ADRENAL DISORDERS – 1.

Dr. Badri Paudel

ADRENAL GLANDS – HISTORICAL MILESTONES

- 1563. Eustachius describes the adrenals
- 1855. Thomas Addison describes the clinical features and autopsy findings of 11 cases of diseases of the suprarenal capsules, at least 6 of which were tuberculous in origin.
- 1856. In adrenalectomy experiments, Brown-Séquard demonstrates that the adrenal glands are essential for life.
- 1932. Harvey Cushing associates the “polyglandular syndrome” of pituitary basophilism first described by him in 1912 with hyperactivity of the pituitary-adrenal glands.
- 1956. Conn describes primary aldosteronism.

ADRENOCORTICAL DISEASES

Glucocorticoid Excess

- In 1912 Harvey Cushing first described a 23-year-old woman with obesity, hirsutism, and amenorrhea and 20 years later postulated that this “polyglandular syndrome” was due to a primary pituitary abnormality causing adrenal hyperplasia.

Terminology:
- Cushing’s syndrome: used to describe all causes
- Cushing’s disease: reserved for cases of pituitary-dependent Cushing’s syndrome

Classification of causes of Cushing`s syndrome

- ACTH-dependent:
  - Cushing’s disease (pituitary-dependent)
  - Ectopic ACTH syndrome
  - Ectopic CRH syndrome
  - Macronodular adrenal hyperplasia
  - Iatrogenic (treatment with ACTH 124)
- ACTH-independent:
  - Adrenal adenoma and carcinoma
  - Primary pigmented nodular adrenal hyperplasia and Carney’s syndrome.
  - McCune-Albright syndrome
  - Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1)
  - Pseudo-Cushing’s Syndromes
    - Alcoholism
    - Depression
    - Obesity

Symptoms (prevalence)

- Weight gain 91%
- Menstrual irregularity* 84%
- Hirsutism* 81%
- Psychiatric dysfunction 62%
- Backache 43%
- Muscle weakness* 29%
- Fractures 19%
- Loss of scalp hair 13%
- * - it helps in distinguishing between simple obesity and Cushing

Signs (prevalence)

- Obesity 97%
  1. Truncal 46%
  2. Generalized 55%
  3. Plethora* 94%
  4. Moon face 88%
  5. Hypertension* 74%
  6. Bruising* 62%
  7. Red-purple striae* 56%
  8. Muscle weakness* 56%
  9. Ankle edema 50%
  10. Pigmentation 4%
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Other findings

- Hypertension 74%
- Diabetes 50%
  1. Overt 13%
  2. IGT 37%
- Osteoporosis 50%
- Renal calculi 15%

Obesity

- Commonest sign
- Centripetal type
- Fat deposits over the thoracocervical spine ("buffalo hump"), in the supraventricular region, and over the cheeks and temporal regions; giving rise to the rounded "moon-like" facies
- The epidural space is another site of abnormal fat deposition, and this may lead to neurologic deficits
- Exophthalmos (increased retro-orbital fat deposition) in about one-third of patients

Reproductive Dysfunction

- Gonadal dysfunction, menstrual irregularity, loss of libido
- Hirsutism (commonest form: vellous hypertrichosis on the face), acne
- Hypogonadism occurs because of a direct inhibitory effect of cortisol upon gonadotropin-releasing hormone pulsatility and LH or FSH secretion and is reversible upon correction of the hypercortisolism.

Psychiatric Abnormalities

- 50% of patients
- Agitated depression and lethargy commonest
- Paranoia and overt psychosis less common
- Memory and cognitive function may be affected
- Increased irritability
- Insomnia
Bone

- In childhood: poor linear growth and weight gain
- Osteoporosis, vertebral collapse, pathologic fractures
- Aseptic necrosis of the femoral and humeral heads, a recognized feature of high-dose exogenous corticosteroid therapy, can occur in endogenous Cushing's syndrome

Skin

- Skin thinning, separation, and exposure of the subcutaneous vascular tissue
- Wrinkling of the skin on the dorsum of the hand may be seen resulting in a “cigarette paper” appearance (Liddle’s sign)
- Easy bruising, resembles “senile purpura.”
- Plethoric appearance (secondary to the thinning of the skin and loss of facial subcutaneous fat)
- Acne and papular lesions over the face, chest, and back
- Red-purple livid striae greater than 1 cm in diameter (abdomen, thighs, breasts, and arms)
- Increased skin pigmentation is rare in Cushing's disease but common in the ectopic ACTH syndrome—due to overstimulation of melanocyte receptors by ACTH.

