

# Metabolic, Biochemical, and Endocrine disorders

## *Organ failure or dysfunction*

### ***Endocrinopathies***

#### **Hyperthyroidism**

- more common in women
- usually presents between 2<sup>nd</sup> and 4<sup>th</sup> decade

#### **Aetiology**

- diffuse toxic hyperplasia (Graves' disease)
- toxic solitary goitre (toxic adenoma)
- toxic multinodular goitre

#### **Psychological features**

- restlessness
- overactivity
- anxiety
- irritability and emotional lability
- hyperacuity of perception and over-reaction to noise
- fluctuating depression
- shortened sleep period
- distractibility and poor concentration
- cognitive impairment (commonly memory)

#### **Psychiatric disorders**

- acute organic reactions (delirium a.k.a. 'thyroid storm') associated with thyroid crises constitute a medical emergency
  - seen in 3-4 % of hyperthyroid patients
  - usually accompanied by high fever, tachycardia, hypotension, vomiting, and diarrhoea
  - sometimes apathy, prostration, stupor, and coma are seen
- affective psychoses (mania > depression)
- schizophrenia (commoner than mania)

#### **Neurological signs**

- chorea
- periodic paralysis
- myopathy
- myasthenia

## **Hypothyroidism**

- more common in women
- disease of middle life

### **Aetiology**

- end-stage chronic thyroiditis
- iatrogenic:
  - LITHIUM treatment
  - CARBAMAZEPINE and PHENYTOIN also affect thyroid function
  - over-treatment of hyperthyroidism

### **Psychological features**

- lethargy
- slowing of cognition (esp. forgetfulness)
- easily fatigued
- psychomotor retardation
- apathy
- irritability, agitation, and sometimes aggression

### **Psychiatric disorders**

- paranoia (can be delusional)
- subacute or acute organic psychosis is commonest - presents as delirium
- auditory and visual hallucinations (usually associated with impaired cognition and clouded consciousness)
- severe depressive episode
- schizophrenia

### **Hypothyroidism and the EEG**

- seen in 33 %
- slowing of dominant rhythm
- reduction in background activity
- corrects after treatment

### **Prognosis**

- better if:
  - for psychotic patients if there has been a clear organic quality to the presentation
  - duration of illness seems related to the degree of residual deficit

## **Cushing's syndrome**

- 4x more common in women
- usually presents in 3<sup>rd</sup> or 4<sup>th</sup> decade

### **Aetiology**

- due to excessive pituitary secretion of ACTH in 75 % of cases

## Psychological features

- cognitive impairment is present in 2/3 - tends to be global with more marked impairment of non-verbal tasks

## Psychiatric disorders

- 50-80 % have psychiatric disorders
- commonest disorder is depression (paranoid symptoms common); tends to be more common in primary pituitary dysfunction
  - severe retardation
  - delusions
  - hallucinations
  - agitation and behavioural disturbance
- suicide has been reported in 3-10 % of cases
- anxiety states frequent
- severe psychoses are usually depressive
- acute confusional states and schizophreniform illnesses are rare
- frank delirium is associated with high cortisol levels, physical complications secondary to the disorder, advanced disease, and old age

## Outcome

- may take up to a year to completely resolve

## Psychiatric aspects of steroid drug treatment

- steroid treatment is most commonly associated with mild *elation* of mood, rather than depression
- symptoms tend to occur in the first 3 weeks of treatment
- dosage is correlated with risk of mental disturbance
- neither dose or duration appear to influence the time of onset, duration, severity, or type of disturbance
- females more prone
- past mental illness does **not** predispose to steroid illness
- symptoms may include:
  - emotional lability
  - euphoria
  - anxiety
  - distractibility
  - insomnia
  - agitation

## Adrenocortical deficiency

- prevalence is 2x greater in women

### Aetiology

- usually due to disease of the adrenal cortex
  - autoimmune > primary adrenocortical insufficiency (*Addison's disease*)
  - tuberculosis
- secondary to:
  - pituitary disease
  - hypothalamic disease
  - iatrogenic

### Psychiatric disorders

- usually present
- slowly progressive fatigue, weakness and apathy - initially periodic, then constant
- depression, irritability, anxiety and paranoia tend to have a fluctuating course with symptom free intervals
- $\frac{3}{4}$  have memory problems - may present as a pseudodementia
- psychosis is rare - usually schizophreniform
- delirium is a feature of acute adrenal crisis but can occur without a crisis

### Outcome

- usually successful
- glucocorticoids more important than mineralocorticoids for reversing the mental symptoms

## Hyperparathyroidism

### Aetiology

- benign adenoma of the parathyroid glands
- may occur familiarly
- MEN type I:
  - **p**arathyroid adenomas
  - endocrine tumours of **p**ancreas
  - **p**ituitary tumours
- MEN type II:
  - parathyroid adenomas
  - phaeochrom**m**ocytomas
  - **m**edullary carcinoma of the thyroid

### Psychiatric features

- seen in 2/3 of cases (all due to increased serum calcium, PTH levels are not related to symptoms)
- early symptoms (subtle):

- personality change
- depressive mood disturbance
- worsening fatigue, listlessness, and apathy
- disturbance of mood and drive:
  - depression with anergia
- delirium (associated with higher calcium levels):
  - seen in 5 %
  - characterized by hallucinations, paranoid delusions and aggression
- cognitive impairment in 12 %
  - impaired attention
  - mental slowing
  - impaired memory
- non-organic psychoses rare but persecutory delusions and hallucinations can occur as calcium levels rise

### Investigations

- EEG shows widespread slow wave activity with paroxysms of frontal  $\delta$  waves when serum calcium is high

### Outcome

- correction of serum calcium usually results in reversal of symptoms, though exceptions occur
- psychosis in the week after treatment (with or without rebound hypocalcaemia) may occur

## Hypoparathyroidism

- usually female

### Aetiology

- **primary** (autoimmune; associated with adrenal, thyroid, and ovarian dysfunction) or **secondary** (iatrogenic; as a consequence of thyroid surgery)
- end-organ unresponsiveness to PTH = pseudohypoparathyroidism

### Psychiatric features

- seen in 50 % of iatrogenic cases (accidental removal/ neck surgery) and nearly 100 % of idiopathic cases
- *Primary hypoparathyroidism:*
  - insidious onset
  - impaired concentration
  - emotional lability
  - impaired cognitive function
- *Secondary hypoparathyroidism:*
  - commonest feature is acute confusional state
  - characterized by florid psychotic manifestations and irritability

