronodular hyperplasia)
ACTH-dependent
disease
• 50% cortisol suppression following high dose
dexamethasone suppression test (2 mg 6 hourly for 48 hours)
• >50% increase serum cortisol post CRH stimulation test
• Normal potassium and bicarbonate
• Positive MRI scan pituitary
Then proceed to
transsphenoidal hypophysectomy
If tests inconclusive (i.e., failure of any above criteria)
Inferior petrosal sinus sampling with CRH
Positive ACTH gradient
Cushing's disease
Transsphenoidal hypophysectomy
No ACTH gradient
Ectopic ACTH syndrome
Appropriate radiology ± venous sampling


24 hour urinary free cortisol
Serum cortisol
NORMAL
No Cushing's syndrome
CUSHING'S SYNDROME
ACTH level
High dose dexamethasone suppression test (8mg)
Low or undetectable ACTH
Lack of suppression
Normal to high ACTH
Lack of suppression
Equivocal results
Normal to high ACTH
Suppression
Adrenal Cushing's syndrome
Ectopic ACTH syndrome
CRH stimulation test
Petrosal venous sampling
Pituitary Cushing's syndrome
CT adrenals
CT abdomen & chest
MRI pituitary

High dose DST

- Pituitary corticotroph adenoma is relatively sensitive to glucocorticoid, while non-pituitary tumours are resistant.
- 2 mg given every 6 h for 48 h and serum cortisol measure at 09.00 h at the beginning and end, OR
- A single 8 mg dose given at 23.00 h and serum cortisol measured the next day at 09.00 h
- Useful when bilateral inferior petrosal sinus sampling (BIPSS) is not available.

Methyrapone test

- Methyrapone blocks cortisol production, thus ↑ACTH (-ve feedback)
- Given 4 hourly x 24 hours
- In CD, exaggerated ↑in ACTH, and ↑deoxycortisol.
- Questionable value
- Does not reliably distinguish between CD and the ectopic ACTH syndrome

CRH test

- Normally, CRF produces a modest rise in ACTH and cortisol
- Administer single dose of CRH ± AVP
- Assay ACTH and Cortisol, every 15 minutes for 1 – 2 hours
- Exaggerated rise of ACTH and Cortisol in CD
- No rise in ectopic ACTH syndrome
- Specificity and a sensitivity of approximately 90%

Inferior Petrosal Sinus Sampling

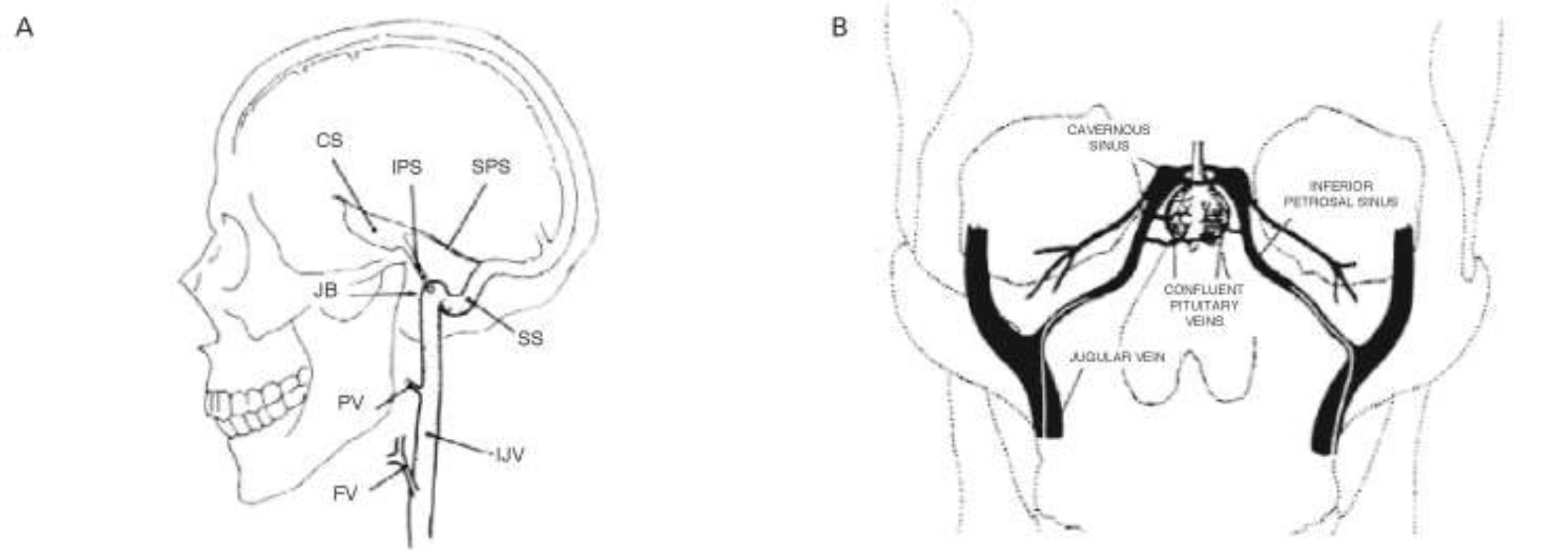


Figure 2. Schematic views of the pituitary venous drainage. **(A)** Sagittal, **(B)** Coronal CS: cavernous sinus, IPS: inferior petrosal sinus, SPS: superior petrosal sinus, JB: jugular bulb, SS: sigmoid sinus, IJV: internal jugular vein, FV: facial vein, PV: pharyngeal vein. [Reproduced from (14,37) with permission]

Inferior Petrosal Sinus Sampling

Table 3. Examples of BIPSS results data represent ACTH levels in pg/ml units.