Easy bruising

Skin thinning

Fragile skin

Acne
Striae

Muscle

- Myopathy - proximal muscles of the lower limb and the shoulder girdle
- complaints of weakness such as inability to climb stairs or get up from a deep chair are relatively uncommon, but testing for proximal myopathy by asking the patient to rise from a crouching position often reveals the problem

Cardiovascular

- Hypertension - 75% of cases
- hypertension is much more common in patients with Cushing's syndrome than in those with simple obesity
- increased cardiovascular mortality in untreated cases (plus diabetes, hyperlipidemia also common in Cushing’s)
- thromboembolic events

Infections

- infections are more common among these patients
- many times asymptomatic and occur because the normal inflammatory response is suppressed
- reactivation of tuberculosis
- fungal infections of the skin (tinea versicolor) and nails
- bowel perforation
- wound infections are commoner and contribute to poor wound healing

Metabolic and Endocrine

- Glucose intolerance occurs, and overt diabetes mellitus is present in up to one third of patients
- Hepatic lipoprotein synthesis is stimulated, leading to hyperlipidaemia
- Hypokalemic alkalosis found in over 95% of patients with ectopic ACTH syndrome (cortisol swamps the normal metabolizing enzyme, 11-HSD type 2 in the kidney, to act as a mineralocorticoid)
- the pituitary-thyroid axis and the pituitary-gonadal axis is suppressed – due to the direct effect of cortisol on TSH and gonadotrophin secretion
- GH secretion is reduced, possibly mediated through an increase in somatostatinergic tone

Diagnostic tests

- **Circadian Rhythm of Plasma Cortisol**
  - In normal nonstressed subjects: plasma cortisol levels highest in the morning and reach a nadir at about midnight (<50 nmol/L (2 µg/dL)
  - In Cushing’s syndrome: circadian rhythm is lost - so 9 AM plasma cortisol is normal but nocturnal levels are raised
  - A midnight cortisol level greater than 200 nmol/L (7 µg/dL) indicates Cushing's syndrome
Urinary Free Cortisol Excretion

- Urinary free cortisol is an integrated measure of plasma free cortisol; as cortisol secretion increases, the binding capacity of CBG (cortisol binding globulin) is exceeded, resulting in a disproportionate rise in urinary free cortisol.
- Normal values are less than 220 to 330 nmol (80 to 120 µg) per 24 hours depending on the assay used.

Overnight Dexamethasone Suppression Tests

- In normal subjects, the administration of a supraphysiologic dose of glucocorticoid results in suppression of ACTH and cortisol secretion. In Cushing's syndrome of any cause there is failure of this suppression when low doses of the synthetic glucocorticoid dexamethasone are given.
- 1 mg of dexamethasone is given at midnight - normal response is a plasma cortisol less than 140 nmol/L (5 µg/dL) between 8 and 9 AM the following morning.
- Post dexamethasone cortisol value of less than 50 nmol/L (2 µg/dL) effectively excludes Cushing's syndrome.

Low-dose dexamethasone test

- In the 48-hour low-dose dexamethasone test, plasma cortisol is measured at 9 AM on day 0 and 48 hours later following dexamethasone given at a dose of 0.5 mg every 6 hours for 48 hours.
- Post dexamethasone plasma cortisol concentration of less than 50 nmol/L (2 µg/dL), this test is reported as having a 97% to 100% true-positive rate and a false-positive rate less than 1%.

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

Finding the Cause of Hypercortisolism

- Baseline plasma ACTH level at 9 AM –
  - in adrenal tumors, plasma ACTH is invariably undetectable (<1 pmol/L)
  - In ectopic ACTH syndrome levels will be high (usually > 20 pmol/L)
  - In Cushing's disease, 50% of patients will be in the normal range (2 to 12 pmol/L)
- Potassium and ABG – hypokalaemic alkalosis in ectopic ACTH syndrome

High-Dose Dexamethasone Suppression Test

- in Cushing's disease there is a resetting of the negative feedback control of ACTH to a higher level than normal - thus, cortisol levels are not suppressed with low-dose but are suppressed with high-dose dexamethasone.
- Dexamethasone given at 2 mg every 6 hours for 48 hours, plasma or urinary free cortisol, or both, are measured at 0 and +48 hours.
- A greater than 50% suppression of plasma cortisol in comparison with the basal sample defines a positive response.
Metyrapone Test