- affective (depression, manic-depression) and schizophreniform psychoses can occur but are rare

### Neurological features

- tetany
- cramps
- generalized seizures
- papilloedema

### Investigations

- skull X-ray may show symmetrical calcification within the basal ganglia in primary hypoparathyroidism

## Acromegaly

- a.k.a. *Marie's disease*

### Aetiology

- results from hypersecretion of growth hormone after puberty
- pituitary adenoma is usual cause

### Psychiatric symptoms

- apathy and lack of spontaneity
- altered emotions:
  - cheerfulness, self-satisfaction, elation, resentment coupled with anxiousness, tenseness and unpleasantness
  - mood swings
- reduced libido
- psychosis is uncommon

### Neurological symptoms

- visual field defects (bitemporal hemianopia)

## Hypopituitarism

### Aetiology

- most commonly due to a pituitary adenoma
- result of infarction caused by post-partum haemorrhage (*Sheehan's syndrome*)
- basal skull fracture
- intracranial infection

- Sarcoidosis
- craniopharyngioma in children
- TB
- Haemochromatosis
- radiotherapy
- Kallmann's syndrome (deficiency of GnRH)

### Psychiatric symptoms

- in most patients
- most frequently an involitional state characterized by varying degrees of:
  - apathy
  - inertia
  - insouciance
- impotence and impaired libido
- generally depressive mood
- delirium represents actual or impending metabolic upset
- schizophreniform psychosis is rare
- patients are prone to coma and death

### Outcome

- symptoms respond well to hormone treatment
- if longstanding, the apathy and impaired drive may not reverse completely

## Diabetes mellitus

### Diabetic coma

1. hypoglycaemic
2. ketoacidotic
  - a) level of consciousness correlates best with plasma osmolality, not glucose or electrolyte levels
3. hyperosmolar non-ketotic
  - a) common in the elderly
  - b) lethargy, changes in cognition, profound dehydration, various neurological signs
4. alcoholic ketoacidosis
5. lactic acidosis

### Premorbid adjustment

- link between course of diabetes and psychological adjustment
- emotional upset is associated with poor diabetic control possibly due to:
  - altered diet
  - alcohol usage
  - changes in routine and activity levels

## Psychiatric symptoms

- fatigue is common
- delirium and dementia result from metabolic disturbance, atherosclerosis, and hypertension

## Medication

- insulin and oral hypoglycaemic agents potentiated by:
  - MAOIs
  - alcohol

## Diabetes insipidus

### Aetiology

- ADH is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, where it is transported to the posterior lobe of the pituitary gland
- in *cranial diabetes insipidus*, ADH is produced in insufficient quantity
  - in rare cases, the condition is familial, being inherited as Mendelian dominant
  - damage to pituitary stalk (often transient)
  - pituitary surgery
  - primary or secondary hypothalamic tumours
- *nephrogenic diabetes insipidus*:
  - can occur as a result of a rare sex-linked recessive disorder affecting males
  - hypercalcaemia
  - potassium depletion
  - prolonged intake of excessive amounts of water
  - LITHIUM therapy

### Clinical features

- production of large volumes of dilute urine, usually accompanied by thirst
- the urine osmolality is low
- the plasma osmolality is usually only slightly raised
- if thirst does not occur, or if fluid intake is prevented, a dangerous degree of hypernatraemia and dehydration may develop

### Treatment

- neurogenic (cranial) DI:
  - in transient states (e.g. post-head injury) vasopressin can be given subcutaneously
  - in the chronic condition, the synthetic analogue, DDAVP is administered as a nasal spray
- nephrogenic DI:
  - treated with thiazide diuretics (mechanism unclear)

## Insulinoma

### Aetiology

- due to insulin-secreting tumours of  $\beta$  cells in the pancreas
- 10 % are malignant
- commonest after childhood and before 60
- part of MEN type I group

### Psychiatric features

- insidious onset
- chronic hypoglycaemic symptoms punctuated by acute hypoglycaemic episodes which increase in frequency
- may present with:
  - neurosis
  - personality change
  - mania
  - depression
  - schizophrenia
  - epilepsy
  - sleep disorder
  - delirium
  - dementia
  - memory blackouts

### Investigations

- diagnosis made by demonstrating fasting hypoglycaemia in the presence of normal or raised plasma insulin levels

## Phaeochromocytoma

- can occur at any age; usually in the 4<sup>th</sup> and 5<sup>th</sup> decades

### Aetiology

- tumour derived from chromaffin cells which secrete catecholamines
- about 10 % are malignant, especially those in extra-medullary sites
- 90 % are found in adrenal medulla, 10 % are bilateral
- in 5 % of cases, there is **autosomal dominant inheritance**
  - seen in Multiple Endocrine Neoplasias (MEN) type IIa and IIb disorders

### Psychiatric features

- paroxysmal attacks:

- headache (bilateral, throbbing, rapid onset)
- perspiration
- palpitations
- pallor
- intense anxiety
- fear
- over-arousal
- usually progressive in frequency and severity
- excitability or confusion may follow an attack
- delirium
- depression
- psychosis
- epileptic fits can occur

#### Medication

- episodes may be precipitated by:
  - opiates
  - ACTH
  - glucagon
  - TCAs
- phaeochromocytoma is an absolute contraindication to ECT

#### Investigations

- routine biochemistry
- retinoscopy
- 24 hr urinary vanillymandelic acid (VMA)

#### Treatment

- Beta-blockade, followed by surgery

### ***Hepatic dysfunction***

#### Aetiology

- viral (e.g. Hepatitis, CMV)
- drugs and toxins
- biliary tract lesions
- metabolic disturbance
- hypoxia
- tumours

#### Neurological features

- motor disorders:
  - exaggeration of tendon reflexes

- unobtrusive tremor
- flapping tremor (*asterixis*)
  - aggravated by fatigue, anxiety, and excitement
  - absent at rest
- characteristic blank or grimacing facial expression
- dysarthria
- ataxia
- muscular rigidity
- clonus
- plantar reflexes are normal until coma is reached
- dysphasia with perseverative speech disturbances
- blurring of vision
- diplopia
- nystagmus
- constructional apraxia