	Peripheral	Left IPS	Right IPS	Highest IPS:peripheral ratio	Lateralization ratio
Pituitary Cushing's					
Basal	32	110	74	110/32 = **3.44**	
3 min post-CRH	34	563	110		563/110 = **5.12**
5 min post-CRH	39	630	176		
10 min post-CRH	43	725	210	725/43 = **18.13**	
15 min post-CRH	54	304	280		
Ectopic Cushing's					
Basal	33	41	38	41/33 = **1.24**	
3 min post-CRH	34	51	35	51/34 = **1.50**	
5 min post-CRH	32	46	36		
10 min post-CRH	30	44	38		
15 min post-CRH	34	41	35		

Imaging studies

- High Resolution CT/MRI Scanning of Pituitary and Adrenals
- Scintigraphy Studies: suspected adrenocortical macronodular hyperplasia, ectopic ACTH syndrome from NETs,

Other Investigations

- Cardiovascular risk assessment
- Other pituitary hormonal profile.
- Other adrenal hormonal profile.

Management: Adrenal causes

- Adrenal adenoma: unilateral adrenalectomy
  - 100% cure rate
  - Temporary glucocorticoid replacement
- Adrenal carcinoma: Attempt adrenalectomy
  - Poor prognosis
  - Mitotane (adrenolytic agent)
  - Etoposide, doxorubicine, cisplatin, Sorefenib
  - Radiotherapy
  - Most die within 2 years of diagnosis

Management: Pituitary causes

- Transsphenoidal hypophysectomy
- In the past, bilateral adrenalectomy
- Careful choice of where we refer.
- Peri-op corticosteroid like for px with potential or confirmed deficit of the HPA axis: *after surgery, the surrounding corticotrophs are usually suppressed – they gradually recover.*
- Radiotherapy: limited role, old Rx, unresponsive px, after bilateral adrenalectomy or in established Nelson's syndrome.
- Recurrent dx: repeat surgery, gamma knife, radiosurgery, medical Rx

Management: ectopic ACTH syndromes

- Depends on the tumour
- If found, and not spread: tumour excision
- When associated with small-cell lung cancer, poor prognosis.
- Medical Rx, while treating the underlying tumor.
- If ectopic source not found, consider bilateral adrenalectomy, then keep monitoring.

IDENTICAL TWINS

Medical Rx: Indications

- While preparing for surgery
- When surgery is not curative
- When surgery is contraindicated
- While waiting for radiotherapy to be effective,
- To correct acute severe physical or psychiatric consequences of hypercortisolaemia.

Medical Rx

- Metyrapone: Inhibits 11β-hydroxylase
- Ketoconazole: blocks steroidogenic cytochrome P450–dependent enzymes and thus lowers plasma cortisol levels.
- Mitotane: destroys adrenocortical cells, inhibits 11β-hydroxylase & SCC
- Etomidate
- Aminoglutethimide: more toxic, blocks earlier steroidogenic enzymes.
- Trilostane: inhibits 3β-HSD. Ineffective in CD.
- Rosiglitazone: ACTH-secreting pituitary tissue expresses PPAR-γ receptor – successful in rats, but failed in humans.

Management

- Treat co-morbidities like hypertension, diabetes, obesity in usual manner, irrespective of primary modality used to treat hypercortisolaemia.

Prognosis

- Before effective Rx, 50% of patients with untreated CS died within 5 years, principally from vascular disease.
- CV risk though reduced, is still high for several years after cure.
- Many patients feel worse for months after treatment before feeling better.
- Features variably improve, but may not return to normal.
- The adrenocortical carcinomas have a 5-year survival rate of ≤ 30%

Summary

- The diagnosis and treatment of Cushing's syndrome remains a challenging problem in clinical practice- despite the advances in medical science. Patients typically spend several years treating the manifestations of the disease, before the diagnosis is made. A high index of suspicion is required, and the results are rewarding if one faces the challenge in a timely and relentless manner.

References

- Willliam’s Textbook of Endocrinology 12ed
- Oxford Textbook of Endocrinology and Diabetes 2ed
- The Diagnosis and Differential Diagnosis of Cushing’s Syndrome and Pseudo-Cushing’s States (The Endocrine Society) By John Newell-Price