

Third edition

Notes & Notes

For physician

By

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Neurology

Updated 2022

The 10 Golden Tips for MRCP written exams you will ever need

1. For MRCP, do not read hard; read smart.
2. Three to six months is usually enough for preparation.
3. Practice the best of the five questions as much as possible.
4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
5. Remember, you are getting ideas and concepts from the questions.
6. Time factor in the exam room is the leading killer after poor preparation.
7. Manage your time wisely.
8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
9. Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
10. Practice, practice and practice.



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Third edition

Notes & Notes

For physician

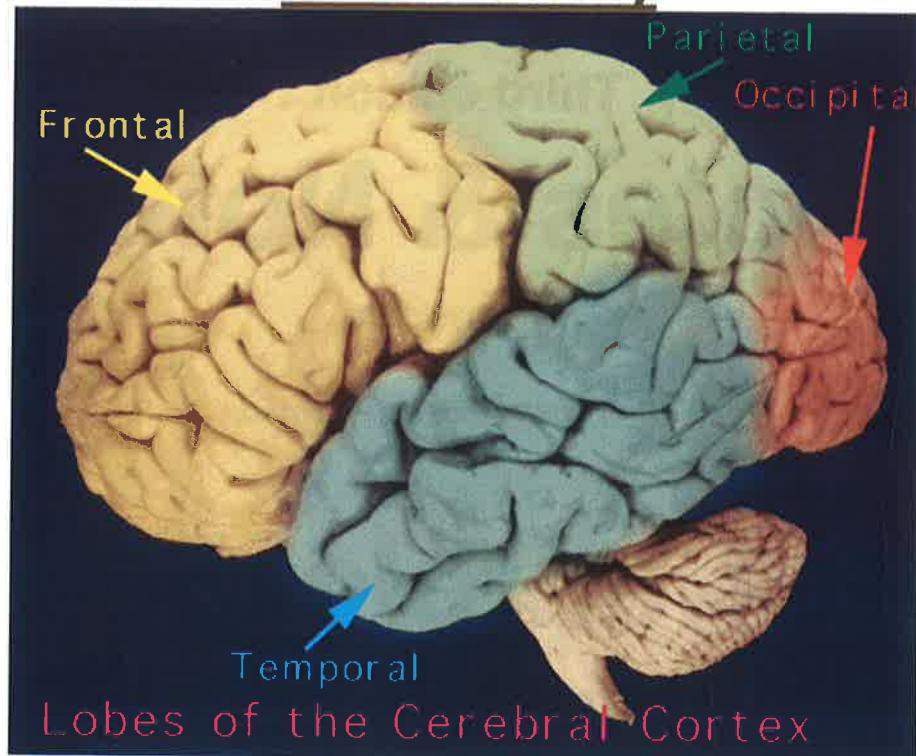
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Neurology

Updated 2022

CNS anatomy



Localisation of a brain lesion

The following neurological disorders/features may allow **localisation of a brain lesion**

Lobes lesions

Lobe lesion	Features
Frontal lobes lesions	<ul style="list-style-type: none"> Difficulties with task sequencing and executive skills Expressive (Broca's) aphasia: (located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus). Disinhibition Perseveration Anosmia primitive reflexes (positive grasp, pout and palmomental reflexes) Inability to generate a list Changes in personality.
Parietal lobes lesions	<ul style="list-style-type: none"> Sensory inattention (contralateral hemihypesthesia) Apraxia Astereognosis (tactile agnosia) Inferior homonymous quadrantanopia Neglect Mild hemiparesis Parietal ataxia Acalculia (inability to perform mental arithmetic). Gerstmann's syndrome (lesion of dominant parietal): Alexia (inability to read), acalculia, finger agnosia and right-left disorientation unilateral impairment of optokinetic nystagmus: a nystagmus that occurs in response to a rotation movement. It is present normally.
Temporal lobes lesions	<ul style="list-style-type: none"> Wernicke's aphasia: <ul style="list-style-type: none"> ⇒ this area 'forms' the speech before 'sending it' to Broca's area. ⇒ Lesions result in word substitution, neologisms but speech remains fluent superior homonymous quadrantanopia auditory agnosia prosopagnosia (difficulty recognising faces) Memory impairment.
Occipital lobes lesions	<ul style="list-style-type: none"> homonymous hemianopia (with macula sparing). may present as Anton syndrome where there is blindness, but the patient is unaware or denies blindness. cortical blindness visual agnosia visual illusions and elementary visual hallucinations.

Visual- spatial awareness deficit

- Due to the Damage to the **right parietal lobe**
- Patient unable to navigate around locations, specially places that are new to him , but also familiar locations

Homonymous quadrantanopias

- **PITS (Parietal-Inferior, Temporal-Superior)**

More specific areas

Area	Associated conditions
Medial thalamus and mammillary bodies of the hypothalamus	Wernicke and Korsakoff's syndrome
Subthalamic nucleus of the basal ganglia	Hemiballism
Striatum (caudate nucleus) of the basal ganglia	Huntington chorea
Substantia nigra of the basal ganglia	Parkinson's disease
Amygdala	<p>Kluver-Bucy syndrome:</p> <ul style="list-style-type: none"> • hypersexuality, • hyperorality (insertion of inappropriate objects in the mouth) • hyperphagia, • visual agnosia <p>increased activation to the amygdala is associated with depression</p>
Hippocampus pathology	Short term memory impairment (for example, Alzheimer's disease).
Lateral geniculate nucleus pathology	visual field defect.
Red nucleus (located in the midbrain).	<ul style="list-style-type: none"> • Tremor, which is present both at rest and during action (for example, multiple sclerosis tremor). • A lesion in this area would cause problems with arm swing and motor co-ordination of the upper limbs, not chorea.
Prefrontal cortex damage	disinhibition and problems with social interaction and judgement and has been implicated in schizophrenia . Left prefrontal cortex → Depression
Anterior hypothalamic nucleus	<ul style="list-style-type: none"> • Plays a crucial role in thermoregulation and circadian rhythms • Situated at the inferior border of the paraventricular nucleus

Chorea is caused by damage to the basal ganglia, in particular the **caudate nucleus**

MRCPUK-part-1-September 2012 exam: (SLE) presents with continuous jerky, irregular movements, which move from one limb to another. Where is the lesion most likely to be?

→ Caudate nucleus

Crossed neurological signs (ipsilateral motor and sensory cranial nerve signs and contralateral hemiplegia) → localise to the **brainstem** (midbrain, pons or medulla).

- Midbrain → (ipsilateral oculomotor nerve palsy , contralateral hemiplegia)
- Pons → (ipsilateral abducens and facial nerves palsy, contralateral hemiplegia)

Stroke and pupils:

- Midbrain lesions typically cause fixed, **midpoint** pupils.
- Pontine haemorrhage typically cause bilateral **pin point** pupils

Lesions at the jugular foramen

- Nasopharyngeal carcinoma is the commonest cause.
- Affected CN → 9,10,11
 - ⇒ CN IX (Glossopharyngeal nerve) & CN X (Vagus nerve) → palatal weakness and swallowing difficulties , **Laryngeal muscle paralysis would result in bovine cough and husky voice.**
 - ⇒ CN XI (Accessory nerve) → shoulder and sternocleidomastoid weakness

Cerebellar lesions

Cerebellar lesion localization:

- Lesions to the **vermis** results in → **truncal ataxia** and nystagmus.
- Cerebellar lesions cause neurological deficits on the **ipsilateral side**
- Lesions to the cerebellar **hemispheres** results in → **ipsilateral** dysmetria, dysdiadochokinesis, **ipsilateral limb ataxia** and fast-beat nystagmus towards the lesion.

A history of vertigo, nystagmus, Slurred speech, intention tremor and past pointing, as well as ataxia, suggest the cerebellum as the site of injury.

Oppenheim's sign is seen when scratching of the inner side of leg leads to extension of the toes. It is a sign of cerebral irritation

Cerebellum lesions: **Charcot's neurological triad:** scanning speech, nystagmus, and **intention tremors**

Transient ischaemic attack (TIA)

Definition

- Temporary cerebral ischemia that results in brief neurologic deficits lasting < 24 hours

Investigations (NICE guidelines. Last updated: March 2019)

- MRI** is the first choice , identifies ischemia earlier than CT, determine the territory of ischaemia, and detect alternative pathologies.
- Do not offer CT brain unless there is clinical suspicion of an alternative diagnosis.**
- Duplex ultrasound for carotid stenosis**
 - urgent for possible carotid endarterectomy.
 - the most appropriate next step if bruits in the neck are heard upon auscultation.**
 - If ultrasound is not available, a CTA or MRA may be used.

Treatment

- Immediate therapy (after initial assessment)**
 - Aspirin** 300 mg immediately unless contraindicated
 - To be seen within 24 hours of onset of symptoms for specialist assessment
 - Do not use scoring systems, such as ABCD2, to assess risk of subsequent stroke or to inform urgency of referral.**
- Secondary prevention (introduced as soon as the diagnosis is confirmed)**
 - Clopidogrel** 300 mg loading dose followed by 75 mg daily.
 - aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel
 - High intensity** (e.g. atorvastatin 20-80 mg daily)
 - started immediately (as per Royal College guideline 2016)
 - Immediate initiation of statin is not recommended as per (NICE guideline 2019)
 - Carotid endarterectomy:** for people with non-disabling stroke or **TIA**:
 - carotid stenosis of **50 to 99%:**
 - referred urgently for carotid endarterectomy
 - medical treatment (BP control, antiplatelets, Statin, lifestyle advice).
 - carotid stenosis of less than 50%:
 - No surgery
 - Medical treatment (BP control, antiplatelets, Statin, lifestyle advice).
 - Control BP: antihypertensive
 - If associated AF → Anticoagulation

Top Tips

Antiplatelets
TIA: clopidogrel
ischaemic stroke: clopidogrel

Brain imaging for TIA and stroke

- **MRI brain with diffusion-weighted imaging** is the preferred modality in patients with suspected TIA.
- Non-contrast cranial CT (gold standard and most important initial imaging in stroke): detects acute hemorrhage **but cannot reliably identify early ischemia**

Ischaemic stroke: Overview

Definition

- Stroke is an acute neurological deficit lasting more than 24 hours due to occlusion or critical stenosis of a cerebral artery.

Epidemiology

- Ischemic stroke (~ 85%)

Risk factors

- older age, hypertension, smoking, diabetes mellitus, dyslipidaemia, atrial fibrillation, sickle cell disease, and history of TIA or stroke.

Mechanisms

- **Thrombotic strokes** (most common)
 - ⇒ **Atherosclerosis** of the extracranial vessels (carotid atheroma) is the most common cause
- **Embolic strokes**
 - ⇒ Cardiac emboli e.g. Atrial fibrillation
 - ⇒ **Paradoxical embolisation:** For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart.
 - **Causes**
 - ❖ patent foramen ovale : present in 20% of the population.
 - ❖ **Transoesophageal echocardiography (TOE) is the investigation of choice for diagnosis**
 - ❖ atrial septal defect - a much less common cause

Assessment

- **ROSIER score (Recognition Of Stroke In the Emergency Room).**
 - ⇒ **It is validated tool recommended by the Royal College of Physicians. useful for medical professionals.**
 - ⇒ Exclude hypoglycaemia first, then assess the following:

Assessment	Scoring
Loss of consciousness or syncope	- 1 point
Seizure activity	- 1 point
New, acute onset of:	
• asymmetric facial weakness	+ 1 point
• asymmetric arm weakness	+ 1 point
• asymmetric leg weakness	+ 1 point
• speech disturbance	+ 1 point
• visual field defect	+ 1 point

⇒ stroke is likely if > 0

Imaging

- CT without contrast for acute presentation (**the best initial test**) → to rule out hemorrhage
- MRI : if the CT is negative → **Diffusion weighted imaging (DWI) MRI is the most sensitive** and specific imaging modality for diagnosing **acute ischaemic stroke**.
- Duplex ultrasound for carotid stenosis

Diagnostic evaluation

- Glucose: **the only lab test which should be done before thrombolysis**
- ECG : to look for cardiogenic thrombus (Atrial fibrillation)
- If an embolic stroke is suspected → Echocardiography
- Thrombophilia screening: if patient is < 50 years old and/or has a history of thrombosis

Only glucose test and CT head are required before thrombolytic therapy. Do not delay treatment to complete the diagnostic evaluation.

Management

- Exclude hypoglycaemia because it is a stroke mimic
- **Admission to a stroke unit** → improve the overall prognosis.
- presentation within 4.5 hours AND thrombolysis not contraindicated → thrombolysis with iv alteplase
- presentation after 4.5 hours OR thrombolysis contraindicated → Supportive care
- Deep vein thrombosis prophylaxis with subcutaneous heparin or low molecular weight heparin
 - ⇒ Pulmonary embolism from DVT is the most common cause of early death in patients with acute stroke.

Vitamin D has a role as a neuroprotective agent towards large artery atherosclerosis. Many patients with ischemic stroke have vitamin D deficiency.

Stroke: Clinical features

Affected cerebral vessels and associated features

Site of the lesion	Associated effects
Anterior cerebral artery (ACA)	<ul style="list-style-type: none"> Contralateral weakness and sensory loss more marked in the lower limbs than in upper limbs Urinary incontinence Dysarthria
Middle cerebral artery	<ul style="list-style-type: none"> Contralateral weakness and sensory loss more marked in the upper limbs than in lower limbs Contralateral homonymous hemianopia Aphasia if in dominant hemisphere (usually left MCA territory) (global aphasia) Hemineglect if in nondominant hemisphere (usually right MCA territory) Gaze deviates toward the side of infarction
Posterior cerebral artery	<ul style="list-style-type: none"> Contralateral homonymous hemianopia with macular sparing Visual agnosia Cortical blindness Visual hallucinations
Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain) Or branches of the basilar artery	Ipsilateral CN III palsy Contralateral weakness
Posterior inferior cerebellar artery (PICA)(lateral medullary syndrome, Wallenberg syndrome) lesion to dorsolateral medulla	<ul style="list-style-type: none"> Ipsilateral: facial pain and temperature loss Contralateral: limb/torso pain and temperature loss. Ataxia, nystagmus
Anterior inferior cerebellar artery (lateral pontine syndrome)	Symptoms are similar to Wallenberg's (see above), but: Ipsilateral: facial paralysis and deafness
Retinal/ophthalmic artery	Amaurosis fugax
Basilar artery	'Locked-in' syndrome

Lateral medullary syndrome (Wallenberg's syndrome)

Lateral medullary syndrome:

- Caused by → PICA lesion
- Characterised by :
 - ⇒ Ipsilateral cerebellar signs (Ataxia, Nystagmus) & Horner syndrome (ptosis, miosis, and anhidrosis).
 - ⇒ Contralateral trunk and limbs sensory loss

Pathophysiology

- Ischemic occlusion of the **Posterior Inferior Cerebellar Artery (PICA)** → lesion to **dorsolateral medulla**
- May be caused by dissection or thrombosis of the vertebral artery, which gives rise to the posterior inferior cerebellar artery (PICA)
- PICA is the largest branch of the vertebral artery and is the most common territory involved in cerebellar infarction.
- The PICA supplies blood to structures of the lateral medulla (vestibular nuclei, spinal cord tracts) and the inferior cerebellar peduncle.