### Psychiatric features

- impairment of consciousness
- hypersomnia (early feature) with inversion of sleep rhythm
- confusion, semi-coma, or coma
- delirium with hallucinations (mainly visual)
  - episodic 'twilight' states with sudden onset and ending may occur
- impairment of recent memory
- confabulation
- mood swings
- personality changes
  - similar to frontal lobe disorder
    - blunted affect
    - loss of drive and initiative
    - defective insight
    - loss of social judgement
  - disinhibited behaviour
- paranoid reactions can occur
- schizophrenia and mania have also been reported

### **Pancreatic dysfunction**

### **Renal dysfunction**

### **Respiratory dysfunction**



## ***Deficiency of substrates of cerebral metabolism***

### **Cerebral anoxia**

#### Aetiology

1. **Anoxic anoxia**
  - a) chronic bronchitis
  - b) emphysema
  - c) pneumonia
  - d) general anaesthesia
  - e) asphyxia
  - f) drowning
  - g) high altitudes
2. **Anaemic anoxia**
  - a) carbon monoxide poisoning
  - b) GI bleeding and blood loss
  - c) severe anaemia
3. **Stagnant anoxia**
  - a) cerebral atherosclerosis
  - b) peripheral circulatory failure (shock)
  - c) congestive cardiac failure
  - d) cardiac arrest
  - e) paroxysmal dysrhythmia
  - f) myocardial infarction
4. **Metabolic (toxic) anoxia**
  - a) hypoglycaemia
  - b) cyanide poisoning
  - c) carbon disulphide poisoning
5. **Overutilization anoxia**
  - a) epileptic seizures

#### Clinical features

- impairment of consciousness of varying severity, confusion, disorientation, or delirium
- muscular twitching or tremor
- seizures
- personality change (may occur with sustained hypoxia, e.g. high altitudes)

#### Cerebral pathology in cerebral anoxia

- if death occurs within a few minutes, there is little to be detected
  - cerebral oedema occurs early
- if the patient survives long enough:
  - widespread degeneration and necrosis of nerve cells with corresponding glial proliferation
- certain cells are more susceptible to damage:
  - cells of the 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> cortical layers (*laminar cortical necrosis*)

- Purkinje cells of the cerebellum
- cells of the corpus striatum - bilateral necrosis of the globus pallidus is often a marked feature
- hippocampus and parastriate cortex
- subcortical U-fibres are characteristically spared (also seen in Binswanger's encephalopathy)
- if blood flow has been abruptly curtailed despite a sustained arterial oxygen tension (e.g. MI):
  - *boundary zone necrosis* is often most severe in the parieto-occipital regions where the territories of the anterior, middle, and posterior cerebral arteries meet
  - involvement of the subcortical white matter is proportional to the severity of the cortical lesion
  - diffuse changes may occur
  - changes are minimal or absent in the hippocampi and diffuse laminar cortical necrosis does not occur

## Carbon monoxide poisoning

### Aetiology

- slow combustion stoves
- car exhaust fumes in enclosed spaces
- blast furnaces
- explosions in mines

### Clinical features

- lowered efficiency and self-control lead imperceptibly to loss of consciousness without intervening delirium
- complete unconsciousness is usually attained quite rapidly, resulting in coma
- diffuse hypertonicity is common:
  - trismus
  - up-going plantar reflexes
  - paroxysms of decerebrate rigidity may occur
- hypotonic forms are rarer and carry a graver prognosis
- sphincter and swallowing difficulties are often present
- corneal and pupillary reflexes are often absent
- poor prognostic indicators:
  - long persistence of coma
  - prolonged circulatory collapse
  - fluctuating pyrexia
  - hyperglycaemia
  - uraemia
  - acidosis

### After effects

- period of disorientation and confusion
- sometimes there is a period of irritability and restlessness
- 1/5 of patients show prolonged delirium, lasting hours to several weeks
- amnesic difficulties are usually present, and often the last to clear
- sometimes a classical Korsakoff psychosis emerges
- extrapyramidal signs which were absent during coma may emerge on recovery

### Latent interval

- a latent period between recovery from coma, and the onset of profound neurological or mental disorder may occur
- normal health is regained, but 2-10 days later, there is an abrupt relapse with extrapyramidal disturbance, delirium, or coma
- complete recovery is again often attained
- some patients progress to neurological disability and dementia
  - demyelination is usually extensive in the cerebral hemispheres

### Enduring sequelae

- extrapyramidal disturbances, usually parkinsonian in nature
- permanent defects of memory
- deterioration of personality:
  - increased irritability
  - verbal aggressiveness
  - violence
  - impulsiveness
  - moodiness

### Pathological findings

- necrosis of the globus pallidus
- similar lesions in Ammon's horn
- cerebral cortex shows necrotic foci
- cerebellum shows necrosis, but with sparing of Purkinje cells

## Hypoglycaemia

### Aetiology

- anatomical lesions:
  - insulinoma (MEN type I)
  - pancreatic hyperplasia
  - pancreatic carcinoma
  - hypopituitarism
  - Addison's disease
  - diffuse liver disease
- severe malnourishment
  - anorexia nervosa

- exogenous agents:
  - oral hypoglycaemics
  - alcohol
  - salicylates
  - ingestion of the Caribbean ackee fruit
- inherited hepatic enzyme deficiencies

### Psychiatric presentations

1. Acute:
  - a) volatile/ bizarre behaviour, inappropriate and out of character
  - b) delirium
  - c) coma
  - d) autonomic symptoms (sweating, palpitations)
  - e) seizures occur in 10-20 % of adults
2. Subacute:
  - a) fluctuating apathy and withdrawal
  - b) excessive sympathetic activity is not seen
  - c) cognitive impairment
  - d) delirium
3. Chronic:
  - a) personality change which mirrors ongoing brain damage
  - b) memory is often affected
4. Nocturnal:
  - a) fatigue and underperformance during the day

### Brain damage

- damage occurs in a rostrocaudal fashion
- in order of decreasing sensitivity and damage:
  - the middle layers of the cerebral cortex (but for the striate area) and the hippocampus
  - basal ganglia and anterior thalamus
  - brainstem and spinal cord are most resistant

## ***Disorders of electrolyte, acid-base, and fluid balance***

### **Uraemia**

#### Aetiology

- renal:
  - failure
- extrarenal
  - shock / dehydration

#### Psychiatric features

- lethargy
- anorexia
- depression
- sluggish comprehension
- difficulty with memory
- delirium:
  - in a third of cases
  - apprehension, bewilderment
  - fleeting hallucinations
- functional psychosis:
  - paranoia
  - depression
- epileptic seizures:
  - in a third of cases
  - more common in acute than chronic uraemia
  - usually a late feature
- peripheral neuropathy - when the cause is chronic renal failure