- Metyrapone blocks the conversion of 11-deoxycortisol to cortisol and DOC to corticosterone by inhibiting 11-hydroxylase.
- This effect lowers plasma cortisol and, through negative feedback control, increases plasma ACTH.
- Metyrapone is given in doses of 750 mg every 4 hours for 24 hours.
- Patients with Cushing's disease exhibit an exaggerated rise in plasma ACTH with 11-deoxycortisol levels at 24 hours exceeding 1000 nmol/L (35 µg/dL).
- In patients with the ectopic ACTH syndrome, there is little or no response, but occasional patients (possibly those producing both ACTH and CRH) give a similar response to that in Cushing's disease.
- This test should be reserved for patients when the results of other tests are equivocal.

Corticotropin-Releasing Hormone (CRH) Test

- IV inj. of CRH in a dose of 1 µg/kg body weight or a single dose of 100 µg.
- After basal sampling, blood samples for ACTH and cortisol are taken every 15 minutes for 1 to 2 hours following the administration of CRH.
- Normal subject: rise in ACTH and cortisol by 15-20%.
- In Cushing's disease: typically ACTH rise > 50% and a cortisol rise > 20% over baseline values.
- No response is seen in the ectopic ACTH syndrome.
- Using an ACTH increase of 100% or a cortisol rise of 50%, a positive response effectively eliminates a diagnosis of ectopic ACTH syndrome, and this is the real benefit of this test.
- Up to 10% of patients with Cushing's disease do not respond to CRH.

Localizing Techniques

- In ACTH-dependent Cushing's syndrome, MRI of the pituitary can demonstrate a pituitary adenoma in about 50% of cases.
- If the pituitary MRI is normal, selective inferior petrosal venous sampling for ACTH is performed (with CRH stimulation) to confirm a pituitary ACTH source.
- Ectopic sources of ACTH: CT scan of the chest and abdomen, with special attention to the lungs (for carcinoid or small cell carcinomas), the thymus, the pancreas, and the adrenals.
- In non-ACTH-dependent Cushing's syndrome, a CT scan of the adrenals can localize the adrenal tumor.

Ectopic ACTH syndrome - Tumor types and their incidence

- Small cell lung carcinoma 50%
- Nonsmall 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 carcinomata of prostate, breast, ovary, gallbladder, colon 10%

Differential Diagnosis

- Alcoholic patients (hypercortisolism, similar clinical manifestations).
- Depressed patients (hypercortisolism, but without clinical signs).
- Anorexia nervosa (muscle wasting and extraordinarily high urine free cortisol levels).
- Severe obesity (abnormal dexamethasone suppression test, but the urine free cortisol and the diurnal variation of serum cortisol is normal).
- Familial cortisol resistance (abnormalrocardinism, hypercortisolism, and hyperandrogenism, but no Cushing's sy).
- Antiretroviral therapy (partial lipodystrophy with thin extremities and central obesity with a dorsocervical fat pad (*buffalo hump*).

Treatment - pituitary adenoma

- Selective transsphenoidal resection. After resection, the rest of the pituitary usually returns to normal, but corticosteroids are suppressed and require 6-36 months to recover, so hydrocortisone replacement therapy is necessary in the meantime.
- Patients who fail to have a remission (or who have a recurrence) can be treated by bilateral laparoscopic adrenalectomy.
- Alternatively, stereotactic pituitary radiosurgery (gamma knife) induces normalization of urine free cortisol in two-thirds of patients within 12 months.
- Conventional radiation therapy - 23% cure rate.
- Patients who are not surgical candidates may be given a trial of ketoconazole in doses of about 200 mg every 6 hours; liver enzymes must be monitored for progressive elevation.
Adrenal neoplasms secreting cortisol are resected laparoscopically. The contralateral adrenal is suppressed, so postoperative hydrocortisone replacement is required until recovery occurs.

Metastatic adrenal carcinomas may be treated with mitotane; ketoconazole or metyrapone can help suppress hypercortisolism in unresectable adrenal carcinoma.

Ectopic ACTH-secreting tumors should be surgically resected. If that cannot be done, medical treatment with ketoconazole or metyrapone (or both) may at least suppress the hypercortisolism; however, metyrapone may exacerbate female virilization. The somatostatin analog octreotide, given parenterally, suppresses ACTH secretion in about one-third of such cases.