Features

- Vertigo, nausea and truncal ataxia are the **most common** presenting features and due to vestibular or cerebellar damage.
- **Hoarseness** (or dysphagia, if present) is fairly **specific** for **lateral medullary syndrome** because it points to a lesion of the nucleus ambiguus (cranial nerves IX, X, XI).
- Damage to the spinal **trigeminal nucleus** can result in **loss of pain and temperature sensation in the ipsilateral face**.
- Damage to the **lateral spinothalamic tract** can result in loss of contralateral pain and temperature sensation below the neck.
- Damage to the **descending sympathetic fibers** that also course through the lateral medulla would result in an **ipsilateral Horner syndrome of ptosis, miosis, and anhidrosis**.
- **Ataxia** is probably due to infarction of the ipsilateral **inferior cerebellar peduncle**.
- Pyramidal tract findings (weakness) are **typically absent** in lateral medullary lesions.

Ipsilateral	Contralateral
<ul style="list-style-type: none"> • Cerebellar signs (Ataxia, dysmetria, dysdiadochokinesia, nystagmus) • Horner syndrome • Loss of pain and temperature in the face (due to 5th CN nucleus damage) 	<ul style="list-style-type: none"> • Loss of pain and temperature in the trunk and limbs

Diagnosis: MRI is the imaging investigation of choice for posterior fossa lesions.

Lateral pontine syndrome vs Lateral medullary syndrome

	Lateral pontine syndrome	Lateral medullary syndrome
Aetiology	Anterior inferior cerebellar artery (AICA)	posterior inferior cerebellar artery (PICA)
Differences	Facial nucleus and facial nerve involvement leads to: <ul style="list-style-type: none"> Ipsilateral paralysis of the upper and lower face (lower motor neuron lesion). Ipsilateral loss of lacrimation and reduced salivation. Ipsilateral loss of taste from the anterior two-thirds of the tongue. Hyperacusis. 	Nucleus ambiguus involvement leads to: Dysphagia, dysarthria, dysphonia
Similarities	Ipsilateral Horner's syndrome. Why? Descending hypothalamic tracts affected. Contralateral loss of pain and temperature. Why? Lateral spinothalamic tract affected. Ipsilateral cerebellar ataxia. Why? Cerebellar peduncles affected. Inferior cerebellar peduncle in medullary and middle cerebellar peduncle in pons. Nausea, nystagmus, vertigo, vomiting. Why? Vestibular nuclei involved. Ipsilateral loss of pain and temperature sensation from the face (facial hemianesthesia). Why? Spinal trigeminal nucleus and tract involved. Ipsilateral hearing loss. Why? Cochlear nuclei and nerve fibers involved.	

Pontine syndromes

Locked-in syndrome

- **Pathophysiology**
 - ⇒ The locked-in syndrome is caused by destructive bilateral brainstem lesions affecting the corticospinal, corticopontine, and corticobulbar tracts.
 - ⇒ The most common cause is ischemic **infarction of the ventral pons**.
- **Features**
 - ⇒ Quadriplegia and inability to speak or swallow with retained consciousness and eyes movement

- ⇒ Because the supranuclear ocular motor pathways are spared, patients can move their eyes and blink.

Ventral pontine syndrome

- Millard-Gubler syndrome (MGS), also known as facial abducens hemiplegia syndrome is one of the classical crossed brainstem syndromes characterized by a unilateral lesion of basal portion of the caudal pons involving fascicles of abducens (VI) and the facial (VII) cranial nerve, and the pyramidal tract fibers
- Classical **Raymond syndrome** also has the same components as Millard-Gubler syndrome, but there is ipsilateral sixth nerve palsy along with contralateral facial paresis and hemiplegia.

Components of Millard-Gubler syndrome (MGS)

1. Ipsilateral weakness of the eye on abduction (VI nerve)
2. Ipsilateral facial muscle weakness (VII nerve)
3. Contralateral hemiparesis or hemiplegia of upper and lower extremities (pyramidal tract involvement)

Inferior medial pontine syndrome

- Inferior medial pontine syndrome, also known as Foville syndrome, is one of the brainstem stroke syndromes occurring when there is infarction of the medial inferior aspect of the pons due to occlusion of the paramedian branches of the basilar artery.
- **Features**
 - ⇒ corticospinal tract: **contralateral** hemiplegia/hemiparesis
 - ⇒ medial lemniscus: **contralateral** loss of proprioception and vibration
 - ⇒ middle cerebellar peduncle: **ipsilateral** ataxia
 - ⇒ facial nerve (CN VII) nucleus: **ipsilateral** facial weakness
 - ⇒ abducens nerve (CN VI) nucleus: lateral gaze paralysis and diplopia

Weber's syndrome

Weber syndrome

- **ipsilateral III palsy**
- **contralateral weakness**

Overview

- **Weber syndrome** is a midbrain stroke syndrome that involves the cerebral peduncle and the ipsilateral fascicles of the oculomotor nerve
- caused by midbrain infarction as a result of occlusion of the paramedian branches of the posterior cerebral artery or of basilar bifurcation perforating arteries.

Features

- **Ipsilateral III palsy**
- **Contralateral weakness**

Parinaud syndrome (Dorsal midbrain syndrome)

Pathophysiology

- **Results from dorsal midbrain lesion**
- **Affected vessel** : Branches of the posterior cerebral artery. Often result from compression, e.g., by **tumor of the pineal gland** → compresses the vertical gaze center at the rostral interstitial nucleus of medial longitudinal fasciculus → **vertical gaze palsy**

Feature

- Vertical gaze palsy (**inability to move the eyes up**). Downward gaze is usually preserved
- Eyelid retraction (Collier sign): development of unilateral or bilateral lid retraction due to a midbrain lesion of the superior colliculi and the medial longitudinal fasciculus.
- Pupillary light-near dissociation (pseudo-Argyll Robertson pupils)
- Convergence-retraction nystagmus

Labyrinthine infarction

Sudden-onset unilateral hearing loss → consider **Labyrinthine infarction** typically due to anterior cerebellar artery dissection after minor head trauma

Anatomy

- The blood supply to the inner ear flows through only 1 main blood vessel, the internal auditory artery (or labyrinthine artery), which typically originates from the anterior inferior cerebellar artery.

Features

- almost always present with acute prolonged vertigo and vestibular dysfunction
- sudden-onset unilateral hearing loss.

Differential diagnosis

- Unlike viral labyrinthine dysfunction, the most common pattern of dysfunction with labyrinthine infarction includes a **combined loss of auditory and vestibular function**.

Posterior communicating artery aneurysm (PCA)

Posterior communicating artery aneurysm will cause → compression of the third nerve, and therefore → isolated **ipsilateral painful** third nerve palsy

- Pupillary involvement (pupil dilation) from compression of the parasympathetic fibres that run on the outside of the third nerve
- Other features of a third nerve palsy include ptosis, and a 'down and out' eye.
- Cerebral aneurysms may be associated with polycystic kidney disease.

Features

- Pupillary dilatation, Ophthalmoplegia, and Ptosis.
- other features suggestive of subarachnoid blood (headache, nuchal rigidity and photophobia).

Investigation

- **Urgent CT angiogram of the cerebral vessels is required for diagnosis.**

- Conventional angiography: the definitive procedure for the detection and characterisation of cerebral aneurysms.
- Digital subtraction angiography:** may be helpful in identifying an acutely ruptured aneurysm.

Differential diagnosis

- Features distinguishing PCA from a cavernous sinus thrombosis are absence of sinusitis or a midface infection, which are common, absence of fever or additional cranial nerve abnormalities.

The **differential diagnoses** in a patient presenting with **headaches and painful diplopia** are:

- posterior communicating aneurysm (PCA)
- Ophthalmoplegic migraine
- Pituitary adenoma
- Cavernous sinus thrombosis, or
- medical mononeuritis.

Ischaemic Stroke management

Initial management

- Aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded **for the initial two weeks.**

Reperfusion therapy for acute ischemic stroke

- Thrombolysis by Alteplase** (recombinant tissue plasminogen activator or tPA) are commonly used

⇒ **Mechanism of action:**

- Alteplase → bind to fibrin in a thrombus (clot) → convert entrapped plasminogen to plasmin → plasmin breaks up the thrombus → fibrinolysis

⇒ **Criteria :** Ischemic stroke with the onset of symptoms <4.5 hours

⇒ **Written consent is not required to administer alteplase**

⇒ **Absolute contraindications**

- Ischemic stroke, head trauma or surgery in the previous three months
- Previous intracranial hemorrhage
- Intracranial neoplasm
- Gastrointestinal malignancy or hemorrhage in the previous 21 days
- Cerebral hemorrhage
- Persistent High BP (systolic ≥185 mmHg or diastolic ≥110 mmHg)
- Haematological bleeding disorders

⇒ **Bleeding risk:** 1 %.

- Mechanical thrombectomy:** a device that can remove a clot

⇒ patients should undergo the procedure **within 6 hours** of symptom onset.

⇒ Indications

- large vessel occlusion (usually in addition to IV thrombolytic therapy) proximal MCA or distal internal carotid artery or basilar artery occlusion.
- Patients who are **ineligible for IV thrombolysis** who present within the appropriate time-frame with large vessel occlusion.

Surgical treatment → decompressive hemicraniectomy

- **Indications:** Patient with middle cerebral artery infarction who meet all of the criteria below:
 1. **Age ≤ 60 years**
 2. Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale (**NIHSS**) of **above 15**.
 3. Decrease in the level of consciousness to give a **score of 1 or more** on item 1a of the **NIHSS**.
 4. Signs on CT of an infarct of at least **50% of the middle cerebral artery** territory

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.

Secondary prevention

- **Clopidogrel** is now recommended by NICE
 - ⇒ if clopidogrel is not tolerated → **Aspirin + dipyridamole lifelong**
- **Anticoagulation treatment for other comorbidities** (e.g. atrial fibrillation):
 - ⇒ Should not be started until brain imaging has excluded haemorrhage, usually **after 14 days** from the onset of an **ischaemic stroke**.
 - ⇒ ischaemic stroke + atrial fibrillation → aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.
 - ⇒ cerebral infarction in patient with prosthetic valves and who are at significant risk of haemorrhagic transformation → **anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted**.
 - ⇒ ischaemic stroke and symptomatic proximal DVT or PE → should receive anticoagulation treatment in preference to treatment with aspirin
 - ⇒ haemorrhagic stroke and symptomatic DVT or PE → prevent further PE using either **anticoagulation or a caval filter**.
 - ⇒ **Prevention of thromboembolic event in stroke patient:**
 - Patients admitted with stroke are very likely to be at high risk of developing a thromboembolic event due to reduced mobility.
 - NICE advises that patients admitted within three days of an acute stroke should have **intermittent pneumatic compression** considered. This should be provided for 30 days or until the patient is mobile or discharged.
- **Statins**
 - ⇒ **All patients who are diagnosed with stroke or TIA should be commenced on statin therapy irrespective of the cholesterol level.**
 - ⇒ If the patient is unable to tolerate a statin (Stroke guidelines by Royal college of physicians 2016):
 - try alternative methods to improve the tolerability of a statin such as a reduced dose, alternate day dosing or a lower-intensity statin
 - Do not use fibrates, ezetimibe, bile acid sequestrants, nicotinic acid or omega-3 fatty acids for cholesterol-lowering after stroke
- **Management of hyperglycaemia**
 - ⇒ The European Stroke Initiative guidelines recommend treatment for glucose >180 mg/dL (>10 mmol/L)

- ⇒ The Joint British Diabetes Society 2012 guidelines recommend a target BM of between 6 and 12 mmol/l for hyperglycaemic patients on NG feed with insulin to be started when BM over 12 mmol/l.
- ⇒ The insulin regime of choice is a **biphasic insulin** with a mixture of intermediate and short acting insulin **twice daily**
- **Management of blood pressure in acute stroke**
 - ⇒ If thrombolytic therapy is indicated → BP should be maintained **≤185/110 mmHg**, before thrombolytic therapy (Labetalol, Nicardipine or Clevadipine are used as first line)
 - ⇒ If thrombolytic therapy is not indicated:
 - treat high BP **only if the systolic BP >220 mmHg or diastolic BP >120 mmHg**
 - cautious lowering of BP by approximately 15% during the first 24 hours.

Top Tips

Time window for :

- Thrombolysis (IV Alteplase): < 4.5 hours
- Mechanical thrombectomy: < 24 hours

Hypertension should not be treated in the initial period following a stroke unless complications develops

Stroke thrombolysis - only consider if less than 4.5 hours and haemorrhage excluded

Haemorrhagic stroke

Spontaneous Intracerebral haemorrhage (ICH)

Epidemiology

- Hemorrhagic stroke (~ 15%)
 - ⇒ The putamen is the commonest site for hypertensive intracerebral haemorrhage

Risk factors

- Hypertension (the most common risk factor), older age , haemophilia, cerebral amyloid angiopathy, anticoagulation, use of illicit sympathomimetic drugs, history of heavy alcohol, and vascular malformations.

Classification by location

- Lobar ICH
 - ⇒ commonly due to **cerebral amyloid angiopathy (CAA)**.
 - **Amyloid deposition** in small-sized to medium-sized cortical perforators may lead to the rupture of these vessels,
- Non-lobar ICH

- ⇒ commonly due to **long-standing high blood pressure** resulting in **lipohyalinosis of small perforating arteries** of the basal ganglia, thalamus, pons and cerebellum, leading to deep haemorrhages, often with extension into the ventricles.

Feature

- ICH should be suspected in any patient with severe headache, vomiting, elevated systolic blood pressures or decreased level of consciousness.
- Fever is common
 - ⇒ Sustained fever after ICH is an independent prognostic factor for worse outcome.

Pontine haemorrhage commonly presents with reduced GCS, paralysis and bilateral pin point pupils

Diagnosis

- **Non-contrast head CT** is highly sensitive and specific

Treatment

- Stabilisation of airway, breathing and circulation (**ABCs**) . **Intubation** for airway protection is indicated in patient with **GCS ≤8** or significant respiratory distress.
- **Intensive lowering of systolic blood pressure to <140 mm Hg**
 - ⇒ Intravenous calcium channel blockers (eg, **nifedipine**) and β-blockers (eg, **labetalol**) are the **treatment of choice** for early BP reduction, given their short half-life and ease of titration.
 - ⇒ **During acute phase**, patients may have **resistant HTN due to sympathetic surge**. A few weeks later, they may require fewer medications and be at risk of hypotension unless the doses of medications are adjusted promptly
- **Hyperosmolar therapy** (Mannitol or hypertonic saline)
 - ⇒ **Peri-haematoma oedema (PHE)** develops within the first few days after ICH and may cause elevated ICP, mass effect, midline shift and brain herniation
 - ⇒ **asymptomatic PHE** require **no specific treatment** except maintaining a normal sodium goal → **Observe**
 - ⇒ symptomatic cerebral oedema and elevated ICP → mannitol and hypertonic saline (HTS) are the first-line
 - Mannitol is an osmotic diuretic. It increases water excretion by the kidneys and reduces cerebral oedema and ICP.
 - HTS increases plasma osmolarity and the flow of excess water from cerebral tissue to the blood via the osmotic gradient.
 - **hypertonic saline** is slightly more effective than **mannitol** for the treatment of elevated ICP.
 - ⇒ keep serum sodium level at 140–150 mEq/L for 7–10 days to minimise oedema expansion and mass effect.