### **Hypernatraemia**

#### Aetiology

- inadequate intake:
  - elderly
  - neonates
  - unconscious patients
  - hypothalamic disease with loss of normal thirst
- loss of water in excess of sodium:
  - unreplaced losses due to vomiting or diarrhoea
  - febrile illness (esp. infants)
  - diabetes insipidus
  - severe hyperglycaemia can lead to spontaneous osmotic diuresis

### Clinical features

- signs of volume depletion and circulatory failure
- lethargy
- drowsiness
- muscle-twitching
- coma secondary to brain-cell dehydration

### Treatment

- slow correction of hyperosmolality (over 48 hrs) - rapid correction can result in cerebral oedema or brain haemorrhage

## Hyponatraemia

### Aetiology

- tropical climates when salt is omitted from the diet
- severe vomiting and diarrhoea
- Addison's disease
- salt-losing nephritis
- post-op, if maintained only on IV dextrose
- SIADH

### Clinical features

- weakness
- dizziness
- pallor
- profuse sweating
- diminution of urine
- rapid pulse and respiration

### Psychiatric features

- in gradual cases:
  - irritability
  - depression without cause
  - intense anxiety
- mental confusion with disorientation, delusions, and hallucinations

### Treatment

- oral salt
- IV saline
- giving water or dextrose can aggravate the hypotonicity

## Hyperkalaemia

### Aetiology

- **Metabolic:**
  - metabolic acidosis
  - renal failure
  - DKA
  - Addison's disease
- **Drugs:**
  - potassium therapy
  - potassium sparing diuretics (e.g. AMILORIDE)
  - ACE inhibitors
  - NSAIDS
  - CYCLOSPORIN
  - HEPARIN
  - SUXAMETHONIUM
  - massive blood transfusion
- **Other:**
  - crush injuries
  - rhabdomyolysis
  - burns

### Psychiatric features

- dullness
- lethargy
- confusion

### Investigations

- ECG:
  - tall, tented T's
  - wide QRS
  - small P-wave

### Treatment

- IV glucose (50g) with 15 units of ACTRAPID insulin
- IV 10 % CALCIUM GLUCONATE (10-30 ml over 5-10 mins) if severe ECG changes are present
- oral CALCIUM RESONIUM (15-20g) t.d.s
- oral LACTULOSE (10-20 ml) t.d.s. causes mild diarrhoea which can help hyperkalaemia

## Hypokalaemia

### Aetiology

- drugs (e.g. diuretics, ACTH, adrenal steroids)

- vomiting and diarrhoea
- intestinal fistula
- Cushing's syndrome
- familial periodic paralysis - due to excessive transfer of potassium into the cells

### Clinical features

- apathy
- weakness
- anorexia
- constipation
- abdominal distention
- paralytic ileus
- marked hypokalaemia (<2.5 mmol/l) results in increased myocardial excitability, which is increased with DIGOXIN

### Psychiatric features

- apprehension
- irritability
- anxiety
- depression
- paranoid ideation
- disturbance of sleep rhythm

### Investigations

- ECG:
  - small T wave
  - prolonged Q-T interval
  - depression of ST segment

### Treatment

- if mild (>2.5 mmol/l):
  - oral potassium supplement
- if severe (<2.5 mmol/l):
  - IV POTASSIUM (not more than 20 mmol/h)

## Hypercalcaemia

### Aetiology

- **Excess PTH:**
  - primary hyperparathyroidism (caused by parathyroid adenomas)
  - tertiary hyperparathyroidism
- **Excess action of Vitamin D:**
  - sarcoidosis
- **Drugs:**
  - thiazides

- **Malignant disease:**
  - secondary metastases (esp. breast, bronchus, thyroid, prostate)
  - myeloma
  - production of osteoclastic factors by tumours
- **Endocrine disease:**
  - thyrotoxicosis
  - Addison's disease
- **Miscellaneous:**
  - long-term immobility
  - excessive ingestion of milk plus an antacid - the 'milk-alkali syndrome'

### Psychiatric features

- early symptoms (subtle):
  - personality change
  - depressive mood disturbance
  - worsening fatigue, listlessness, and apathy
- disturbance of mood and drive:
  - depression with anergia
- delirium (associated with higher calcium levels):
  - seen in 5 %
  - characterized by hallucinations, paranoid delusions and aggression
- cognitive impairment in 12 %
  - impaired attention
  - mental slowing
  - impaired memory
- non-organic psychoses rare but persecutory delusions and hallucinations can occur as calcium levels rise

### Hypocalcaemia

#### Aetiology

- **Increased phosphate:**
  - chronic renal failure
  - phosphate therapy
- **Decreased calcium:**
  - hypoparathyroidism
  - pseudohypoparathyroidism
- **drugs:**
  - CALCITONIN
  - DIPHOSPHONATES
  - anticonvulsants
- **miscellaneous:**
  - acute pancreatitis
  - citrated blood in massive transfusion
  - chronic steatorrhoea

- chronic nephritis
- hyperventilation (anxiety/ brain lesions)

### Psychiatric symptoms

- in children:
  - convulsions
  - laryngeal stridor
  - carpopedal spasm
- insidious onset
- impaired concentration
- emotional lability
- impaired cognitive function
- acute confusional state
  - characterized by florid psychotic manifestations and irritability
- affective (depression, manic-depression) and schizophreniform psychoses can occur but are rare

### Neurological features

- tetany
- cramps
- perioral and peripheral paraesthesiae
- generalized seizures

## Hypermagnesaemia

### Aetiology

- acute or chronic renal failure patients given magnesium-containing laxatives or antacids
- magnesium-containing enemas
- mild hypermagnesaemia can occur in patients with adrenal insufficiency

### Clinical features

- neurological and cardiovascular depression
- weakness with hyporeflexia
- narcosis
- respiratory paralysis
- cardiac conduction deficits

## Hypomagnesaemia

### Aetiology

- deficient intake:

- starvation
- prolonged parenteral feeding
- defective gut absorption:
  - small gut disease
  - extensive small bowel resection
- excessive gut or urinary loss:
  - severe diarrhoea
  - GI / biliary fistula
  - prolonged NG suction
  - diuretic states:
    - loop diuretics
    - DKA
  - chronic alcoholism
  - hypothyroidism
- acute pancreatitis

