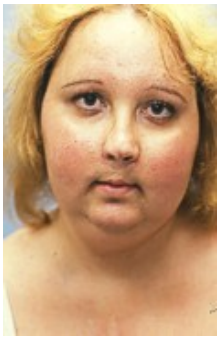
## CASE FOUR

**Short case number: 3_17_4**
**Category: Endocrine & Reproductive Systems.**
**Discipline: Medicine**
**Setting: Medical outpatient Clinic**
**Topic: Cushing Disease [SDL]**

### Case

**During your medical rotation you are attending the endocrinology outpatient clinic; Anna Finster is a 28-year-old female who has been referred to the clinic by her general practitioner who is concerned that she has Cushing's disease because of her facial features. [pictured below]**



### Questions

1. The consultant asks you to summarise the biochemistry and endocrinology of glucocorticoid axis.
2. In your assessment of Anna, what are the key symptoms and clinical signs of Cushing syndrome and how do they correlate with underlying pathophysiology?
3. Outline the steps in the assessment of the patient in order to confirm the diagnosis of Cushing syndrome.
4. Once Cushing syndrome is diagnosed summarise the investigations undertaken to determine the cause.
5. Briefly summarise the principles of management of Cushing syndrome, as related to the cause of the problem.

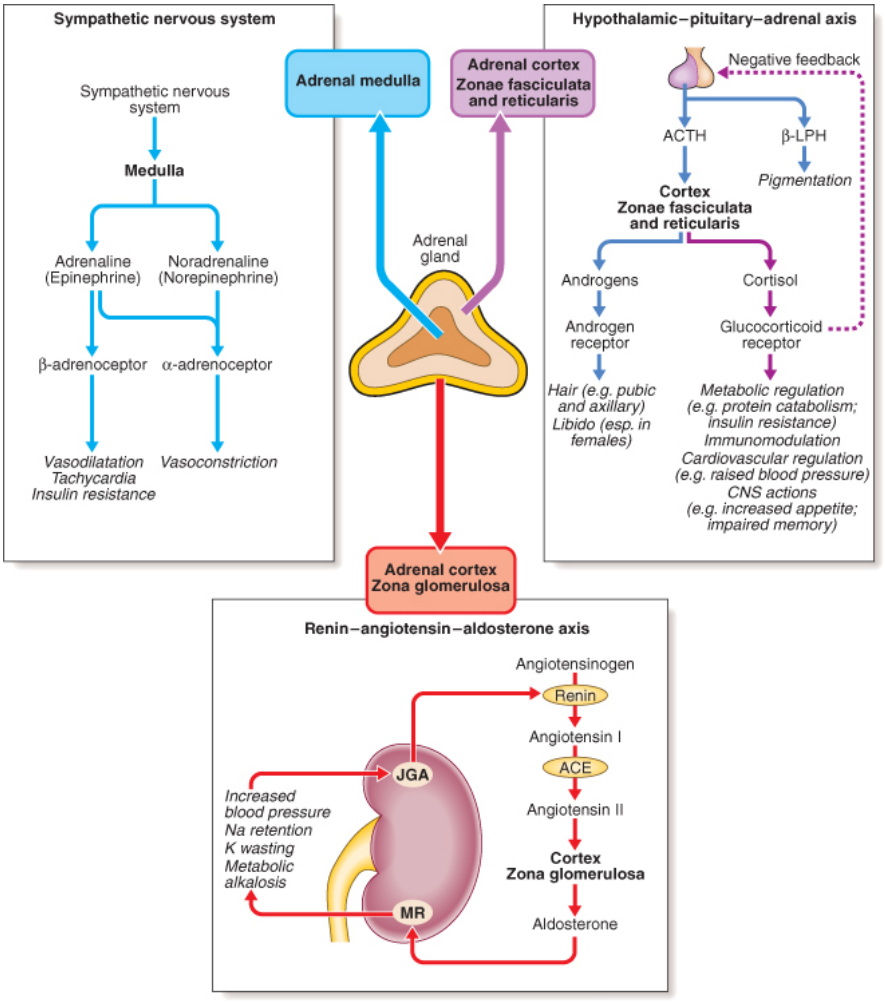
**Suggested reading:**


- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.

