Cushing’s Syndrome

<table>
<thead>
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<th>Moon face, plethora</th>
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<tr>
<td>Acne and hirsutism</td>
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<td>Supraclavicular fat pads</td>
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<td>Hypertension</td>
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<tr>
<td>Truncal obesity</td>
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<tr>
<td>Striae</td>
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<tr>
<td>Proximal myopathy</td>
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<tr>
<td>Thin limbs</td>
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<td>Thin skin, ? leg ulcers</td>
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<tr>
<td>Bruising</td>
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<td>Check urine for glucose</td>
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Cushing’s syndrome

Examination Scheme

Introduce yourself
Ask permission and explain the purpose of the examination
General inspection- truncal obesity, plethoric face with “mooning”

Hands and forearms:
Thin skin: check skin-fold thickness by gently lifting a pinch of skin from forearm
Easy bruising- note purpura over forearms and back of hands (common sites of minor trauma)

Upper arms
Check or ask for blood pressure reading
Note if they are thin compared with trunk
Check for proximal myopathy- elbows in the air, “don’t let me push down”
(Avoid comparing the patient to an “orange on matchsticks” in their presence)

Face and neck
Look from in front to see if cheeks obscure junction of ear with side of face- ie mooning
Note plethoric red complexion of cheeks
Note any androgenic effects of steroids- greasy acneiform skin or hirsutism
Neck- observe and feel supraclavicular fossae for fat pads

Chest
Note any wheeze or breathlessness in case steroids have been given for a respiratory problem.

Abdomen
Note scars of adrenalectomy
Look for purple striae

**Legs**

Thin legs
Proximal myopathy- “cross your arms over your chest and try to stand from sitting”
Thin skin with bruising and ?evidence of leg ulcers

Is there anything else you’d like to do?
1) Check the urine for glucose
2) Look at the drug chart to see if steroids are being administered
3) Examine the back for an interscapular fat pad (avoid the term buffalo hump; even though memorable, it may cause offence)
4) Ask for results of bone mineral density and comment on stature and any clinical evidence of osteoporosis- scoliosis or loss of distance between lower ribs and top of pelvis due to crush fractures of lumbar vertebrae

**What are the causes of Cushing’s?**
Exogenous steroids
Pituitary adenoma (Cushings’ DISEASE)
Adrenal adenoma or carcinoma
Ectopic ACTH syndrome (wasting due carcinoma, pigmentation, hypokalaemia)

**How would you distinguish someone with Cushingoid features from someone with simple obesity?**

Clinical features:
1) Thin skin over the arms with easy bruising (rather than thickened skin with excess subcutaneous fat)
2) Purple striae
3) Truncal distribution of obesity
4) Proximal myopathy
5) NB Hypertension and diabetes unhelpful as both are common in obesity

**Screening tests to confirm hypercortisolaemia**
1) 24 hour urinary free cortisol
2) Low dose dexamethasone test
3) Morning and midnight cortisol- with loss of diurnal rhythm

**Dexamethasone**
Dexamethasone is a synthetic steroid, which is not detected on the cortisol assay. Normally after two days of low dose dexamethasone, people without Cushings will “turn off” their own endogenous steroid production and cortisol levels will be suppressed. For this reason, the low dose dexamethasone test is used as one of three available screening tests for hypercortisolaemia- failure of suppression of cortisol will occur. The three tests are:
1) 24 hour urinary free cortisol
2) Low dose dexamethasone test
3) Morning and evening cortisol to show loss of diurnal rhythm

Once it has been established that there is hypercortisolaemia, the next stage is to try to sort out the cause.
Causes of Cushing’s syndrome

1) Cushing’s disease- pituitary basophil adenoma producing excess ACTH, which drives the adrenals to produce excess steroids
2) Adrenal Cushings- adenoma or carcinoma producing excess steroids autonomously- these feedback to pituitary and turn off ACTH output
3) Iatrogenic- steroid treatment for rheumatoid, severe asthma, inflammatory bowel disease etc
4) Ectopic ACTH syndrome- usually a patient with lung cancer, pigmentation and low serum potassium; does not usually look Cushingoid

The real challenge is to sort out pituitary from adrenal Cushing’s.

There are two important problems:

1) The tumours are often tiny and frequently neither CT scanning nor MRI can distinguish for sure the site of the lesion
2) The ideal test would be an ACTH assay- high in pituitary Cushing’s and low (suppressed) in adrenal Cushing’s; unfortunately ACTH degrades rapidly after venepuncture and even when samples are spun and frozen on the ward within minutes of taking blood, the results are not always reliable.

Dynamic tests
This is why endocrinologists have developed 2 alternative tests as indirect measures of ACTH.

1) The high dose dexamethasone test. In pituitary Cushing’s, a high dose of dexamethasone will cause some suppression of pituitary ACTH output and hence some fall in cortisol levels- even though much less suppression than in a normal, non-Cushingoid person. By contrast, in adrenal Cushing’, there is an autonomous output of steroids which is not dependent on ACTH- the patient’s ACTH is already suppressed and giving excess steroids in an attempt to suppress it further will be ineffective. Hence cortisol levels will not be lowered in the normal way.

2) The metyrapone test. Metyrapone blocks the penultimate stage in cortisol synthesis. When there is a lot of ACTH about, all the metabolic processes prior to the block will be stimulated and there will be a high output of metabolites when measured in the urine. In adrenal Cushing’s, metyrapone reduces the output of steroids, but as there is no ACTH around the metabolic pathways prior to the block are not stimulated and there is no excess of metabolites in the urine.
The Small Print

Are any other tests needed?
Yes, in Cushing’s disease, it is important to check the function of the rest of the anterior pituitary.

How would you assess anterior pituitary function?
You know you’re doing well if you are asked this question!
When a non-hormone secreting pituitary tumour (eg chromphobe adenoma) increases in size, other anterior pituitary hormones tend to be compromised in a characteristic order:

1) GH goes first
2) Gonadotrophins (LH/FSH) lost second
3) TSH lost next
4) ACTH lost last
5) Prolactin levels usually preserved or high

Basal levels
Basal levels of gonadotrophins are reasonably reliable and newer assays of TSH can distinguish between low normal and suppressed levels (Up to the 1990s TSH assays could only really tell the difference between normal and high). Prolactin levels are also reliable; note that many tumours cause a modest rise in prolactin by interfering with the blood supply to the anterior pituitary and so reducing the supply of dopamine, which is the tonic inhibitor of prolactin. It is easy to over-diagnose prolactinomas if you are unaware of this. (True prolactinomas usually have PL levels well over 800IU).

Dynamic testing
If you wish to test anterior pituitary function fully, a dynamic test is required for testing GH and ACTH reserve. ACTH is very difficult to measure directly as levels in the sample fall very rapidly after venepuncture. Instead an insulin tolerance test is performed in order to induce controlled hypoglycaemia. Hypoglycaemia is a powerful stimulus to GH and ACTH output; GH is measured directly and ACTH reserve is assessed by measuring cortisol levels as an indirect measure of ACTH activity. In those who would be at risk from hypoglycaemia (epileptics, children, ischaemic heart disease), glucagon is sometimes used as an alternative though it is thought to be less reliable.

Typical Patterns of Pituitary Adenoma