### Clinical features

- tremor
- ataxia
- carpopedal spasm
- hyperreflexia

### Psychiatric features

- irritability
- confusion
- hallucinations
- epileptiform seizures

## Zinc deficiency

### Aetiology

- malnourishment
- populations where bread with a high phytate content is consumed
- regional enteritis
- malabsorption syndromes

### Clinical features

- diminished acuity of taste and smell (hypogeusia, hyposmia)
- dizziness
- cerebellar symptoms:
  - ataxic gait
  - intention tremor

### Psychiatric features

- precipitation of profound depression

- memory impairments
- pronounced emotional lability
- schizophreniform presentations have been described

## **Acidosis**

### Aetiology

- hyperglycaemia
- salicylate overdose
  - restlessness
  - facial flushing
  - sweating
  - hyperventilation
  - tinnitus
  - impaired sensorium
- renal disease

### Physical and Psychiatric features

- fatigue
- progressive depression of consciousness
- seizures
- Kussmaul breathing (deep and fast)

## **Alkalosis**

### Aetiology

- hyperventilation caused by:
  - anxiety or habit
  - salicylate poisoning
  - metabolic acidosis
  - hypercapnia
  - pregnancy

### Basic science

- CO<sub>2</sub> is blown off and arterial PCO<sub>2</sub> falls leading to a rise in pH
- cerebral blood flow is decreased as a result of vasoconstriction of cerebral blood vessels
- the alkalosis causes haemoglobin to bind O<sub>2</sub> more avidly, reducing tissue availability

## Psychiatric features

- fatigability and general weakness
- atypical chest pain
- impaired concentration and memory
- derealization
- mild delirium
- hallucinations
- may precipitate epilepsy

## Water intoxication

### Aetiology

- may be due to a functional renal abnormality such as SIADH
- seen in schizophrenia, neurosis, and personality disorder - '*psychogenic polydipsia*'
  - ? due to a delusional belief, changes in the secretion of ADH, or abnormalities in the hypothalamic centre that regulates thirst and fluid intake

### Psychiatric features

- headache
- blurred vision
- polyuria
- vomiting
- exacerbation of psychosis
- delirium
- stupor
- coma

### Neurological features

- tremor
- muscle cramps
- ataxia
- convulsions

### Investigations

- diagnosis on basis of symptomatic patient having a plasma sodium less than 120 mmol/l
- fluid retention is maximal late in the afternoon so blood tests should be done then

### Differential diagnosis

- diabetes mellitus
- diabetes insipidus
- chronic renal failure
- hypocalcaemia
- drugs such as LITHIUM, alcohol, diuretics

- hyponatraemia induced by:
  - AMITRIPTYLINE
  - DESIPRAMINE
  - TRANYLCYPROMINE
  - THIORIDAZINE
  - FLUPHENAZINE
  - TRIFLUOPERAZINE
  - HALOPERIDOL

### Management

1. monitor patient's weight
  2. distracting the patient
  3. optimizing medication
- over correction of hyponatraemia has been implicated as a cause of *central pontine myelinolysis*

### Water depletion

#### Aetiology

- simple unavailability (e.g. shipwreck)
- severe weakness from physical illness
- dysphagia
- coma
- elderly are at higher risk

#### Biochemical features

- signs of dehydration are less obvious than in sodium depletion since the greatest loss is from the intracellular compartment
- rise in plasma sodium, chloride, and urea

#### Psychiatric features

- increasing confusion gives way to delirium and coma
- treatment with 5 % glucose usually leads to rapid restoration of normal mental function

## **Disorders of vitamins**

### **Vitamin B deficiency**

#### Thiamine (Vitamin B<sub>1</sub>)

- co-enzyme involved three major enzyme systems:
  - pyruvate dehydrogenase (energy production - involved in Kreb's cycle)
  - transketolase (maintenance of myelin sheaths in the nervous system)
    - exists in two or more forms in different patients
  - 2-oxo-glutarate dehydrogenase (synthesis of Acetylcholine, GABA, and glutamate)
- deficiency leads to:
  - beriberi (chronic depletion)
  - Wernicke's encephalopathy (acute and fulminating depletion)

#### Nicotinic Acid

- nicotinic acid and its amide act as constituent parts of co-enzymes necessary for glucose metabolism
- deficiency leads to:
  - pellagra
  - encephalopathy

#### Pyridoxine (Vitamin B<sub>6</sub>)

- pyridoxine is crucial co-enzyme for *glutamic acid decarboxylase (GAD)*, the enzyme which synthesizes GABA from glutamic acid
- deficiency leads to:
  - convulsions
  - mental deterioration
  - ? depressive illness

#### Riboflavin (Vitamin B<sub>2</sub>)

- part of co-enzyme necessary for glucose metabolism
- deficiency leads to:
  - glossitis
  - angular stomatitis
  - lachrymation
  - photophobia
  - personality change

#### Pantothenic acid

- concerned with the formation of acetylcholine
- deficiency leads to:
  - has been incriminated in the 'burning feet syndrome'
  - a role in psychiatric disorder has yet to be established

## **Pellagra (nicotinic acid deficiency)**

### Aetiology

- multiple vitamin deficiencies, with nicotinic acid being the most important
- alcoholic pellagra encephalopathy

### Pathological features

- central chromatolysis (retrograde cell degeneration) in the Betz cells of the motor cortex
- pontine, dorsal vagal, gracile, and cuneate nuclei are affected
- Purkinje cells of cerebellum are spared
- degeneration of the posterior and lateral columns of the spinal cord

### Clinical features

- triad of:
  1. gastrointestinal disorder
  2. skin changes:
    - roughening and reddening of the dorsum of the hands
    - pigmentation over bony prominence
    - stomatitis and glossitis
  3. psychiatric disturbance

### Psychiatric features

- prodromal:
  - general deterioration of mental and physical health
- symptoms characteristically fluctuate from one day to the next
  - anorexia
  - insomnia
  - nervousness
  - apprehension
  - palpitations
  - irritability
  - emotional instability
- depression can be severe with considerable risk of suicide
- longer and more severe deficiency leads to:
  - acute organic reaction with disorientation, confusion, and impairment of memory
  - wild excitement and outbursts of violent behaviour
  - depression
  - paranoia
  - hallucinations
  - delusions of persecution
- Wernicke's or Korsakoff's may develop, despite treatment

## Alcoholic Pellagra Encephalopathy

### Aetiology

- due to deficiency of niacin in association with chronic alcohol misuse
- much less common than WKS