- Reversal of coagulopathies

intracerebral haemorrhage in association with	reversed with
Vitamin K antagonist (warfarin)	combination of prothrombin complex concentrates (PCC) and intravenous vitamin K. If not PCC not available → fresh frozen plasma (FFP).
Dabigatran	Idarucizumab
Factor Xa inhibitors (eg, rivaroxaban, apixaban and edoxaban) OR other Direct thrombin inhibitors apart from Dabigatran.	Prothrombin complex concentrate (PCC)
Low-molecular-weight heparin	Protamine
Thrombolytic (eg, recombinant tissue plasminogen activator (rtPA))	1 st line → cryoprecipitate administration. 2 nd line (If cryoprecipitate is contraindicated or unavailable) → tranexamic acid (anti-fibrinolytic agent)

- Neurosurgery: Patient with a decreased level of consciousness from **intraventricular haemorrhage with hydrocephalus**, mass effect or brainstem herniation should receive **ventriculostomy**.
- Venous thromboembolism (VTE) prophylaxis with **intermittent pneumatic compression (IPC)** devices

Top tips

Haemorrhage associated with dabigatran → Idarucizumab

Cerebral venous thrombosis (CVT)

Patients with a hypercoagulable state (e.g. pregnancy) and papilloedema with neurological signs should be investigated for **cerebral venous thrombosis**.

Basics

- Structure: reflections in dura mater where meningeal and periosteal layers split
- Function: return blood from cerebral veins to internal jugular vein
- veins contain **NO** valves

Epidemiology

- more common in young women. Sex: ♀ > ♂, 3:1. Age of onset: ≤ 40 years

Types

- **Superior sagittal sinus thrombosis (SSST) is the most common type of dural venous sinus thrombosis**
- **Cavernous sinus thrombosis (CST)** → 3rd, 4th and ophthalmic (V1) and maxillary (V2) divisions of the 5th cranial nerve affected

- **Superior orbital fissure syndrome:** similar to the cavernous sinus syndrome except for the presence of **proptosis**.
- **Lateral sinus thrombosis** → 6th and 7th cranial nerve palsies

Risk factors

- Local infection : e.g. Sinusitis, furuncle (*Staphylococcus aureus* is the most common)
- Diabetes mellitus
- Hypercoagulable states: pregnancy, **post-partum period**
- Malignancy
- Clotting disorders (e.g., factor V Leiden, protein C and S deficiencies, antiphospholipid syndrome)
- Polycythemia
- Medications: **Oral contraceptive pill**, Corticosteroids

Features

- **Raised intracranial pressure (ICP)**
 - ⇒ **Headache: the most common presenting symptom**
 - ⇒ Nausea & vomiting: Vomiting in the morning is characteristic of raised ICP as it follows a period of lying flat.
 - ⇒ visual disturbance.
 - ⇒ Papilloedema.
- **Peri-orbital oedema**
 - ⇒ may be the **earliest** physical finding
 - ⇒ Chemosis, oedema and cyanosis of the upper face occur due to obstruction of the ophthalmic vein.
 - ⇒ **Eye swelling begins as a unilateral process and spreads to the other eye within 24-48 hours via the intercavernous sinuses.** This is **pathognomonic for cavernous sinus thrombosis (CST)**.
- **Cranial nerve symptoms** (e.g. Ophthalmoplegia):
 - ⇒ CN VI → Lateral gaze palsy (patient cannot abduct eye) is usually seen first.
 - ⇒ CN III → Ptosis, mydriasis, and eye muscle weakness
 - ⇒ CN V → Hyperesthesia of upper face and eye pain
- **Seizures** (focal or generalized)

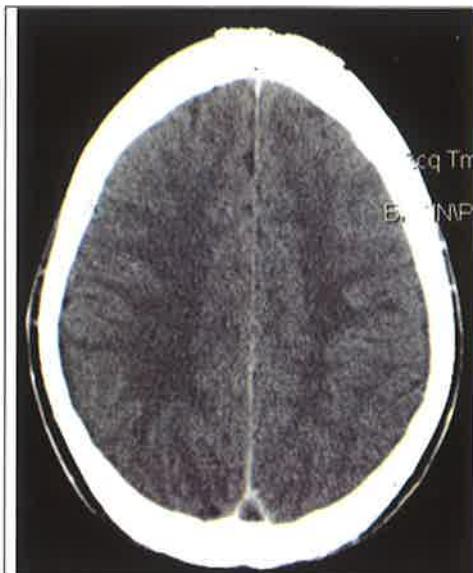
Investigations

- If CVT is suspected, D-dimer levels and imaging studies are first steps of diagnosis
- Contrast-enhanced CT scan is the test of choice to confirm the diagnosis
 - ⇒ shows a **filling defect** in a vein or sinus, the **reverse delta sign** (that is, empty triangle sign).
 - ⇒ **On contrast CT → empty delta sign (is a specific to the superior sagittal sinus)**
 - ⇒ Plain CT/MRI help detect only edema and/or infarcts, but the **thrombus itself can be visualized by means of venography**.
- Evaluation for possible causes (e.g. CBC, CRP, Thrombophilia screen, antibody studies)

Treatment

- Anticoagulants (full-dose heparin then warfarin).
- Dexamethasone can be used to reduce cerebral oedema.
- Surgical therapy (e.g. Shunt or clot removal) indications:

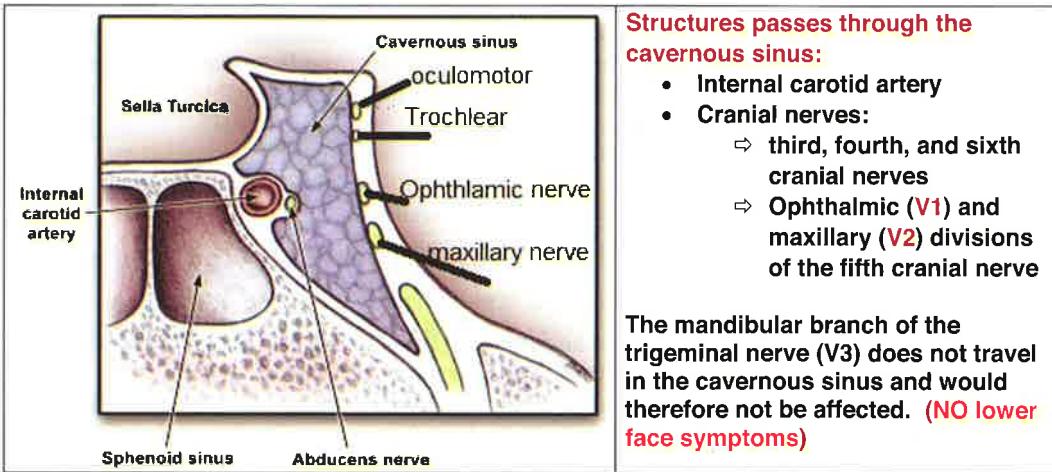
- ⇒ Progressive neurologic worsening (despite adequate anticoagulation)
- ⇒ Acute rise in intracranial pressure
- ⇒ Impending herniation



Empty delta sign indicating a superior sagittal sinus thrombosis

- CT with contrast demonstrating a superior sagittal sinus thrombosis showing the typical empty delta sign.
- Look at the 'bottom' of the scan for the triangular shaped dural sinus.
- This should normally be white due to it being filled with contrast.
- The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx.
- This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

Cavernous sinus contents



Which group of nerves run through the cavernous sinus?

→ III, IV, (V-1, V-2), and VI

MRCPUK-part-1-September 2012: Left-sided eye pain & diplopia for the past 2 days + 6th & 3rd cranial nerve palsy on the left side + hyperesthesia of the upper face on the left side. Where is the likely lesion?

→ Cavernous sinus

Cervical vascular dissection (Carotid and Vertebral artery dissection)

Stroke provoked by minimal trauma (e.g. exercise) is likely due to Cervical vascular dissection until proven otherwise

Triad of carotid dissection:

- 1. unilateral (ipsilateral) headache
- 2. **ipsilateral Horner's syndrome** and
- 3. **contralateral** hemisphere signs (aphasia, neglect, visual disturbance,

Overview

- **Important causes of stroke in young patients**
- The two commonest causes of young onset stroke (less than 40 years) are
 - 1. Cardio-embolism and
 - 2. Cervical artery dissection.
- Dissection of the internal carotid artery can occur intracranially or extracranially
 - ⇒ Extracranially is more common. 75% of carotid dissections affect the internal carotid artery (that is, extracranially)

Mechanism of ischaemia

- Emboli from the site of the dissection (85-95%) of cases → ischaemic symptoms
- vessel narrowing (5-15%): subintimal tears → intramural haematomas → protrude inward and narrow the vessel lumen.

Causes

- Mechanical forces (eg, trauma, blunt injury, and stretching)
- Arteriopathies (eg, Ehlers-Danlos syndrome, Marfan syndrome and other connective tissue disorders)

Features

- **Pain** (Headache, neck or facial pain): is the initial common symptom, ipsilateral to the dissected artery.
- **Ischaemic neurological features** (transient or completed strokes): **Sudden-onset**
- **Partial Horner** syndrome (Ptosis with miosis)
 - ⇒ usually **painful** when caused by internal carotid artery dissections
 - ⇒ The term partial Horner syndrome is used for the oculosympathetic palsy because **anhidrosis is absent**. Because the **sympathetic fibers innervating the facial sweat glands** are anatomically **located on the external** rather than the internal carotid artery

Diagnosis

- Plain CT head **first** to exclude haemorrhagic stroke
- **Computed tomography angiography (CTA) head and neck**
 - ⇒ the diagnostic modality of choice.

Carotid dissection

- Younger age group <50 years.
- Neck pain.
- Associated with vigorous exercise or event that sustains severe neck movement (e.g., roller coaster ride, motor vehicle accident).
- May have Horner's syndrome or history of genetic collagen abnormality.

Vertebral artery dissection:

The typical presentation of vertebral artery dissection is a **young person** (average age 40 years) with severe **occipital headache** and **neck pain** following a **recent head or neck injury**. The trauma is often trivial but is usually associated with some form of cervical distortion.

Vertebral artery dissection presents with:

- Brainstem Stroke or transient ischaemic attack
- Pain in the ipsilateral neck, face or head.
- Commonly occurring in young people following a recent head or neck injury.

Carotid artery stenosis**Carotid endarterectomy for stroke or TIA in the carotid territory only indicated if:**

1. ≥50% ipsilateral carotid stenosis
2. The patient not severely disabled

- Carotid artery stenosis causes 10% to 15% of all ischaemic strokes.
- the annual risk of stroke in patients with asymptomatic carotid disease is between 1% and 2%

Pathophysiology

- Atherosclerotic plaque in the cervical carotid artery is the most common cause.
- Plaque disruption and athero-embolisation into the intracranial circulation is the most common mechanism for stroke.
- The most common site of carotid Atherosclerosis:
 - ⇒ usually at the fork where the common carotid artery divides into the internal and external carotid artery.

Features

- The majority are asymptomatic.
- TIA or stroke
 - ⇒ Plaques rupture → embolism to intracranial arteries → (TIA or stroke) or embolism to retinal arteries → (amaurosis fugax or retinal strokes).
- Cervical bruit

Diagnosis

- **Duplex ultrasonography** is the preferred **initial** mode of diagnosis and screening.
 - ⇒ sensitivity of 99%, specificity of 86%
 - ⇒ If the stenosis is less than 50% → no further imaging is needed.

- ⇒ If the stenosis > 50% → **CTA or MRA** for more detailed plaque characterization.
- CT or Magnetic resonance **angiography (CTA or MRA)** helps to define the anatomy **if intervention is indicated.**

Management

- Initial management → Antiplatelet therapy, Statin and risk factor modification.
- **Carotid revascularization → Endarterectomy**
 - ⇒ Indications:
 - Significant stenosis:
 - ❖ Carotid stenosis **> 70%** according ECST criteria (European Carotid Surgery Trial' Collaborative Group) or **> 50% according to NASCET** (North American Symptomatic Carotid Endarterectomy Trial) **criteria.**
 - **TIA or resolving stroke** (The patient not severely disabled):
 - ❖ **The benefit of endarterectomy is prevention of future stroke, with dense strokes, if there is no recovery, the benefits are greatly reduced due to end-organ damage.**
 - ❖ **Asymptomatic carotid stenosis ≥ 70% : 1st line → antiplatelet therapy and cardiovascular risk reduction. the best course of action? → Discharge and outpatient follow up**
 - ⇒ Contraindications:
 - 100% carotid stenosis
 - ❖ usually requires a **bypass** procedure, as risk of endarterectomy outweighs benefit.
 - previous stroke with persistent neurological symptoms
 - ⇒ Timing of surgery:
 - should be performed within two weeks. ("urgent" endarterectomy within 2 weeks)
 - ⇒ Benefit:
 - **It reduces the risk of disabling stroke or death by 48%** in a person with severe symptomatic carotid stenosis (>70%) who has had a TIA.
- **Carotid stenting**
 - ⇒ used as an alternative to endarterectomy: Indications
 - **Restenosis.**
 - **Previous radiotherapy to the neck** may make endarterectomy difficult, and stenting may be preferred.

MRCPI-part-2-april-2018: left-sided hemiparesis of more than 8 hours' duration. carotid ultrasound scan, shows 80% stenosis of the left carotid artery, **50% stenosis of the right carotid artery.** What is the most appropriate treatment for long-term stroke prevention?

- ⇒ **Clopidogrel**
 - endarterectomy is not recommended in:
 - ☞ significant stenosis but asymptomatic side (left carotid in this case)
 - ☞ symptomatic side but there is less than 70% (right carotid in his case).

Carotid artery atherosclerosis is an important cause of ipsilateral amaurosis fugax.

Localisation of speech problems

Only 1 out of 3 features of speech are affected:

- poor comprehension with normal fluency and repetition → Transcortical sensory aphasia
- poor fluency with normal comprehension and repetition → Transcortical motor aphasia
- poor repetition with normal fluency and comprehension → Conduction aphasia

2 out of 3 features of speech are affected:

- Poor comprehension and fluency with normal repletion → Transcortical mixed aphasia
- Poor comprehension and repetition with normal fluency → Wernicke (receptive) aphasia
- Poor fluency and repetition with normal comprehension → Broca's (expressive) aphasia.