## ANSWERS

1. The consultant asks you to summarise the biochemistry and endocrinology of glucocorticoid axis.

look @ endocrine summary notes

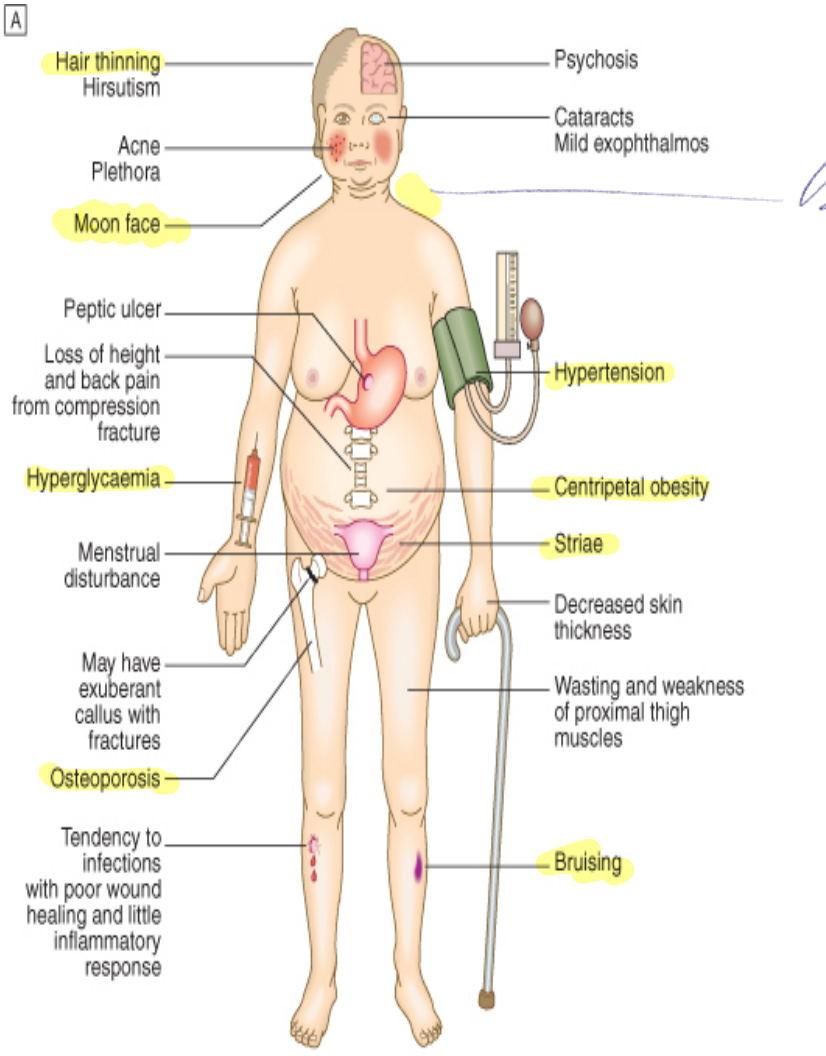





***Glucocorticoids***

Cortisol is the major glucocorticoid in humans. Levels are highest in the morning on waking and lowest in the middle of the night. Cortisol rises dramatically during stress, including any illness. This elevation protects key metabolic functions (e.g. maintaining cerebral glucose supply during starvation) and puts an important 'brake' on potentially damaging inflammatory responses to infection and injury. The clinical importance of cortisol deficiency is, therefore, most obvious at times of stress.

2. In your assessment of Anna, what are the key symptoms and clinical signs of Cushing syndrome and how do they correlate with underlying pathophysiology?