### Clinical features

- encephalopathic syndrome:
  - confusion
  - oppositional hypertonus
  - myoclonus
- cogwheel rigidity
- grasping and sucking reflexes
- hallucinations
- insomnia
- tremor
- ataxia
- urinary and foecal incontinence

### Treatment

- responds rapidly to treatment with nicotinic acid

## Wernicke's encephalopathy

- first described by Wernicke in 1881

### Epidemiology

- M:F = 2:1

### Aetiology

- occurs in people with gradual thiamine depletion who then have an *acute* event (e.g. glucose load) which causes a sudden fall in thiamine
- alcohol misuse:
  - the pattern most associated with WKS appears to be steady drinking over several months with inadequate intake of food
- carcinoma of the stomach
- pregnancy
- vomiting
- hyperemesis gravidarum
- toxaemia
- pernicious anaemia
- dietary deficiency, anorexia nervosa
- widespread tuberculosis

## Clinical features

- prodromal anorexia, nausea, and vomiting
- characterized by:
  1. abrupt onset of confusion
  2. impairment of consciousness
  3. ataxia and ophthalmoplegia
- peripheral neuropathy is often seen
- may present as lethargy and hypotension
- may also present with unexplained hypothermia and hypotension
- ocular abnormalities in 96 %:
  - nystagmus
  - 6<sup>th</sup> nerve palsies
- ataxia in 87 %
  - varies from inability to stand, to difficulties with heel-toe walking
- peripheral neuropathy in 82 %
  - usually confined to the legs
  - complaints of weakness, paraesthesia, and pain

## Psychiatric features

- mental abnormalities (90 % of patients):
  - global confusion with disorientation, apathy, and derangement of memory
  - drowsiness
  - misidentifications
- mild delirium:
  - perceptual distortions
  - hallucinations
  - insomnia
  - agitation
  - autonomic overactivity
- emotional abnormalities
- amnesia and confabulation

## Pathological features

- symmetrical lesions in parts of the limbic and memory systems:
  - the walls of the 3<sup>rd</sup> ventricle
  - periaqueductal region
  - floor of 4<sup>th</sup> ventricle
  - certain thalamic nuclei
  - mamillary bodies
  - terminal portions of the fornices
  - brain stem
  - superior vermis of the cerebellum
- sparing of the cerebral cortex, corpus striatum, subthalamic and septal regions, cingulate gyri, and hippocampal areas
- ophthalmoplegia due to lesions in 3<sup>rd</sup> and 4<sup>th</sup> cranial nerve nuclei
- nystagmus due to lesions of the vestibular nuclei

- ataxia due to lesions of the vestibular nuclei and anterior lobes and vermis of the cerebellum
- amnesia is associated with lesions in the medial dorsal nuclei of the thalamus

### Investigations

- EEG shows diffuse slowing
- CSF may show mild elevation of protein
- blood pyruvate level is raised in the acute phase of the disease

### Treatment

- at least 500 mg of thiamine is required for 3-5 days
- there is some evidence that ophthalmoplegia responds more rapidly than confusion

### Outcome

- of those who get Wernicke's,
  - 10 % recover
  - 20 % die
  - 70 % develop Korsakoff's

## **Korsakoff's psychosis**

### Epidemiology

- F:M = 1:1.7
- females tend to present 10-20 years earlier than men
- 1 in 9 long stay psychiatric patients have alcohol brain damage
- large increase between 1990 and 1995 - due to withdrawal of parenterovite from the market

### Clinical features

- presentation of Korsakoff psychosis is often insidious
- features include:
  1. amnesia
  2. disorientation
  3. confabulation

### Pathological features

- specific topographic pattern of lesions:
  - mamillary bodies (maintenance of consciousness and waking state)
  - periventricular thalamic nuclei
  - structure in the floor of the fourth ventricle
  - involvement of the dorso-medial nucleus of the thalamus appears to be particularly associated with memory disturbance

### Investigations

- SPECT scanning reveals:
  - reduced blood flow in:

- *anterior temporal lobe and frontal lobe*
- atrophy of the *thalamus* and *mamillary bodies*

## Vitamin B<sub>12</sub> (cyanocobalamin) deficiency

### Aetiology

- Low dietary intake:
  - vegans
- Impaired absorption:
  - **pernicious anaemia**
    - atrophy of gastric mucosa
    - failure of intrinsic factor production and vitamin B<sub>12</sub> malabsorption
    - disease of the elderly
    - association with other autoimmune diseases (thyroid disease, Addison's disease, vitiligo)
    - parietal cell antibodies are present in all patients
    - intrinsic factor antibodies are found in 50 % but are diagnostic
  - gastrectomy
  - small bowel disease e.g. coeliac disease
  - small bowel resection
- Pancreatic disease:
  - chronic pancreatitis
  - Zollinger-Ellison syndrome
- Miscellaneous:
  - Nitrous oxide - inactivates B<sub>12</sub>

### Clinical features

- megaloblastic anaemia (MCV > 110 fl)
- weight loss
- glossitis and angular stomatitis
- neurological signs:
  - polyneuropathy progressively involving the posterior and lateral columns of the cord (subacute combined degeneration)
  - symmetrical paraesthesiae in the fingers and toes
  - early loss of vibration sense and proprioception
  - progressive weakness and ataxia
  - optic atrophy
  - dementia

### Psychiatric features

- Functional psychiatric disorders:
  - little evidence to prove associations with schizophrenia, depression, or paranoia
- Organic psychiatric disorders:

- objective impairment of memory
- presenile dementia

## **Folic Acid deficiency**

### **Aetiology**

- pregnancy
- old people who are incapacitated
- those suffering from psychiatric disorder

### **Depressive illness**

- clinically significant low folate in depressed patients
- commonest disturbance is depression
- folate deficiency could interfere with the synthesis of catecholamines and 5-HT

### **Dementia**

- occasional case reports have pointed to a close relationship between folic acid deficiency and organic psychiatric illness, including frontal lobe dementia
- sufferers of dementia may have lower levels of folate - slight correlation between scores of mental impairment and the red cell folate

### **Epilepsy**

- low serum folate can result from the administration of anticonvulsants
- PHENOBARBITONE, PHENYTOIN, and PRIMIDONE are all responsible
- folate levels seem to be lower in mentally abnormal epileptics than those who are free from psychiatric symptoms

## **Vitamin excess**

## ***Disorders of temperature regulation***

### **Hypothermia**

### **Hyperthermia**

- occurs when core body temperature is  $> 40.6^{\circ}\text{C}$
- can be exertional or non-exertional in nature

### **Aetiology**

- patients taking medication with anticholinergic effects during hot weather
- NMS
- complicates overdose with:
  - LITHIUM
  - MAOIs
  - AMPHETAMINE

### **Psychiatric features**

- agitation
- delirium (main symptom)
- coma
- lethargy
- hallucinations
- stupor
- seizures

### **Physical signs**

- hot, dry skin
- tachycardia
- flaccid muscles with reduced/ absent reflexes
- hypotension
- hypoventilation
- DIC is a potentially fatal complication

### **Management**

1. removal of clothes
2. trunk and limb massage to reduce peripheral vasoconstriction
3. spray patient with tepid water
4. chilled IV fluids
5. monitor rectal temp, urine output, and FBC, U&Es etc.