All 3 features of speech are affected:

- Poor fluency, comprehension and repetition → global aphasia

Overview

- The speech area is in the left, dominant side of the brain in about 99% of right-handed people
- Thus, impairment of the speech area with a stroke, causing left-sided weakness, is rare. It will occur in virtually no right-handers and in only 30% of left-handers.
- As a general rule, a lesion of the left hemisphere will cause dysphasia whilst, in the right hemisphere, it will cause neglect, visuo-spatial and cognitive problems
- Wernicke's aphasia and pure aphasia (that is, without alexia) are middle cerebral artery.
- **Comprehension, fluency and repetition are the three main variables that allow for localisation of speech problems**
- The three, general, areas are:
 1. **Wernicke's area (posterior, superior temporal lobe)** - lesions produce normal fluency, impaired comprehension, impaired repetition
 - receptive aphasia
 - They are unaware of their language difficulties
 2. conduction (arcuate fasciculus) - lesions produce normal fluency, normal comprehension, diminished repetition
 3. **Broca's area (inferior frontal lobe)**
 - lesions produce impaired fluency, intact comprehension, impaired repetition.
 - **Unlike Wernicke's aphasia, Broca's patients are aware of their language difficulties.**

Aphasia Syndromes

Aphasia	Lesion	Fluency	Comprehension	Repetition
Broca's (expressive)	Broca's area (inferior frontal lobe) superior division of the left middle cerebral artery (MCA) lesion	No	Yes	No
Wernicke (receptive)	(superior temporal lobe) inferior division of the left MCA lesion	Yes	No	No
Conduction	arcuate fasciculus peri-Sylvian area	Yes	Yes	No
Transcortical motor	anterior cerebral artery (ACA)-MCA watershed infarct	No	Yes	Yes
Transcortical sensory	posterior cerebral artery (PCA)-MCA watershed infarct	Yes	No	Yes
Transcortical mixed	Can be secondary to both an ACA-MCA and PCA-MCA infarct	No	No	Yes
Global	proximal MCA occlusion affecting both superior and inferior division of the MCA	No	No	No

- **Mixed aphasia** (or transcortical mixed aphasia)
 - ⇒ **patients can often repeat words but not understand commands.**
 - ⇒ **Not specific for stroke , commonly caused by** Alzheimer's disease, bilateral cerebral damage, tumours, and thalamic lesions.
- **Transcortical sensory aphasia**
 - ⇒ The main problem lies within the brain in a region known as the **temporal-occipital-parietal junction**, located behind Wernicke's area.
 - ⇒ The patient has **intact repetition but is unable to follow verbal commands**. He has fluent grammatical speech.
- **Anomic aphasia or nominal aphasia results in word finding difficulties.**
- **Aphemia** is a type of aphasia in which there is **severe dysarthria and impairment of verbal output**. There is intact comprehension.

MRCPUK-part-1-January 2008 exam: H/O difficulty in finding the right words whilst speaking. With normal comprehension. Where is the likely lesion?

- ⇒ **Posterior frontal lobe** (expressive aphasia due to a lesion in Broca's area, located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus)

Pupil conditions

Pupillary control

- Oculomotor nerve carries **parasympathetic** efferent to the **sphincter pupillae** muscle.
- Optic nerve carries **sympathetic** postganglionic fibres to the **dilator pupillae** muscle.

Pupillary control

- **Parasympathetic fibers lead to pupillary constriction (miosis)**
 - ⇒ light enters the eye → retinal ganglion → optic nerve → optic chiasm → optic tract → **preoptic nucleus** → **Edinger-Westphal nucleus** → ciliary ganglion → pupillary constrictor muscles → causing uniform bilateral miosis
- **Sympathetic fibers lead to pupillary dilation (mydriasis)**
 - ⇒ hypothalamic nuclei → T1 and T2 spinal cord levels → paravertebral sympathetic chain (via the white ramus) → superior cervical ganglion → pupillary dilator muscle
- **Causes of small pupils include:**
 - ⇒ Horner's syndrome
 - ⇒ Old age
 - ⇒ **Pontine haemorrhage**
 - ⇒ Argyll Robertson pupil
 - ⇒ Drugs, and
 - ⇒ Poisons (opiates, organophosphates).
- **Causes of dilated pupils include:**
 - ⇒ Holmes-Adie (myotonic) pupil
 - ⇒ Third nerve palsy
 - ⇒ Drugs, and
 - ⇒ Poisons (atropine, CO, **ethylene glycol**).

Pupil	Lesion
Slightly smaller but reactive	Early stage of thalamic damage
Fixed dilatated (7 mm) non-reactive	Oculomotor nerve lesion
Fixed midsized pupil (5 mm)	Midbrain lesion
Pinpoint pupil (1 – 1.5 mm)	Pontine lesion/ opioid overdose
Asymmetrical pupils	Normal in 20% of population but reactive. If one pupil is sluggish to react than the other think of midbrain or oculomotor

• Equality of pupils diameter

- ⇒ **Afferent** pupillary defect (e.g. optic neuritis) → pupils are **isocoric** (equal diameter)
- ⇒ **Efferent** (impulse transmission to the iris sphincter muscle) pupillary defect (i.e. impairment of the pupillary reflex) → pupils are **anisocoric** (unequal diameter)

Hippus

- Hippus is papillary athetosis.(athetosis → abnormal muscle contraction causes involuntary writhing movements).
- **It is a spasmodic rhythmical dilation and contraction of the pupil.**
- It is typically a benign finding.

Tonic pupil (Holmes-Adie pupil)

Holmes-Adie → dilated pupil

Definition

- Tonic pupil or Holmes-Adie pupil is a **dilated pupil** caused by parasympathetic damage.

Pathophysiology

- parasympathetic denervation at the level of the ciliary ganglion and postganglionic nerves.

Causes

- Idiopathic (Most cases)
- Local causes: infections , trauma
- Systemic autonomic neuropathies
 - ⇒ **Ross syndrome** is characterized by a triad of tonic pupil, hyporeflexia, and segmental anhidrosis
 - ⇒ Horner syndrome

Features

- Anisocoria (unequal pupil diameter)
 - ⇒ Although the tonic pupil is usually larger than the uninvolved fellow eye, over time the pupil tends to become smaller (the "little old Adie" pupil).
- Hypersensitivity to dilute pilocarpine drops.

Diagnosis

- Clinically : poor pupillary reaction to light + normal test for a pupillary near response (light-near dissociation).
- **The usual diagnostic test is to use weak pilocarpine eye drops**, which induce vigorous pupil contraction on the affected side, but only weak contraction of the pupil on the unaffected side.
- Patients with unexplained bilateral tonic pupils should have serologic testing for syphilis

Treatment

- benign condition → **observe**

Ross's syndrome: The triad of

1. abnormal pupil size,
2. loss of deep tendon reflexes, and
3. excessive sweating.

Although some doctors will still diagnose the condition as a **variant of Holmes-Adie pupil**.

Argyll Robertson Pupil (ARP)

Argyll-Robertson

Bilateral small irregular pupils that do not react to light but react to accommodation.

Referred to as the "Whore's Eye" because of the association with tertiary syphilis and because of the convenient mnemonic that, like a prostitute, they "accommodate but do not react"

Causes : **neurosypilis**, Multiple Sclerosis, Sarcoidosis, DM



Argyll Robertson Pupil (ARP)

- **Bilateral small pupils**
- Prostitute's pupils → reduce in size on a near object (they "accommodate"), but **do not constrict when exposed to bright light** (they **do not "react"** to light).
- They are a highly specific sign of neurosyphilis and might also be a sign of diabetic neuropathy.

Pupillary Defect	Comments
Argyll Robertson pupil	<ul style="list-style-type: none"> • Pupils accommodate but do not react to direct or indirect light A type of light-near dissociation where <ul style="list-style-type: none"> ⇒ Bilateral miosis ⇒ the eye does not constrict in response to light as much as it does with accommodation ⇒ pupil has an absent light reflex • Associated with neurosyphilis
Adie's myotonic pupil	<ul style="list-style-type: none"> • A type of light-near dissociation where <ul style="list-style-type: none"> ⇒ the eye does not constrict in response to light as much as it does with accommodation ⇒ light reflex is merely <u>reduced</u> ⇒ Affected eye is dilated usually • Secondary to <ul style="list-style-type: none"> ⇒ degeneration of the ciliary ganglion

Visual field defects

Visual field defects:

- **left homonymous hemianopia** means visual field defect to the left, i.e. lesion of right optic tract
- **homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)**
- incongruous defects = optic tract lesion; congruous defects= optic radiation lesion or occipital cortex

Bitemporal hemianopia:

- lesion of optic chiasm
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

The main points for the exam are:

- left homonymous hemianopia means visual field defect to the left, i.e. Lesion of right optic tract
- homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)
- incongruous defects = optic tract lesion; congruous defects = optic radiation lesion or occipital cortex
- A congruous defect simply means complete or symmetrical visual field loss and conversely an incongruous defect is incomplete or asymmetric. Please see the link for an excellent diagram.

Homonymous hemianopia

- incongruous defects: lesion of optic tract
- congruous defects: lesion of optic radiation or occipital cortex
- macula sparing: lesion of occipital cortex

Homonymous quadrantanopias

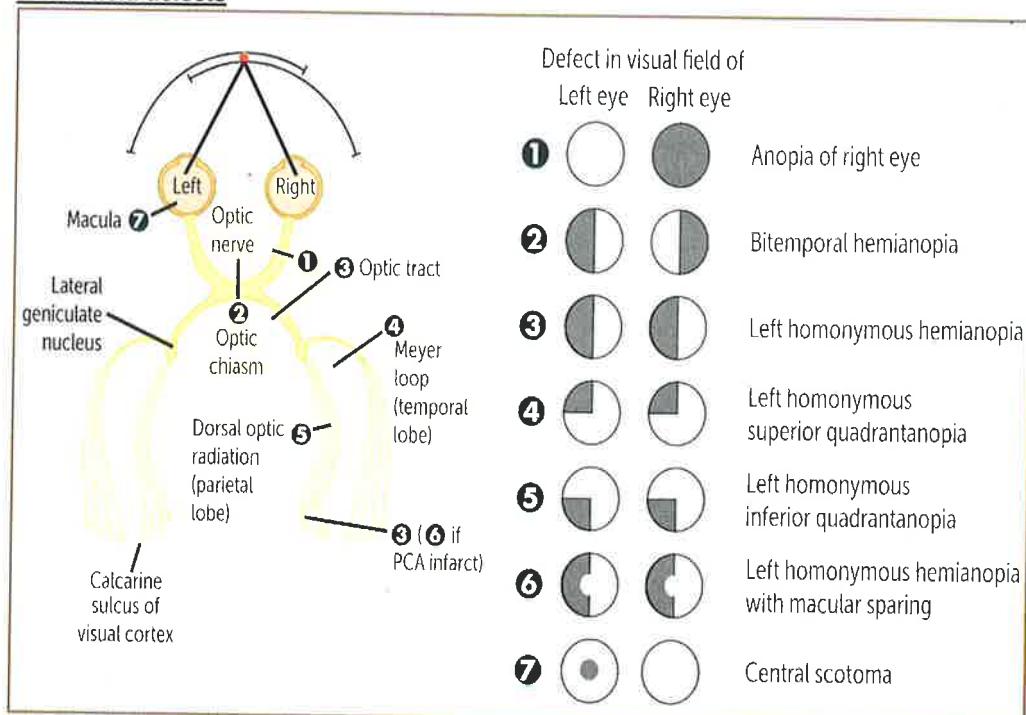
- superior: lesion of temporal lobe
- inferior: lesion of parietal lobe
- **mnemonic = PITS (Parietal-Inferior, Temporal-Superior)**

Bitemporal hemianopia

- **lesion of optic chiasm**
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

Cortical blindness

- Patients with cortical blindness frequently have visual hallucinations and occasionally deny that they are blind.
- Pupillary reactions and fundoscopy are normal.

Visual field defects

Bilateral internal carotid artery displacement can cause **binasal incongruous hemianopia** if the optic nerves are compressed.

MRCP-part-1-September 2012 exam: What sort of visual field defect is expected following an operation to remove a meningioma in left temporal lobe?

→ **Right superior homonymous quadrantanopia**

Mrcpuk-part-1-January 2009 exam: In a left congruous homonymous hemianopia. Where is the lesion most likely to be?

→ **Right occipital cortex**

Cranial nerves

The major characteristics of the 12 cranial nerves

Nerve	Functions	Clinical	Pathway/foramen
I (Olfactory)	Smell		Cribriform plate
II (Optic)	Vision		Optic canal
III (Oculomotor)	Eye movement (MR, IO, SR, IR) Pupil constriction Accommodation Eyelid opening	Palsy results in <ul style="list-style-type: none"> • ptosis • 'down and out' eye • dilated, fixed pupil 	Superior orbital fissure (SOF)
IV (Trochlear)	Supplies superior oblique (SO) → (depresses eye, moves inward)	Palsy results in defective downward gaze → vertical diplopia	SOF
V (Trigeminal)	Facial sensation Mastication	Lesions may cause: <ul style="list-style-type: none"> • trigeminal neuralgia • loss of corneal reflex (afferent) • loss of facial sensation • paralysis of mastication muscles • deviation of jaw to weak side 	V ₁ : SOF, V ₂ : Foramen rotundum, V ₃ : Foramen ovale
VI (Abducens)	Eye movement (LR)	Palsy results in defective abduction → horizontal diplopia	SOF
VII (Facial)	Facial movement Taste (anterior 2/3rds of tongue) Lacration Salivation	Lesions may result in: <ul style="list-style-type: none"> • flaccid paralysis of upper + lower face • loss of corneal reflex (efferent) • loss of taste • hyperacusis 	Internal auditory meatus
VIII (Vestibulocochlear)	Hearing, balance	Hearing loss Vertigo, nystagmus Acoustic neuromas are Schwann cell tumours of the cochlear nerve	Internal auditory meatus
IX (Glossopharyngeal)	Taste (posterior 1/3rd of tongue) Salivation supplies the parotid salivary gland controlling salivary secretions. Swallowing Mediates input from carotid body & sinus	Lesions may result in; <ul style="list-style-type: none"> • hypersensitive carotid sinus reflex • loss of gag reflex (afferent) 	Jugular foramen

Nerve	Functions	Clinical	Pathway/foramen
X (Vagus)	Phonation Swallowing Innervates viscera supplies the palatal muscles	Lesions may result in; <ul style="list-style-type: none"> uvula deviates away from site of lesion loss of gag reflex (efferent) 	Jugular foramen
XI (Accessory)	Head and shoulder movement	Lesions may result in; <ul style="list-style-type: none"> weakness turning head to contralateral side 	Jugular foramen
XII (Hypoglossal)	Tongue movement	Tongue deviates towards side of lesion	Hypoglossal canal

The fourth cranial nerve palsy → superior oblique palsy → vertical diplopia (eg: missing steps when walking down the stairs, bumping head when trying to get out of a car)

Cranial nerve locations

- 4 CN are above pons (I,II,III,IV).
- 4 CN exit the pons (V,VI,VII,VIII).
- 4 CN are in medulla (IX,X,XI,XII).

