Metabolic, Biochemical, and Endocrine disorders

Organ failure or dysfunction

Endocrinopathies

Hyperthyroidism
- more common in women
- usually presents between 2nd and 4th 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 3rd or 4th 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 confused 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
- ¾ 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 familially
- MEN type I:
  - parathyroid adenomas
  - endocrine tumours of pancreas
  - pituitary tumours
- MEN type II:
  - parathyroid adenomas
  - phaeochromocytomas
  - medullary 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 δ 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, resentfulness 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 involutional 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 β 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 4th and 5th 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 3rd, 4th, and 5th 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**
• CO₂ is blown off and arterial PCO₂ 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 O₂ 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
  • TRANYLCPROMINE
  • THIORIDAZINE
  • FLUPHENAZINE
  • TRIFLUOPERAZINE
  • HALOPERIDOL

Management
1. monitor patient’s weight
2. distracting the patient
3. optimizing medication

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 B₁)
• 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 B₆)
• 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 B₂)
• 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 faecal 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
  - 6th 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 3rd ventricle
  - periaqueductal region
  - floor of 4th 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 3rd and 4th 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 $B_{12}$ (cyanocobalamin) deficiency

Aetiology
- Low dietary intake:
  - vegans
- Impaired absorption:
  - pernicious anaemia
    - atrophy of gastric mucosa
    - failure of intrinsic factor production and vitamin $B_{12}$ 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 $B_{12}$

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°C
- can be exertional or non-exertional in nature

**Aetiology**

- patients taking medication with anticholinergic effects during hot weather
- NMS
- complicates overdosage 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 if 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 B6 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) schizophréniform 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 lipofuscinosi

Aetiology
- both autosomal dominant (Parry type) and recessive (Kufs type) forms exist
- onset in infancy or childhood is known as Batten-Beilschowsky 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-β-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

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**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

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**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