## **Miscellaneous disorders**

### **Wilson's disease**

- worldwide prevalence of 1 per 30,000
- most cases present in the first two decades
- two types:
  1. Early onset (7-15 years) Juvenile type
    - more fulminant
  2. Later onset (19-35 years) Adult type
    - less fulminant

### **Aetiology**

- autosomal recessive
- to inability of hepatic microsomes to excrete copper that has been cleaved from caeruloplasmin into bile
- inability of hepatocytes to store copper due to deficiency of caeruloplasmin
- leads to copper deposition in various organs, especially the liver and the brain

### **Course**

- onset usually in childhood, with liver disease, renal disease, or haemolytic anaemia
- individuals with adult-onset (rare beyond 40 years) present with neurological or psychiatric features

### **Clinical features**

- Kayser-Fleischer ring usually visible in the outer margin of the cornea in psychiatric patients due to copper deposition in Descemet's membrane

### **Psychiatric features**

- psychopathology in 51 % of cases
  - irritability
  - aggression
  - changes in personality and behaviour
  - depression
  - cognitive impairment
- schizophreniform psychoses are rare
- psychiatric symptoms are related to the severity of the neurological rather than the hepatic symptoms

### **Neurological features**

- movement disorders:
  - tremor (resting and intention tremor)
  - rigidity
  - dystonia
  - choreo-athetoid movements
- bulbar symptoms:
  - dysphagia

- spastic dysarthria
- cerebellar features
- hemiplegia
- epilepsy
- intermittent coma

### Investigations

- diagnosis is confirmed if patient has Kayser-Fleischer rings and low serum caeruloplasmin levels; or low serum caeruloplasmin and elevated hepatic copper levels (on biopsy)
- 5 % of cases have normal serum caeruloplasmin levels
- urinary copper excretion is usually elevated
- CT evidence of structural brain changes commonly occurs in both those with predominantly neurological and those with predominantly hepatic disease
  - ventricular dilatation
  - cortical atrophy
  - brain stem atrophy
  - basal ganglia hypodensities

### Management

- treatment with PENICILLAMINE, a copper-chelating agent can prevent virtually every manifestation of the disease
- vitamin B<sub>6</sub> is required to counteract the antipyridoxine action of PENICILLAMINE

### Outcome

- high mortality in cases who stop treatment
- main improvement occurs in first 2 years of treatment
- hepatic disturbance responds less well than neurological or psychological

## Porphyria

### Aetiology

- all types are autosomal dominant or recessive
- due to a partial deficiency of enzymes responsible for haem synthesis
- excessive production of haem precursors results and these are readily oxidized to porphyrins

### Basic science

- four types are indistinguishable clinically:
  1. acute intermittent porphyria (AIP)
  2. hereditary coproporphyria (HC)
  3. variegate porphyria (VP)
  4. porphobilinogen-synthase deficiency (PBGSD)

## Clinical and Psychiatric features

1. Abdominal pain
2. Psychiatric disturbances
  - a) 25-75 % have psychiatric symptoms
  - b) personality changes
  - c) neurotic disorders (minor depression, anxiety, hysteria)
  - d) acute depression with restlessness and occasional violence
  - e) emotional lability common
  - f) delirium
  - g) schizophreniform and paranoid reactions not uncommon
  - h) epilepsy and coma
3. Peripheral neuropathy

- Neurological features
  - rapidly spreading, symmetrical, predominantly motor polyneuropathy
  - cranial nerve lesions
  - Guillan-Barré syndrome

## Precipitation of episodes

- drugs:
  - TCAs
  - MAOIs
  - barbiturates
  - older anticonvulsants
  - sulpiride
  - zuclopenthixol
  - thioridazine
  - amphetamine
- fever
- alcohol
- menstrual change
- pregnancy

## Investigations

- in AIP, urine left to stand may turn to a purple-red colour
- EEG shows slowing of dominant frequencies and excess of intermediate slow activity. May be normal

## Mitochondrial myopathy

### Aetiology

- rare group of metabolic disorders which are clinically and biochemically heterogenous, but show structural mitochondrial abnormalities on skeletal muscle biopsy

- clinical features are caused by defects in the enzyme-protein complexes of the respiratory chain for oxidative phosphorylation
- most cases present before the age of 20
- maternal to paternal transmission is 9:1

### Clinical features

- three overlapping clinical groups are reported:
  1. external ophthalmoplegia and limb weakness
  2. limb weakness alone
  3. CNS manifestations:
    - ataxia, dementia, deafness, involuntary movements, pigmented retinopathy, seizures

### Psychiatric features

- may present as a chronic fatigue syndrome, hysteria, or progressive dementia at an early age

## Neuroacanthocytosis

### Aetiology

- refers to a constellation of metabolic disorders characterized by the occurrence of neurological disorder in conjunction with acanthocytic red blood cells

### Clinical features

1. **Neurological:**
  - a) orofacial dyskinesia
  - b) dysarthria
  - c) chorea
  - d) tics (need to exclude this disease in atypical cases of Tourette's syndrome)
  - e) dystonia
  - f) parkinsonism
  - g) muscle disorder
2. **Psychiatric:**
  - a) personality change (frontal lobe type)
  - b) depression
  - c) anxiety
  - d) paranoid delusions
  - e) OCD
  - f) mild cognitive impairment
  - g) exclude diagnosis in patient presenting with movement disorder, personality change and progressive intellectual deterioration

### Investigations

- blood film
- caudate head shrinkage on CT (seen in Huntington's chorea) is also seen