Cranial nerve reflexes

Reflex	Afferent limb	Efferent limb
Corneal	Ophthalmic nerve (V ₁)	Facial nerve (VII)
Jaw jerk	Mandibular nerve (V ₃)	Mandibular nerve (V ₃)
Gag	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Carotid sinus	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Pupillary light	Optic nerve (II)	Oculomotor nerve (III)
Lacration	Ophthalmic nerve (V ₁)	Facial nerve (VII)

Brain stem (Mid brain, Pons, Medulla Oblongata) lesions are typically characterized by ipsilateral cranial nerve involvement and contralateral body involvement.

Petros apex lesion

- Features
 - ⇒ **Abducens nerve palsy** → horizontal diplopia
 - ⇒ **Trigeminal nerve involvement at the Meckel cave** → ipsilateral facial pain or sensory disturbance (**numbness**)
- Causes → Meningioma or nasopharyngeal carcinoma of the petrous apex is the most common cause now

Lesions of the **cerebellopontine angle** causes compression of cranial nerves **V** (trigeminal), **VII** (facial) and **VIII** (vestibulocochlear).

Optic nerve palsy

Anatomy

- The optic nerve is part of the central nervous system; hence its myelin sheaths are derived from oligodendrocytes, not Schwann cells.
- Accordingly, diseases of the peripheral nervous system and radiculopathies don't target the optic nerve.
- The physiological blind spot results from absence of photoreceptors in the area of the retina where the optic nerve leaves the eye.

Causes

- Ischemic optic neuropathy
- multiple sclerosis
- optic nerve glioma
- ethambutol

Features

- Complete transection → ipsilateral blindness and loss of direct pupillary light reflex
- Compression (e.g., tumor) → optic atrophy
- Pituitary adenoma → compression to the optic chiasm → bitemporal hemianopia

Oculomotor (third nerve) palsy

Ipsilateral 3rd CN palsy + contralateral hemiplegia → Weber's syndrome

Ipsilateral 3rd CN palsy + contralateral hemiataxia → Benedikt syndrome

Ipsilateral 3rd CN palsy + ipsilateral hemiparesis + Contralateral homonymous hemianopsia → Uncal herniation

Compression of the oculomotor nerve can cause isolated pupillary dilation due to injury of the parasympathetic fibers.

Microangiopathy (e.g., due to diabetes mellitus) typically affects the deeper somatic fibers first, causing ophthalmoplegia without pupillary dilation

Features

- Divergent squint - affected eye deviated 'down and out'.
 - Downward displacement result from unopposed action of the superior oblique (innervated by the fourth cranial or trochlear nerve). due to paralysis of superior rectus, inferior rectus and inferior oblique.
 - outward displacement results from unopposed action of the lateral rectus (innervated by the sixth cranial nerve). due to paralysis of the medial rectus muscle.
- Ptosis
- Dilated pupil (mydriasis), sometimes called a 'surgical' third nerve palsy.
 - the parasympathetic fibers run on the outside of the nerve. Therefore, 3rd nerve compression → mydriasis appear before ptosis and "down and out" position are seen.
 - pupillary abnormalities are more commonly associated with trauma than with ischemia.

- ⇒ A patient with a third nerve palsy with pupillary involvement should be considered to have a posterior communicating artery aneurysm until proven otherwise → **requires urgent neurosurgical evaluation**.
- **Unreactive pupil to light:** Lesions of the autonomic (parasympathetic) portion → absence of the pupillary reaction

Causes

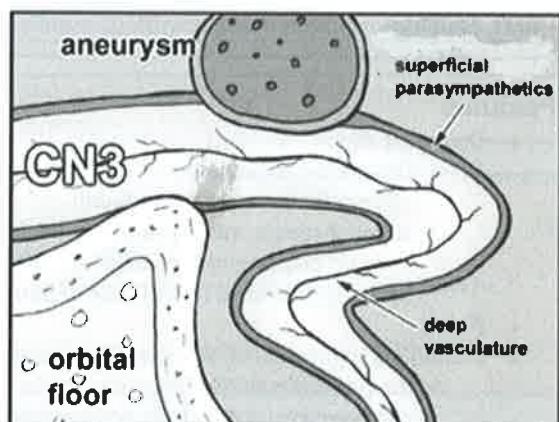
- Vascular causes (usually does not affect the pupil): Diabetic neuropathy, vasculitis, Weber's syndrome
- Compressive lesions: Posterior communicating artery aneurysm (painful, pupil dilated) → Urgent CT angiogram of the cerebral vessels is required for diagnosis.
- Cavernous sinus thrombosis
- Others causes: amyloid, multiple sclerosis

Parasympathetic fibers are located more superficially than motor fibers, causing the following features:

- Prominent motor dysfunction and sparing of the pupil in ischemic lesions due to **vascular disease** (e.g., vasculitis, diabetes): parasympathetic fibers are less affected by decreased diffusion of nutrients from the vasa nervorum
- Severely impaired pupillary reaction with relatively spared motor function in **compressive lesions** (e.g., uncal herniation, aneurysm of the posterior communicating artery): parasympathetic fibers are affected by compression first

Raised ICP can cause a third nerve palsy due to herniation

Painful third nerve palsy = posterior communicating artery aneurysm



Trigeminal neuralgia

Trigeminal neuralgia - carbamazepine is first-line

Overview

- Sensation over the face is supplied by the trigeminal nerve
- Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain.
- Most often affecting women ♀ > ♂ (2:1)
- Peak age incidence: 60–70 years

Classification

- Idiopathic trigeminal neuralgia**
 - ⇒ Most common type
 - ⇒ no identifiable cause (unremarkable findings on MRI and electrophysiological tests)
- Secondary trigeminal neuralgia**
 - ⇒ Caused by a major underlying neurological disease, most frequently multiple sclerosis, a tumor at the cerebellopontine angle, or arteriovenous malformation.
 - ⇒ **Red flag features suggesting a serious underlying cause**
 - Sensory changes
 - Deafness or other ear problems
 - History of skin or oral lesions that could spread perineurally
 - Pain only in the ophthalmic division of the trigeminal nerve (eye socket, forehead, and nose), or bilaterally
 - Optic neuritis
 - A family history of multiple sclerosis
 - Age of onset before 40 years
 - ⇒ Should be referred to neurology
 - ⇒ **MRI of the brain is the next management step**

Features

- The International Headache Society defines trigeminal neuralgia as: Unilateral disorder characterised by brief **electric shock-like pains**, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
 - ⇒ Lasts several seconds (in rare cases, several minutes) and may occur up to 100 times per day
 - ⇒ Typically shoots from mouth to the angle of the jaw on the affected side
 - ⇒ Usually **triggered** by movements such as chewing, talking, or touch (e.g., brushing teeth, washing face); becomes worse with stimulation

Management

- Carbamazepine is first-line
- Failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

MRCPUK-part-1-January 2015 exam: History of electric shock like pains on the right side of the face. around 10-20 episodes a day which, each lasting for around 30-60 seconds. What is the most suitable first-line management?

→ Carbamazepine

What is the nerve supply to the angle of the jaw?

- ⇒ **The angle of the jaw is supplied by nerve roots C2/C3 and not the trigeminal nerve.**
- ⇒ In patients with non-organic sensory loss, that loss usually extends to the edge of the jaw.

Abducens (VIth) nerve palsy

Anatomy

- **Location:** The abducens nucleus located in the caudal pons
- **Course:** The nerve leaves the brainstem at the junction of the pons and medulla and runs upward into the subarachnoid space, travelling through the cavernous sinus alongside the internal carotid artery. It enters the orbit through the superior orbital fissure, like the other ocular cranial nerves, and innervates the lateral rectus, which serves to abduct the eye.
- **Function:** The VIth nerve is motor to the lateral rectus muscle. **It is responsible for abduction of the ipsilateral eye.**

Features

- Horizontal diplopia that worsens when looking at distant objects
- Inability to abduct the eye
- In the neutral position the affected eye is deviated medially due to unopposed action of the medial rectus.
- **In patients with diplopia the 'cover test' can be used to determine the eye that has the problem.**
 - ⇒ On covering the affected eye, the outermost image disappears.
 - ⇒ Eg : diplopia on right horizontal gaze , improved on covering the right eye → the right abducens is affected

Causes

- Most common ocular cranial nerve palsy
- Trauma
- Pseudotumor cerebri
- Cavernous sinus thrombosis
- Due to the long course and anatomy of the VIth nerve it can be damaged in any condition causing raised intracranial pressure. It can therefore be a 'false localising sign'.

Which nerve passes alongside the internal carotid artery within the cavernous sinus?

- **Cranial nerve VI, the abducens nerve.**



Abducens nerve palsy

- The patient is unable to abduct the right eye.
- Abducens nerve innervates the ipsilateral lateral rectus muscle that is necessary for lateral movement of the eye.

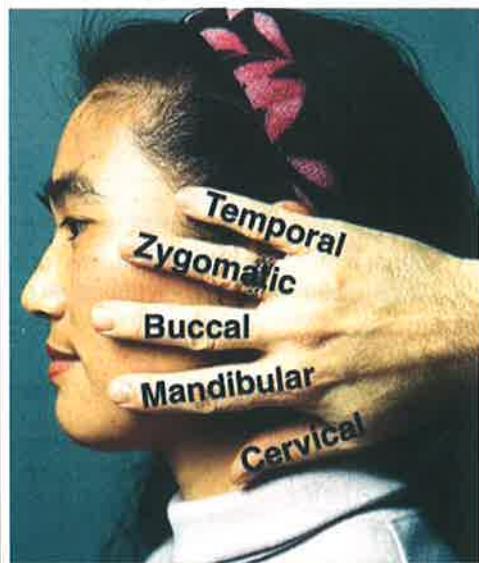
Facial (VII) nerve

Facial nerve branches (mnemonic)

(superior to inferior) as they exit the anterior border of the parotid gland: **To Zanzibar By Motor Car**

- T:** temporal
- Z:** zygomatic
- B:** buccal
- M:** mandibular
- C:** cervical

Branches of the Facial Nerve



Facial Palsy + convergent squint



lesion in Pons
as VI th is encircled by VII th

Facial nerve paralysis is often accompanied by:

- loss of taste,
- hyperacusis, and
- decreased salivation.

Supply - 'face, ear, taste, tear'

- face: muscles of facial expression
- ear: nerve to stapedius (**Hyperacusis is due to paralysis of stapedius**)
- taste: supplies anterior two-thirds of tongue
- tear: parasympathetic fibres to lacrimal glands, also salivary glands
- **Orbicularis oculi** is affected causing inability to blink/close eyelids.

Causes of bilateral facial nerve palsy

1. Sarcoidosis
2. Guillain-Barre syndrome
3. polio,
4. Lyme disease

Causes of unilateral facial nerve palsy - as above plus

Lower motor neuron	Upper motor neuron
<ul style="list-style-type: none"> • Bell's palsy • Ramsay-Hunt syndrome (due to herpes zoster) • Acoustic neuroma • Parotid tumours • HIV • Multiple sclerosis* ⇒ may also cause an UMN palsy • Diabetes mellitus 	<ul style="list-style-type: none"> • Stroke

LMN vs. UMN

- upper motor neuron lesion 'spares' upper face i.e. forehead
- lower motor neuron lesion affects all facial muscles

Lesions

- The majority of facial nerve palsy cases result from infranuclear lesions.
- The most common cause of facial nerve paralysis is Bell's palsy.

Bell's palsy**Definition**

- acute, unilateral, idiopathic, facial nerve paralysis.

Causes

- unknown
- although the role of the herpes simplex virus has been investigated previously.

Epidemiology

- The peak incidence is 20-40 years
- more common in pregnant women.

Features

- lower motor neuron facial nerve palsy - forehead affected
- other features
⇒ post-auricular pain (may precede paralysis),

- ⇒ altered taste,
- ⇒ dry eyes,
- ⇒ hyperacusis (seen in around a third of patients)

Management

- prednisolone 1mg/kg for 10 days should be prescribed for patients within 72 hours of onset of Bell's palsy.
- Adding in aciclovir gives no additional benefit
- eye care is important - prescription of artificial tears and eye lubricants should be considered

Prognosis

- if untreated around 15% of patients have permanent moderate to severe weakness

MRCPUK-part-1-January 2012 exam: Which features would be most consistent with a diagnosis of Bell's palsy?

→ Hyperacusis

MRCPUK-part-1-May 2010 exam: What is the current evidenced base approach to the management of Bell's palsy?

→ Prednisolone

Ramsay Hunt syndrome

vesicular rash around the ear (or anterior 2/3rds of the tongue and the soft palate): suggest a diagnosis of Ramsey Hunt syndrome.

Aetiology

- Ramsay Hunt syndrome (herpes zoster oticus) is caused by the **reactivation** of the varicella zoster virus in the **geniculate ganglion** of the seventh cranial nerve.

Features

- auricular pain is often the **first feature**
- facial nerve palsy
- **vesicular rash around the ear**
- tinnitus
- vertigo

Management

- oral aciclovir and corticosteroids

Acoustic neuroma

Loss of corneal reflex → think acoustic neuroma

Overview

- Acoustic neuromas (more correctly called vestibular schwannomas) are benign tumors of the vestibular nerve (8th nerve).
- account for 5% of intracranial tumours and 90 % of cerebellopontine angle
- Bilateral acoustic neuromas are seen in **neurofibromatosis type 2**

Features

- can be predicted by the affected cranial nerves
 - ⇒ cranial nerve V: absent corneal reflex
 - ⇒ cranial nerve VII: facial palsy
 - ⇒ cranial nerve VIII: **hearing loss**, vertigo, **tinnitus**, gait disturbances and imbalance.

Investigation

- **MRI of the cerebellopontine angle is the investigation of choice → mass**

Treatment

- surgical removal remains the treatment of choice

Abnormal gait

Lesions of cerebellar vermis cause → truncal ataxia and tendency to fall backwards.