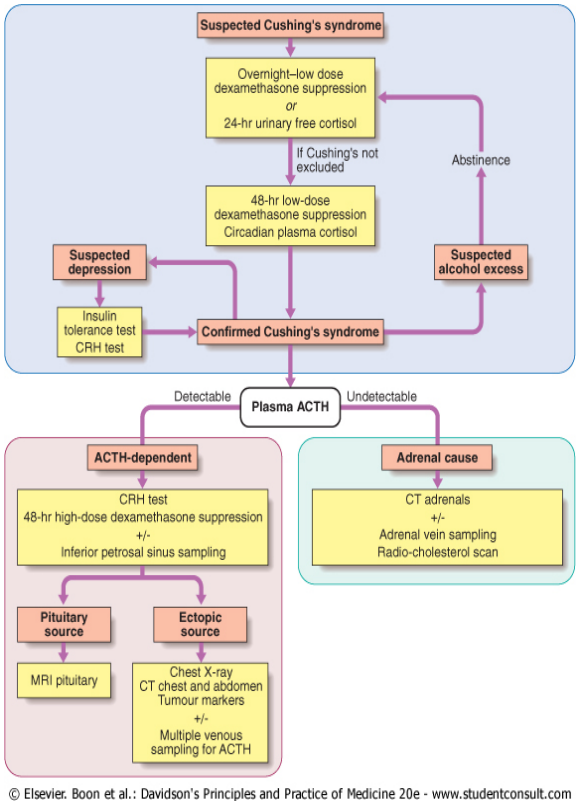





**Cushing's syndrome.** Clinical features common to all causes.

3. Outline the steps in the assessment of the patient in order to confirm the diagnosis of Cushing syndrome.

4. Once Cushing syndrome is diagnosed summarise the investigations undertaken to determine the cause





**Sequence of investigations in suspected spontaneous Cushing's syndrome.** (CRH = corticotrophin-releasing hormone)

| Test | Protocol | Interpretation |
|---|---|---|
| **Urine free cortisol** | 24-hr timed collection (some centres use overnight collections corrected for creatinine) | Normal range depends on assay |
| **Overnight dexamethasone suppression test** | 1 mg orally at midnight; measure plasma cortisol at 0800-0900 hrs | Plasma cortisol < 60 nmol/l (< 2.2 µg/dl) excludes Cushing's |
| **Diurnal rhythm of plasma cortisol** | Sample for cortisol at 0900 hrs and at 2300 hrs (requires acclimatisation to ward for at least 48 hrs) | Evening level > 75% of morning level in Cushing's |
| **Low-dose dexamethasone suppression test** | 0.5 mg 6-hourly for 48 hrs; sample 24-hr urine cortisol during second day and 0900-hr plasma cortisol after 48 hrs | Urine cortisol < 100 nmol/day (36 µg/day) or plasma cortisol < 60 nmol/l (< 2.2 µg/dl) excludes Cushing's |
| **Insulin tolerance test** | | Peak plasma cortisol > 120% of baseline excludes Cushing's |
| **High-dose dexamethasone suppression test** | 2 mg 6-hourly for 48 hrs; sample 24-hr urine cortisol at baseline and during second day | Urine cortisol < 50% of basal suggests pituitary-dependent disease; > 50% of basal suggests ectopic ACTH syndrome |
| **Corticotrophin-releasing hormone test** | 100 µg ovine CRH i.v. and monitor plasma ACTH and cortisol for 2 hrs | Peak plasma cortisol > 120% and/or ACTH > 150% of basal values suggests pituitary-dependent disease; lesser |

| | | |
|---|---|---|
| | | responses suggest ectopic ACTH syndrome |
| **Inferior petrosal sinus sampling** | Catheters placed in both inferior petrosal sinuses and simultaneous sampling from these and peripheral blood for ACTH; may be repeated 10 minutes after peripheral CRH injection | ACTH concentration in either petrosal sinus > 200% peripheral ACTH suggests pituitary-dependent disease; < 150% suggests ectopic ACTH syndrome |

5. Briefly summarise the principles of management of Cushing syndrome, as related to the cause of the problem.

Untreated Cushing's syndrome has a 50% 5-year mortality. Most patients are treated surgically with medical therapy given for a few weeks prior to operation. A number of drugs are used to inhibit corticosteroid biosynthesis, including metyrapone, aminoglutethimide and ketoconazole. The dose of these agents is best titrated against 24-hour urine free cortisol.

Drugs OR Surgery

*Cushing's disease*

Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice. Experienced surgeons can identify microadenomas which were not detected by MRI and cure about 80% of patients. If the operation is unsuccessful then bilateral adrenalectomy is an alternative.

If bilateral adrenalectomy is used in patients with pituitary-dependent Cushing's syndrome, then there is a risk that the pituitary tumour will grow in the absence of the negative feedback suppression previously provided by elevated cortisol levels. This can result in Nelson's syndrome, with an aggressive pituitary macroadenoma and very high ACTH levels causing pigmentation. Nelson's syndrome can be prevented by pituitary irradiation.

*Adrenal tumours*

Adrenal adenomas are removed via laparoscopy or a loin incision. Adrenal carcinomas are resected if possible, the tumour bed irradiated and the patient given the adrenolytic drug mitotane. Cytotoxic chemotherapy may retard disease progression in patients with metastases.

*Ectopic ACTH syndrome*

Localised tumours causing this syndrome (e.g. bronchial carcinoid) should be removed. During treatment or palliation of non-resectable malignancies, it is important to reduce the severity of the Cushing's syndrome using medical therapy (see above).