**Paraneoplastic syndromes**

**Carcinoid syndrome**

## **Other metabolic disorders**

### **Kufs disease (cerebral ceroid lipofuscinosis)**

#### Aetiology

- both autosomal dominant (Parry type) and recessive (Kufs type) forms exist
- onset in infancy or childhood is known as *Batten-Beilshowsky* or *Spiel-meyer-Vogt*

#### Pathological features

- pathogenesis unclear
- abnormal lipopigment deposits in the CNS consist of a ceroid-like material akin to lipofuscin
- finding at autopsy is distension of nerve cells with autofluorescent lipopigment, along with neuronal degeneration and reactive gliosis

#### Clinical features

- symptoms begin in adolescence or early adulthood, with an insidious dementia accompanied by motor manifestations
- extrapyramidal disturbances and cerebellar disorder appear to be commoner than spasticity in adults
- myoclonic and other forms of seizures are reported
- progress tends to be slow, with death 8-9 years after initial presentation

### **Leigh disease (subacute necrotizing encephalomyelopathy)**

#### Aetiology

- inherited as autosomal recessive
  - the genetic defect may have varying degrees of expression
- due to a disturbance of thiamine metabolism
- site of pathology is in the classical Wernicke location

#### Clinical features

- usually presents in the first 2 years of life
- presents as progressive psychomotor retardation with feeding difficulties, respiratory disorder, hypotonia, and weakness
- neurological features include loss of vision, ataxia, cortico-spinal tract signs, seizures and movement disorders
- death usually occurs within 4 years, and often within a year
- some cases have been reported in adults
  - presented as insidious development of strabismus, visual loss, a broad-based gait, and impairment of intellect from early schooldays onwards

## **Hallervorden-Spatz syndrome**

### Aetiology

- rare extrapyramidal syndrome
- more than one family member tends to be affected

### Clinical features

- typically onset at young age, although late onset cases exist (non-familial)
- extrapyramidal motor disorder:
  - rigidity
  - dystonia
  - choreoathetoid movements
  - dysarthria
  - spasticity can occur
  - myoclonus and tremor
  - abnormalities of posture
- change in personality:
  - moodiness
  - depression
  - outbursts of aggressive behaviour
- intellectual deterioration and dementia, progressing to mutism
- EEG slows as the disease progresses, sometimes with spikes and sharp waves

### Pathological features

- CT scan may resemble Huntington's chorea, with prominent atrophy of the basal ganglia
- generalized atrophy of the cortex, brain stem, and cerebellum
- reddish-brown discolouration of the globus pallidus and para reticulata of the substantia nigra, due to accumulation of iron-containing pigment
- the Purkinje cells of the cerebellum may be depleted

## ***The Sphingolipidoses - lysosomal storage diseases***

1. Gaucher's disease
2. Niemann Pick disease
3. Tay-Sach's disease

### **Gaucher's disease**

#### Aetiology

- autosomal recessive

- high incidence in Ashkenazi Jews (1 in 3000 births)
- enzyme defect is *glucocerebroside- $\beta$ -glucosidase*

#### Pathological features

- accumulation of glucocerebroside in the reticuloendothelial system, particularly the liver, bone marrow, and spleen
- Gaucher cells are found in the bone marrow

#### Clinical features

- three clinical types:
  - *chronic (type I)* - presents in adult life with insidious onset of hepatosplenomegaly
  - *acute (type II)* - presents in infancy or childhood with rapid onset of hepatosplenomegaly with neurological involvement due to Gaucher cells in the brain
  - *subacute (type III)* - brain involvement is less marked
- patients have a characteristic pigmentation on exposed parts, particularly the forehead and hands
- patients develop anaemia, evidence of hypersplenism, and pathological fractures
- many have a normal life-span, although generally the prognosis is poor

### Niemann-Pick disease

#### Aetiology

- particularly prevalent in the Jewish race
- enzyme defect is *sphingomyelinase*

#### Pathological features

- accumulation of sphingomyelin
- typical foam cells are found in the marrow, lymph nodes, liver, and spleen

#### Clinical features

- Type A:
  - 70 % of cases
  - usually presents within the first 6 months of life with mental retardation and hepatosplenomegaly
- Type B:
  - presents later in infancy, with hepatosplenomegaly and pulmonary infiltration
  - CNS is spared
- Types C and D:
  - sphingomyelinase levels are normal
  - usually present in adolescence with varying degrees of progressive mental deterioration and hepatosplenomegaly

## **Tay Sachs disease (GM2 gangliosidosis)**

### Aetiology

- particularly common in Ashkenazi Jews (1 in 2000 live births)
- autosomal recessive
- enzyme deficiency is *hexosaminidase A*

### Pathological features

- accumulation of GM2 gangliosides and related glycolipids in the central nervous system and peripheral nerves

### Clinical features

- in infantile Tay-Sachs disease there is progressive degeneration of all cerebral function, with fits, epilepsy, dementia, and blindness leading to dementia
- death usually occurs before 2 years of age
- the macula has a characteristic cherry spot appearance

## ***The Leucodystrophies***

1. Metachromatic
2. Krabbe's
3. Adrenoleucodystrophy

### Pathological features

- characterized by diffuse symmetrical demyelination and gliosis of:
  - the white matter of the cerebral hemispheres
  - cerebellum
  - brain stem
  - spinal cord

### Clinical features

- various combinations of:
  - mental deterioration
  - motor impairment
  - peripheral neuropathy

## ***Metachromatic leucodystrophy***

- childhood (60 %), juvenile and adult forms

## Aetiology

- autosomal recessive
- lysosomal storage disease resulting in disorder of myelin formation
- if there is lysosomal enzyme deficiency, engorgement of lysosomes with the enzyme's substrate occurs, leading to impairment of cell and tissue function
- the enzyme *aryl sulphatase A* is deficient

## Psychiatric features

- progressive impairment of motor function often preceded by:
  - personality change
  - affective disorder
  - schizophreniform psychosis

## Investigations

- low or absent urinary aryl sulphatase A
- metachromatic material seen in Schwann cells from rectal or sural nerve biopsy
- CSF protein usually raised

## Outcome

- progressive dementia accompanies a relentless deterioration in neurological function

## Familial idiopathic calcification of the basal ganglia

## Cerebrotendinous xanthomatosis

## Lowe's syndrome

- oculocerebrorenal dystrophy
- generalized amino-aciduria combined with mental retardation, hypotonia, congenital cataracts and an abnormal skull shape