Phenytoin toxicity → broad-based ataxic gait

Abnormal gait	Diagnosis
Shuffling gait	Parkinson's disease
Spastic hemi-paretic gait (circumducted)	Stroke
Waddling gait (with excessive hip swing)	proximal myopathy
Steppage gait (High stepping, Neuropathic gait)	If bilateral: <ul style="list-style-type: none"> • Charcot–Marie–Tooth disease • Polio • Multiple sclerosis • Syphilis • Guillain–Barré syndrome If unilateral: <ul style="list-style-type: none"> • Foot drop: peroneal nerve palsy and L5 radiculopathy.
Choreiform Gait (Hyperkinetic Gait)	Sydenham's chorea, Huntington's Disease
Ataxic Gait	Cerebellar disease, Phenytoin toxicity
Sensory Gait (Sensory ataxia) <ul style="list-style-type: none"> • occurs when there is loss of this proprioceptive input • the patient will slam the foot hard onto the ground in order to sense it. 	large fiber peripheral neuropathies <ul style="list-style-type: none"> • diabetic neuropathy disorders of the dorsal columns: <ul style="list-style-type: none"> • B12 deficiency, • tabes dorsalis

Sensory ataxia is distinguished from cerebellar ataxia by positive Romberg's sign (normal coordination when the movement is visually observed by the patient, and worsened when the eyes are closed)

Nystagmus

Upbeat nystagmus → cerebellar vermis lesions

Downbeat nystagmus → foramen magnum lesions (Arnold-Chiari malformation)

Definition

- involuntary oscillations of the eyes.

Relation to directions of the gaze

- constant direction regardless of the direction of gaze, suggests → a labyrinthine or cerebellar lesion.
- changes with the direction of gaze suggests widespread central involvement of vestibular nuclei.
- presents only on lateral gaze → lesion of the brain stem or cerebellum.
- Nystagmus restricted to the abducting eye on lateral gaze (ataxic nystagmus) is due to a lesion of the medial longitudinal bundle between the pons and mid-brain as in multiple sclerosis (MS).

Causes

- Visual disturbances
- Lesions of the labyrinth
- Central vestibular connections, Brain stem or cerebellar lesions
- Wernicke's encephalopathy
- Nystagmus confined to one eye suggests:
 - ⇒ a peripheral lesion of the nerve or muscle,
 - ⇒ or a lesion of the medial longitudinal bundle.

Vertical VS horizontal nystagmus

- Vertical nystagmus:
 - ⇒ Upbeat nystagmus (occurring on upward gaze: due to a lesion in the mid-brain
 - ⇒ Downbeat nystagmus (fast phase downwards) suggests a lesion in the lower part of the medulla. It is therefore typical of the Arnold-Chiari malformation (Chiari type I malformation).
- Horizontal nystagmus:
 - ⇒ occurs in unilateral disease of the cerebral hemisphere, with the fast phase directed to the side of the lesion.

MRCPUK-part-1-May 2007 exam: Which disorder is most associated with downbeat nystagmus?

→ Arnold-Chiari malformation

Spinocerebellar ataxia (SCA)

Spinocerebellar ataxia (SCA):

- autosomal dominant
- should be suspected in patients with progressive loss of coordination, unsteady gait and overall weakness.

Hemiballism

Hemiballism is caused by damage to the subthalamic nucleus

The presence of severe **flinging movements** affecting proximal muscles and following no particular pattern is typical for hemiballism.

Overview

- damage to the subthalamic nucleus of the basal ganglia → Hemiballism → decreased suppression of involuntary movements.
- Ballistic movements are involuntary, sudden, jerking movements which occur contralateral to the side of the lesion.
- The ballistic movements primarily affect the proximal limb musculature whilst the distal muscles may display more choreiform-like movements
- It is always unilateral, but it is common for arms and legs to move together.
- Bilateral ballismus is rare and implicates a metabolic cause, usually non-ketotic hyperosmolar coma.
- **Symptoms may decrease whilst the patient is asleep.**
- The movements worsens with activity and decrease with relaxation.

Causes

- vascular events (stroke). **infarction being the commonest cause.**
- traumatic brain activity
- amyotrophic lateral sclerosis
- hyperglycaemia
- malignancy
- vascular malformations
- tuberculomas, and
- demyelinating plaques.

Treatment

- tetrabenazine is the treatment of choice.
- Anti-dopaminergic agents (e.g. Haloperidol) are the mainstay of treatment.
- Topiramate can be used, as can intrathecal baclofen, botulinum toxin and **tetrabenazine**.
- Functional neurosurgery can be used for cases which have failed to respond to other treatment.

Prognosis

- Usually the flinging movements stop spontaneously in the next 4-8 weeks

MRCPUK-part-1-September 2012 exam: H/O involuntary, jerking movements of arms, resolved during asleep. Damage to which structure may lead to hemiballism? Subthalamic nucleus

Epilepsy: Classification

Basics

- two main categories are generalised and partial seizures
- partial seizures may progress to general seizures
- other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

Generalised - no focal features, consciousness lost immediately

- **Tonic-clonic** (grand mal)
- **Absence seizures** (petit mal)
 - ⇒ absences last a few seconds and are associated with a quick recovery
 - ⇒ mostly seen in children
 - ⇒ **1st line treatment** → **ethosuximide**
 - ⇒ good prognosis - 90-95% become seizure free in adolescence
- myoclonic: brief, rapid muscle jerks
- partial seizures progressing to generalised seizures

Partial - focal features depending on location

- Simple (no disturbance of consciousness or awareness)
- Complex (consciousness is disturbed)
- **Jacksonian seizure**
 - ⇒ also known as a focal (partial) motor seizure.
 - ⇒ In this condition an uncontrolled, spontaneous discharge of electricity from one motor cortex presents with contralateral motor signs.
 - ⇒ The patient has preserved consciousness as it is a partial seizure
 - ⇒ after the seizure it is common to have a Todd's paralysis where the limb is weak.
- **Temporal lobe epilepsy**
 - ⇒ Focal seizure with impaired awareness (**complex partial seizure**)
 - ⇒ Can take the form of automatisms such as chewing and swallowing repeatedly, scratching the head or searching for an object.
 - ⇒ **Most commonly arise in the temporal lobes.**
 - ⇒ **MRI is an appropriate investigation**
 - ⇒ The commonest finding is **hippocampal sclerosis**
- **Gelastic seizures**
 - ⇒ Gelastic seizures should be suspected in cases of **erratic laughing or crying**.
 - ⇒ typically arise from **hypothalamic hamartomas**

Absence seizure (petit mal)

- presents with a blank stare, 3 Hz brain waves and do not show postictal confusion.
- **Good prognosis:** 90 -95% become seizure free in adolescence.

Somatosensory seizures

- Spread of symptoms ('marching') in seconds
- The usual source is the parietal lobe.
- Example → tingling sensation starts in fingers and spreads in seconds to affect the whole arm and leg.
 - ⇒ Positive symptoms (jerking, tingling) usually signify epilepsy.
 - ⇒ Negative symptoms (weakness, numbness) are usually caused by transient focal ischaemia.
- Spread of symptoms ('marching') indicates migraine (in 5-20 minutes) or seizures (in seconds).

Atonic seizure (also known as "drop seizure" or "drop attack")

- Sudden loss of muscle tone: sudden head drop or collapse (lasts < 15 seconds)
- Frequently mistaken for syncope

Epilepsy: investigations

- **Electroencephalogram (EEG)**
 - ⇒ should be performed only to support a diagnosis
 - ⇒ An EEG should not be performed in the case of probable syncope because of the possibility of a false-positive result.
 - ⇒ should not be used in isolation to make a diagnosis of epilepsy.
 - ⇒ should not be used to exclude a diagnosis of epilepsy in whom the clinical presentation supports a diagnosis of a non-epileptic event.
 - ⇒ can be used to assess the risk of seizure recurrence in patient presenting with a first unprovoked seizure.
 - ⇒ When a standard EEG has not contributed to diagnosis, a sleep EEG should be performed.
 - ⇒ Long-term video or ambulatory EEG may be used in case of diagnostic difficulties after clinical assessment and standard EEG.
- **Neuroimaging:** to identify underlying gross pathology
 - ⇒ MRI is the imaging investigation of choice.
 - ⇒ CT should be used if MRI is not available or is contraindicated.
 - ⇒ In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness.
 - ⇒ Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalised epilepsy has been made.

Epilepsy: treatment

Epilepsy medication: first-line

- generalised seizure: sodium valproate
- partial seizure: carbamazepine

Patients cannot drive for 6 months following a seizure

When to start antiepileptics?

- Antiepileptics is generally recommended **after a second epileptic seizure**.
- NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:
 - ⇒ the patient has a neurological deficit
 - ⇒ brain imaging shows a structural abnormality
 - ⇒ the EEG shows unequivocal epileptic activity
 - ⇒ the patient or their family or carers consider the risk of having a further seizure unacceptable

Which antiepileptics?

- **Focal seizures**
 - ⇒ Female of childbearing potential:
 - 1st line → lamotrigine
 - 2nd line → levetiracetam
 - 3rd line → oxcarbazepine (can impair the effectiveness of hormonal contraceptives)
 - ⇒ Male or female who are not of childbearing potential:
 - 1st line → lamotrigine or carbamazepine
 - 2nd line → levetiracetam, oxcarbazepine or sodium valproate
- **Generalised tonic-clonic (GTC) seizures**
 - ⇒ Female of childbearing potential
 - 1st line → lamotrigine
 - 2nd line → levetiracetam, clobazam, or topiramate
 - ⇒ Male or female who are not of childbearing potential
 - 1st line → sodium valproate
 - 2nd line → lamotrigine, carbamazepine, oxcarbazepine
- **Absence seizures (Petit mal)**
 - ⇒ Female of childbearing potential
 - 1st line → ethosuximide
 - 2nd line → lamotrigine
 - 3rd line → combination of ethosuximide and lamotrigine
 - ⇒ Male or female who are not of childbearing potential
 - 1st line → ethosuximide or sodium valproate
 - 2nd line → lamotrigine
 - 3rd line → combination of two of these three AEDs: **ethosuximide, lamotrigine or sodium valproate**

- Myoclonic seizures

⇒ Female of childbearing potential

- 1st line → levetiracetam or topiramate (topiramate can impair the effectiveness of hormonal contraceptives.)

- 2nd line → add levetiracetam, or topiramate

⇒ Male or female who are not of childbearing potential

- 1st line → sodium valproate

- 2nd line → levetiracetam or topiramate

Indications for monitoring of AED blood levels

- detection of non-adherence to the prescribed medication
- suspected toxicity
- adjustment of phenytoin dose
- management of pharmacokinetic interactions (for example, changes in bioavailability, changes in elimination, and co-medication with interacting drugs)
- specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy

Stopping of anti-epileptic drugs (AED)

- Can be considered if seizure free for at least 2 years, with AEDs being stopped slowly over 2-3 months (withdrawing benzodiazepines and barbiturates may take up to 6 months or longer)
- Benzodiazepines should be withdrawn over a longer period.

Vagus nerve stimulation

- indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication

If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy (JME) is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

AED cessation can be considered if seizure free for > 2 years – Stop AEDs over 2-3 months

MRCPUK-part-1-January 2015 exam: Which one of the antiepileptic drugs is most associated with weight gain? Sodium valproate

MRCPUK-part-1-September 2012 exam: What is the most appropriate first-line antiepileptic for myoclonic seizures? Sodium valproate

Antiepileptic drugs (AED)

Overview

- Only start after a minimum of two fits.
- Only use one drug at a time, and begin with a small dose, and gradually increase it, until control is achieved, toxic affects occur, or the maximum dose is reached.
- The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first-line AED.
- If the initial treatment is unsuccessful, then monotherapy using another drug can be tried.

- If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.

Drug	Mechanism	Side effects	Clinical uses
Benzodiazepines	↑ GABA action	Sedation, tolerance, dependence, respiratory depression	1 st line for acute
Phenobarbital	↑ GABA action	Sedation, impairment of motor and cognition systems after long term use, megaloblastic anaemia	Rarely used due to sedation – been superseded by phenytoin
Phenytoin	Inhibits sodium channels Blocks Na ⁺ channels ;zero-order kinetics	Giant hypertrophy, arrhythmias Cytochrome P-450 induction, Pseudo-lymphoma, Hirsutism, Nystagmus, Yellow-brown skin, Teratogenicity (fetal hydantoin syndrome), Osteopenia, Inhibited folate absorption, Neuropathy. Rare: SJS, DRESS syndrome, drug-induced lupus. Toxicity leads to diplopia, ataxia, sedation.	Partial and generalised attacks, but not in absence. High doses may precipitate attacks
Carbamazepine	Inhibits sodium channels	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, SJS , skin rash	1 st line for partial seizures. 2 nd or 3 rd line, when other drugs unsuccessful.
Ethosuximide	Blocks thalamic T-type Ca ²⁺ channels	Fatigue, Headache, Itching, SJS	Useful for absence seizures
Lamotrigine	Blocks voltage-gated Na ⁺ channels, inhibits the release of glutamate	SJS (must be titrated slowly), hemophagocytic lymphohistiocytosis (black box warning)	Generalised seizures – 2 nd line treatment
Sodium valproate	❖ ↑Na ⁺ channel inactivation ❖ ↑GABA concentration by inhibiting GABA transaminase	Alopecia, Hepatotoxic, Pancreatitis, P-450 inhibition (reduces efficacy of contraceptive pill), Rash, Weight gain, Tremor, Teratogenesis (neural tube defects).	❖ 1 st line for: Absence seizures & Generalised seizures ❖ 2 nd line for partial seizures
Levetiracetam	❖ SV2A receptor blocker; ❖ May modulate GABA and glutamate release, ❖ Inhibit voltage-gated Ca ²⁺ channels	Neuropsychiatric symptoms (eg, personality change), fatigue, drowsiness, headache	For partial and generalised

Which antiepileptic drugs does not have interactions with warfarin?

- Lamotrigine has no effect on liver enzymes and is the treatment of choice for patient taking warfarin
- Phenytoin, carbamazepine, primidone and phenobarbital are liver enzyme inducers
- Sodium valproate is a liver enzyme inhibitor

If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures.

Which antiepileptic drug is most likely to cause renal stones side-effects?

- Topiramate (The side effects of topiramate include: weight loss, renal stones and cognitive and behaviour changes).

MRCPUK-part-1-September 2008 exam: H/O complex partial seizures, not able to tolerate either carbamazepine or sodium valproate. What is the most appropriate next line drug?

- Lamotrigine

What is the likelihood of controlling seizures in a patient never previously on anti-epileptic medication?

A study of patients with previously untreated epilepsy demonstrated that:

- With a single first-line anti-convulsant agent → 47% achieved control of seizures
- 14% became seizure-free during treatment with a second or third drug.
- An additional 3% became seizure-free with the use of two drugs simultaneously.

Carbamazepine and oxcarbazepine but be aware of the risk of exacerbating myoclonic or absence seizures

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy is the **most common** primary generalised epilepsy, but is underdiagnosed due to lack awareness of the condition by doctors

Overview

- is a common form of idiopathic generalised epilepsy, representing 10% of all patients with epilepsy.
- typically, first manifests itself **between the ages of 10 and 20** with brief episodes of involuntary muscle twitching occurring early in the morning.

Genetic

- The condition is genetically linked to the short arm of chromosome 6.

Presentation

- Bilateral symmetrical myoclonic jerks, primarily after awakening, without impaired consciousness
- Generalized tonic-clonic seizures
- Absence seizures with impaired consciousness
- Myoclonic jerks, especially of the upper limbs, which predominantly occur in the mornings shortly after waking (and may be so subtle as to be interpreted as 'clumsiness' when eating breakfast)
- Triggers: sleep deprivation, alcohol consumption, flickering lights

Investigations

- Interictal EEG is diagnostic showing → generalised spike- and polyspike-wave activity; a photosensitive response may also be present

Management

- Female of childbearing potential
 - ⇒ **1st line** → lamotrigine, levetiracetam or topiramate
 - ⇒ **2nd line** → add lamotrigine, levetiracetam or topiramate
- Male or female who are not of childbearing potential
 - ⇒ **1st line** → sodium valproate
 - ⇒ **2nd line** → add lamotrigine, levetiracetam, or topiramate

Prognosis

- Prognosis is extremely favourable if the condition is treated correctly, with many patients becoming seizure-free.

Status epilepticus

Definition

- **≥5 minutes of continuous seizure activity, or more than one seizure without recovery in between**

Treatment

- Initial management: ABC. **Maintain airway and circulation with intubation**
- **1st line anticonvulsant:** two doses of benzodiazepines (**Lorazepam** is preferred).
- **2nd line anticonvulsant:** parenteral anti-epileptics (**intravenous phenobarbital or phenytoin**)
 - ⇒ **Fosphenytoin**: (a pro-drug of phenytoin)

- advantages over phenytoin:
 - ❖ it can be given IV or IM (phenytoin can only be given IV)
 - ❖ can be given at infusion rates three times faster than phenytoin
 - ❖ therapeutic levels are achieved within 10 minutes
 - ❖ it has a lower incidence of adverse events than phenytoin.
 - ❖ If the patient is already taking phenytoin, either IV phenytoin or fosphenytoin should still be given: it is likely that plasma levels are subtherapeutic.
- ⇒ **Phenytoin is not recommended in patients with underlying liver impairment therefore not used in status epilepticus secondary to alcohol withdrawal.**
- **3rd line: ICU for general anaesthesia (Midazolam or propofol)**
 - ⇒ **Monitoring:** By EEG in unconscious patients to differentiate between sedation and nonconvulsive seizures → EEG pattern:
 - Focal or focal with secondary generalization → nonconvulsive status epilepticus
 - Generalized slowing, attenuation, lateralizing periodic discharges → postictal.

The use of phenytoin is not recommended in patients with underlying liver impairment therefore not used in status epilepticus secondary to alcohol withdrawal.

If a patient in generalised status epilepticus does not respond to lorazepam and adequate doses of intravenous phenytoin, what is the next step in their management?

→ Transfer to an Intensive Therapy Unit

Epilepsy: pregnancy and breast feeding

Epilepsy + pregnancy = 5mg folic acid

Overview

- Epilepsy is not a contraindication to pregnancy.
- the risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus

Risk of congenital defects

- Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.
- All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy until at least the end of the first trimester to minimise the risk of neural tube defects.

What is the effect of pregnancy on epilepsy?

- Two-thirds will not have seizure deterioration in pregnancy
- The overall chance of **postpartum** seizures is **relatively higher than during pregnancy**.

Management

- Exposure to sodium valproate and other AED polytherapy should be minimised by changing the medication **prior to conception**.
- We suggest NOT making changes to antiseizure drug regimen for the purpose of reducing teratogenic risk in **established pregnancy**
- Aim for monotherapy. The lowest effective dose of the most appropriate AED should be used.
- Some women who have been seizure free for a prolonged period may reasonably choose to discontinue antiseizure drug prior to conception.
- Women with epilepsy taking AEDs who become unexpectedly pregnant: It is never recommended to stop or change AEDs abruptly without an informed discussion.
- the **levetiracetam** has a favorable reproductive safety profile and has a broad spectrum of action across multiple seizure types.
- If seizures are focal and begin after the first trimester, **carbamazepine** is another option. (**carbamazepine** often considered **the least teratogenic of the older antiepileptics**)
- **Sodium valproate should not be used during pregnancy and in women of childbearing age unless she is on a pregnancy prevention programme.** Associated with neural tube defects and neurodevelopmental delay.
- **Phenytoin:**
 - ⇒ associated with cleft palate
 - ⇒ It is advised that **pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn.**
- **Lamotrigine:**
 - ⇒ the rate of congenital malformations may be low.
 - ⇒ The dose of lamotrigine may need to be increased in pregnancy
- **Breast feeding** is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

Pseudoseizures

Suspected psychogenic non-epileptic seizures → do Video-EEG recording

Overview

- Pseudoseizures are commonly misdiagnosed as true seizures and treated inappropriately with anti-epileptic drugs.
- patients of any age can present with pseudoseizures.
- features such as tongue biting and urinary incontinence are not absolute features of an organic seizure, they are often present in pseudoseizures.

Factors favouring pseudoseizures

- pelvic thrusting
- family member with epilepsy
- more common in females
- accompanying underlying psychiatric concerns , e.g. **crying after seizure**, tearful around the time of the seizure.
- attacks in public and absence of nocturnal events (don't occur when alone)

- gradual onset
- **prolonged nature of the attacks (15-30 minutes)**
- Violent shaking
- **resistance to passive eye opening**
- **very short post-ictal state**
- normal vital signs

Urinary incontinence can also occur in pseudoseizures, but tongue biting is rare

Factors favouring true epileptic seizures

- tongue biting
- raised serum prolactin

Diagnosis

- **Video telemetry is useful for differentiating**

Treatment

- Simple **observation** is the appropriate management.

Rett syndrome

Overview

- Rett syndrome is a neurodevelopmental disorder of the **grey matter**
- inherited as an **X-linked dominant** disorder.
- mostly affecting **girls**.
⇒ Males affected by Rett syndrome die in utero or shortly after birth.
- related to the **MECP2 gene on the X chromosome**

Feature

- Small hands and feet with deceleration of head growth.
- Epileptic → **repetitive hand movements** such as **hand wringing**.
- loss of development, verbal abilities and cognition, ataxia
- GI problems, such as constipation.

Tourette syndrome

Definition

- a chronic neurologic disorder that manifests with motor and vocal tics

Epidemiology

- Tourette syndrome presents before 18 years of age and many children grow out of it.
- more common in males (4:1)

Pathogenesis

- due to genetic, environmental, and social factors resulting in an abnormality in the **mesolimbic spinal system**
- the condition is familial in most cases

Features

- The motor tics often have a build-up that the patient is aware of, like an itch.
- **Commonly they involve blinking, throat clearing or shoulder shrugging.**
- Shouting of swear words is a typical vocal tic of Tourette's.

Associated conditions

- 90% of patients have a comorbid psychiatric disorder such as attention deficit hyperactivity disorder (~60% of cases)

Management

- **first-line:** Cognitive behavioural therapy
- Second line: pharmacotherapy **alpha-2 agonist** (e.g., clonidine and guanfacine).

Huntington's disease (HD)

Pathophysiology

- **Autosomal dominant** → Increased number of CAG repeats (trinucleotide repeat disorder) in the huntingtin gene on chromosome 4 (coding for glutamine) → **formation of abnormal proteins which have abnormal number of glutamine residues** (huntingtin) → degeneration of GABAergic neurons (**gamma-amino-butyric acid**-ergic neurons in the **striatum** (particularly in the **caudate** nucleus) of the **basal ganglia**).
- The striatum normally controls movement via inhibitory outputs to the globus pallidus internus.
- **Anticipation:** **increase in the number of CAG repeats in subsequent generations** (The disease may develop earlier in life in each successive generation)

Epidemiology

- Symptom onset usually between 20 and 50 years of age

Features

- **Personality changes** (e.g. irritability, disinhibition, apathy, depression) and intellectual impairment (**the earliest symptom**)
- Chorea
 - ⇒ **Athetosis** is a hyperkinetic movement symptom characterized by slow, involuntary, writhing movements. **Huntington disease** and cerebral palsy are the most common causes.
- Lack of coordination and an unsteady gait
- Dystonia
- Saccadic eye movements
- Dementia
- Dopamine levels are increased
- Gamma-aminobutyric acid levels are decreased
- Acetylcholine levels in the central nervous system are decreased

Diagnosis

- **DNA analysis is the most useful diagnostic test**
 - ⇒ (e.g., **via PCR**)
 - ⇒ Trinucleotide CAG repeat expansion in the Huntington gene is diagnostic
- **MRI → caudate nucleus atrophy**
 - ⇒ Atrophy of the caudate nucleus, putamen, and deep cerebral cortex are the hallmark features of Huntington's disease.
 - ⇒ Hydrocephalus ex vacuo
 - **Hydrocephalus ex vacuo** is an expansion of the cerebral ventricles and surrounding subarachnoid space caused by atrophy of the underlying brain tissue, and not an expansion of CSF volume primarily.

- ⇒ The role of neuroimaging is primarily to rule out other intracranial causes of a patient's symptoms, rather than to diagnose HD.

Treatment

- **Tetrabenazine and reserpine works as a VMAT-inhibitor (vesicular monoamine transporter 2)**, involved in transportation of monoamines. It is indicated for Huntington's chorea to reduce hyperkinetic movements.
- Haloperidol is a dopamine-2 antagonist used to treat movement disorders, hallucinations, and delusions in Huntington disease.

Prognosis

- progressive and incurable
- Average life span after clinical onset is about 15 years (premature death).

In Huntington disease, increased number of CAG repeats leads to the damage to the Caudate nucleus and results in decreased acetylcholine (Ach) and GABA.

Cluster headache

Cluster headache - acute treatment: subcutaneous sumatriptan + 100% O₂

Epidemiology

- More common in men (5:1) and smokers.
- **More common in younger males below the age of 40**

Features

- pain typically occurs once or twice a day, each episode lasting **15 mins - 2 hours**
- clusters typically last 4-12 weeks
- intense pain around one eye (recurrent attacks 'always' affect same side)
- The attacks are often nocturnal and are associated with parasympathetic overactivity.
- patient is restless during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

Management

- **Acute:** 100% oxygen, subcutaneous or a **nasal triptan**
 - ⇒ the use of 100% oxygen at least 12 litres per minute via a non-rebreathable mask
 - ⇒ It is not recommended to offer paracetamol, NSAIDS, opioids, ergots or oral triptans for the acute treatment of a cluster headache.
- **prophylaxis:** First line → **verapamil**, prednisolone , with other options including lithium, sodium valproate and gabapentin
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging



Cluster headaches may involve pain around one eye, along with drooping of the lid, tearing and congestion on the same side as the pain

Differential diagnosis

- The main differential is between cluster headaches and **chronic paroxysmal hemicrania** (CPH; which is treated with indomethacin).

Distinguishing cluster headaches and Chronic Paroxysmal Hemicrania

Cluster headache	Chronic Paroxysmal Hemicrania
more common in males	more common in females
frequency of attacks is 1 - 4 (maximum 8) in 24 hours.	the frequency of attacks is higher , usually more than 15 in 24 hours
The duration of headaches is (15-60 min).	The duration of headaches is shorter (2-25 min)
Not responds to indomethacin	responds very well to indomethacin

Migraine

Diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for **migraine without aura**:

Point	Criteria
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)
C	Headache has at least two of the following characteristics: <ul style="list-style-type: none"> • 1. unilateral location • 2. pulsating quality (i.e., varying with the heartbeat) • 3. moderate or severe pain intensity • 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D	During headache at least one of the following: <ul style="list-style-type: none"> • 1. nausea and/or vomiting • 2. photophobia and phonophobia
E	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

- NICE suggests migraines may be unilateral or bilateral

Migraine with aura

- seen in around 25% of migraine patients
- tends to be easier to diagnose with a typical aura being progressive in nature
- may occur hours prior to the headache.
- Typical aura include:
 - ⇒ transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent').
 - ⇒ **Spreading (over minutes) sensory and motor symptoms**
 - ⇒ Word-finding difficulties are also a common migraine aura symptom.
 - ⇒ autonomic symptoms such as a Horner syndrome
 - ⇒ negative auras of dark holes and **tunnel vision**
 - ⇒ Dizziness and fatigue are quite common prior to a migraine attack
 - ⇒ Patients may have mixed positive and negative auras.
 - ⇒ Positive auras include bright or shimmering light or shapes at the edge of their field of vision called scintillating scotoma. They can enlarge and fill the line of vision.
 - ⇒ Other positive aura experiences are zigzag lines or stars.
- may occur with or without headache
- NICE also give more detail about **typical auras**:
 - are fully reversible
 - develop over at least 5 minutes

- last 5-60 minutes
- The following aura symptoms are atypical and may prompt further investigation/referral;
 - ⇒ motor weakness
 - ⇒ double vision
 - ⇒ visual symptoms affecting only one eye
 - ⇒ poor balance
 - ⇒ decreased level of consciousness.
- **Complicated migraine**
 - ⇒ **Complicated migraine** is one which results in hemi sensory or hemi motor findings associated with a typical migraine presentation.
- **Confusional migraine** involves alteration in sensorium rather than limb involvement.

Other features:

- family history of similar headaches is common
- Bilateral fortification spectra
 - ⇒ Fortification spectra (jagged lines resembling battlements) and teichopsia (flashes) are common features of migraine.
- Precipitation by oral contraceptives (contraindicated in migraine with aura)
- Frequency reduced by tricyclic antidepressants (can be useful in the prophylaxis of migraine)
- Third nerve palsy
 - ⇒ seen in **ophthalmoplegic migraine**
 - ⇒ ophthalmoplegic migraine was reclassified as a **cranial neuralgia** in the most recent International Headache Society classification.
 - ⇒ most commonly affects the third nerve,
 - ⇒ the deficits can be permanent.
 - ⇒ A subset of these patients will have gadolinium enhancement of the cisternal segment of the cranial nerve
 - ⇒ it is thought some of these patients actually have a demyelinating neuropathy.

Migraine: management

Migraine

- acute: triptan + NSAID or triptan + paracetamol
- prophylaxis: topiramate or propranolol

acute → 5-HT agonists

prophylaxis: β-blocker, 5-HT2 antagonist

- 5-HT receptor agonists are used in the acute treatment of migraine
- 5-HT receptor antagonists are used in prophylaxis.

Acute treatment

- first-line:
 - ⇒ combination of oral triptan and NSAID, **OR** oral triptan and paracetamol
 - for young people aged 12-17 years: **nasal triptan** is preferred than oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide* or prochlorperazine and consider adding a non-oral NSAID or triptan
 - ⇒ *caution should be exercised with young patients as acute dystonic reactions may develop with metoclopramide.

Prophylaxis

- prophylaxis should be given if patients are experiencing 2 or more attacks per month.
- Modern treatment is effective in about 60% of patients.
- NICE advise either **topiramate** or **propranolol** or **amitriptyline** 'according to the person's preference, comorbidities and risk of adverse events'.
 - ⇒ **Propranolol** should be used **in preference to topiramate in women of child bearing age** as it may be **teratogenic** and it can **reduce the effectiveness of hormonal contraceptives**
- if these measures fail NICE recommend 'a course of up to 10 sessions of **acupuncture** over 5-8 weeks'
- gabapentin are not recommended now because evidence shows that it is not effective in preventing migraine. (NICE 2015)
- NICE recommend: 'Advise people with migraine that **riboflavin** (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
 - ⇒ **riboflavin** also known as **vitamin B₂**
 - safe during pregnancy.
- for women with **predictable menstrual migraine** treatment:
 - ⇒ NICE recommend either **frovatriptan** (2.5 mg twice a day) or **zolmitriptan** (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- pizotifen is no longer recommended.
 - ⇒ Adverse effects such as weight gain & drowsiness are common

Efficacy of Paracetamol in migraine

- Migraine → ↓ gastric emptying → ↓ Paracetamol absorption → ↓ Paracetamol effects
- Metoclopramide may be useful in accelerating gastric emptying.
- paracetamol absorption technique is used to study gastric emptying.

MRCPUK-part-1-January 2006 exam: Which type of medication would be most appropriate to reduce the frequency of migraine attacks?

→ **Beta-blocker** (Topiramate is also recommended by NICE as first-line prophylaxis against migraine. However, a beta-blocker is a better choice in a female of child-bearing age)

Migraine: pregnancy, contraception and other hormonal factors

Migraine during pregnancy

- paracetamol 1g is first-line
- aspirin 300mg or ibuprofen 400mg can be used second-line in the first and second trimester

Migraine and the combined oral contraceptive (COC) pill

- if patients have migraine with aura then the COC is absolutely contraindicated due to an increased risk of stroke (relative risk 8.72)

Migraine and menstruation

- many women find that the frequency and severity of migraines increase around the time of menstruation
- SIGN recommends that women are treated with mefanamic acid or a combination of aspirin, paracetamol and caffeine. Triptans are also recommended in the acute situation

Migraine and hormone replacement therapy (HRT)

- safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

Triptans

Action

- Triptans are specific **5-HT1 agonists** used in the acute treatment of migraine.
- They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points

- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

- 'tripitan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications

- patients with a history of, or significant risk factors for, ischaemic heart disease or cerebrovascular disease

Epilepsy is not a contraindication to the use of triptans

Idiopathic intracranial hypertension (IIH)

Obese, young female with headaches / blurred vision : think idiopathic intracranial hypertension

Postural headache but normal imaging → idiopathic intracranial hypertension

Suspected Idiopathic intracranial hypertension → lumbar puncture to confirm the diagnosis is the next step

Overview

- also known as pseudotumour cerebri and formerly benign intracranial hypertension
- classically seen in young, overweight females.

Risk factors

- obesity
- female sex
- pregnancy
- drugs:
 - ⇒ **oral contraceptive pill (eg: Dianette),**
 - ⇒ Danazol (synthetic androgen used to treat endometriosis)
 - ⇒ **steroids,**
 - ⇒ **tetracycline,**
 - ⇒ **vitamin A,**
 - ⇒ Nalidixic acid
 - ⇒ *if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

Features

- headache
 - ⇒ chronic postural headache (suggested by its improvement as the day progresses)
 - ⇒ 10% of cases are free of headaches.
- blurred vision, (Horizontal diplopia)
 - ⇒ Diplopia is common due to sixth nerve palsy.
- papilloedema (usually present)
- **enlarged blind spot**
- Reduction in colour vision is common
- sixth nerve palsy may be present
- normal appearances of the magnetic resonance imaging (MRI). Normal ventricular size, anatomy and position. Normal CSF cell count and protein content.
- **plantars are flexor**
 - ⇒ Extensor plantars suggest alternative diagnosis.
- **Absence of retinal venous pulsations**

Diagnosis

- the diagnosis is confirmed by finding an **elevated CSF opening pressure** (more than 20 cm H₂O). CSF protein, glucose and cell count will be normal.
- CT and MRI scans are often normal
 - ⇒ CT brain is needed to exclude a space occupying lesion and obstructing hydrocephalus.
 - ⇒ **MRI venogram is recommended afterwards to exclude cerebral sinus thrombosis.**

Management

- weight loss
- diuretics e.g. acetazolamide
- topiramate (anticonvulsant) is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery:
 - ⇒ A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure
 - ⇒ optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve.
 - **In progressive visual loss → Lumbo-peritoneal (LP) shunt is the treatment of choice.**
 - ❖ Optic nerve fenestration is an alternative.
 - ❖ There are no comparative studies between the two interventions.

Complication

- Progressive visual loss and optic atrophy

Scenario

A young, obese female presents with a progressive blurring in her vision over the last 12 months but **denies any headache**. On fundoscopy she has bilateral blurred and **heaped up optic discs** which are obviously **pale**. CT head scan was reported as normal. Which appropriate investigation for this patient?

→ **Brain MR venography**

- The description of the pale but prominent optic discs goes with early secondary optic atrophy and hence should promote a search for a cause for a longstanding papilloedema.
- She is likely to have idiopathic intracranial hypertension; 10% of cases are free of headaches.
- The next most appropriate investigations would be assessment for any underlying causes and include magnetic resonance venography (MRV) (exclude cerebral sinus thrombosis) and cerebrospinal fluid (CSF) analysis with assessment of the opening pressure and other CSF parameters as a confirmatory step.

MRCPUK-part-1-September 2008 exam: Sudden loss of vision in left eye + headaches + bilateral papilloedema. Which drug is most likely to be responsible?

→ **Prednisolone → intracranial hypertension**

Spontaneous intracranial hypotension (SIH)

Strong postural relationship with the headache generally much worse when upright and easy with lying horizontal. Patients may therefore be bed-bound

Definition

- Low (CSF) pressure headache, (< 6 cm CSF)
- The lower limit of the normal range for CSF pressure is 10 cm H₂O

Causes

- The most common cause → following lumbar puncture,
 - ⇒ The leak is typically from the thoracic nerve root sleeves.
- Other possible causes:
 - ⇒ following an episode of possible minor trauma to meninges (eg sports injury to neck or back)
 - ⇒ without apparent cause (SIH).

Mechanism and features

- CSF leak leads to → low CSF pressure → orthostatic headache in association with one or more of the following symptoms:
 - ⇒ nausea, vomiting
 - ⇒ horizontal diplopia
 - ⇒ unsteadiness or vertigo
 - ⇒ altered hearing
 - ⇒ neck pain/stiffness
 - ⇒ interscapular pain
 - ⇒ visual field abnormalities

Diagnosis

- **CSF opening pressure** at lumbar puncture:
 - ⇒ opening CSF pressure is low, (< 6 cm CSF), and often a 'dry' tap is encountered
 - ⇒ However, the pressure may be normal
 - ⇒ CSF fluid analysis is normal
- **MRI with gadolinium**
 - ⇒ confirming the diagnosis
 - ⇒ demonstrates distinctive dural gadolinium enhancement and downward displacement of brain on sagittal views.
 - ⇒ typically reveal diffuse pachymeningeal enhancement, frequently in association with 'sagging' of the brain, tonsillar descent and posterior fossa crowding

Treatment

- usually conservative (**first-line**): bed rest, analgesia, increased fluid intake
- if this fails an **epidural blood patch** may be tried

Medication overuse headache

Medication overuse headache

- **Simple analgesia + triptans: stop abruptly**
- **Opioid analgesia: withdraw gradually**

Definition

- a headache occurs ≥ 15 days per month due to overuse of headache medication (e.g. opioid, paracetamol, triptans and NSAIDs) for > 3 months.

Epidemiology

- Prevalence: 1 to 2% and is higher in females than males.

Features

- A history of symptomatic medication use more than two to three days per week in association with chronic daily headache is suggestive.
- Commonly occurs daily or nearly daily.
- Butalbital-containing analgesics and opioids has the highest risk of medication overuse headache.

Management

- **Simple analgesics and triptans should be withdrawn abruptly** (may initially worsen headaches)
- Opioid analgesics should be gradually withdrawn
- Withdrawal symptoms are likely to occur, including worsening headache, nausea, agitation and sleep disturbance. These usually settle within seven days, and headaches should stop within approximately three weeks.
- While discontinuing the overused medication, some patient may require bridge therapy such as long-acting NSAIDs; eg, naproxen or oral prednisone.

Parkinsonism

Definition

- Parkinsonism refers to clinical syndromes that mimic the symptoms of Parkinson's disease (PD) (e.g. tremor, bradykinesia, rigidity).

Causes

- **Parkinson disease (PD):** Idiopathic
- **Secondary parkinsonism**
 - ⇒ Drug-induced e.g. antipsychotics, metoclopramide
 - ⇒ Progressive supra-nuclear palsy
 - ⇒ Multiple system atrophy
 - ⇒ Wilson's disease
 - ⇒ Post-encephalitis
 - ⇒ Dementia pugilistica (secondary to chronic head trauma e.g. boxing)
 - ⇒ Toxins: carbon monoxide, MPTP
 - ⇒ **Drugs-induced Parkinsonism**
 - Phenothiazines: e.g. chlorpromazine, prochlorperazine
 - Butyrophenones: haloperidol, droperidol
 - Metoclopramide
 - Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects

Parkinson's disease (PD)

Parkinson's disease - most common psychiatric problem is depression

Definition

- Progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.

Epidemiology

- The second most common neurodegenerative disorder following Alzheimer disease
- Prevalence is 1-2 per 1000 people
- More common in men (2:1)
- Mean age of diagnosis is 65 years

Risk factors

- Advanced age (>60 years)
- Family history
- Male sex
- Environmental pesticides.

Pathophysiology

- In normal circumstances
 - ⇒ There are two pathways in the brain that promote motion, the direct (stimulatory) pathway and the indirect (inhibitory) pathway.
 - ⇒ In normal circumstances, the stimulatory pathway is activated while the inhibitory pathway is deactivated, allowing for smooth motion.
 - ⇒ Dopamine **stimulates** the **Direct Pathway** and **inhibits** the **Indirect Pathway**.
 - ⇒ The substantia nigra (part of the basal ganglia) produces dopamine, which binds the **D1** receptors in the striatum, **inhibiting the globus pallidus**, leading to **activation of the thalamus** and allowing movement (**activation of the direct stimulatory pathway**)
 - ⇒ Also, dopamine binds the **D2** receptor, inhibiting the inhibitory pathway (**inhibition of the indirect pathway**).
- In Parkinson disease
 - ⇒ Aggregates of α-synuclein proteins → form Lewy bodies → loss of the dopamine-producing neurons in the substantia nigra.
 - ⇒ Decreased dopamine causes **increased inhibitory output** from the **globus pallidus** via both the direct and indirect pathways → ↓ motion.
 - ⇒ ↓ dopamine → ↓ activation of **D1** receptor on striatum → ↓ **excitatory** (stimulatory) direct pathway → ↑ **globus pallidus internus** output → ↓ thalamic function → ↓ motion.
 - ⇒ ↓ dopamine → ↓ activation of **D2** receptor on striatum → **disinhibiting the inhibitory pathway**
 - ⇒ **The classical signs of bradykinesia, resting tremor and rigidity start to appear after approximately 50% of the dopamine neurons, and 75-80% of striatal dopamine is lost.**

Decreased dopamine impairs movement by which mechanisms?

- ⇒ **Decreased activation of the D1 and D2 receptors**

Which mechanism underlying the neurodegeneration seen in Parkinson's?

- ⇒ Impaired protein degradation
- ⇒ Mutations in either the **parkin gene** or **UCHL1** lead to impaired protein degradation.
- ⇒ **Alpha-synuclein** is a synaptic protein accumulates in Lewy body dementia and Parkinson's disease.

What is the characteristic microscopic finding in Parkinson's disease?

- ⇒ **Lewy body**

Features

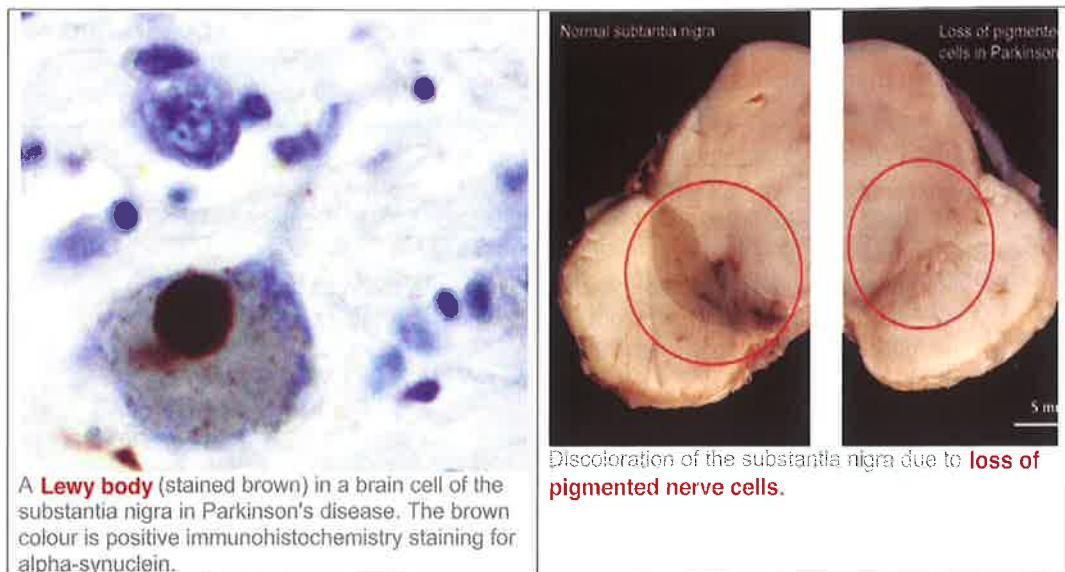
The classic triad of features: bradykinesia, tremor and rigidity

The symptoms of Parkinson's disease are characteristically asymmetrical.

- **Bradykinesia**
 - ⇒ poverty of movement also seen, sometimes referred to as hypokinesia
 - ⇒ short, shuffling steps with reduced arm swinging
 - ⇒ difficulty in initiating movement
- **Tremor**
 - ⇒ **most marked at rest, 3-5 Hz**
 - ⇒ worse when stressed or tired
 - ⇒ typically, 'pill-rolling', i.e. in the thumb and index finger
 - ⇒ The tremor of parkinsonism only disappears during REM sleep.
- **Rigidity**
 - ⇒ lead pipe
 - ⇒ cogwheel: due to superimposed tremor
- **Other characteristic features**
 - ⇒ mask-like facies
 - ⇒ flexed posture
 - ⇒ micrographia
 - ⇒ drooling of saliva
 - ⇒ psychiatric features:
 - **depression is the most common feature (affects about 40%);**
 - dementia, psychosis and sleep disturbances may also occur
 - ⇒ impaired olfaction
 - ⇒ **REM sleep behaviour disorder**
 - **The earliest feature** (During REM sleep, the patient may be seen kicking, laughing, punching, or fighting invisible enemies.)
 - ⇒ **Intestinal pseudo-obstruction**
 - a common feature of advanced Parkinson's
 - results in symptoms of intermittent abdominal bloating and vomiting.

Drug-induced parkinsonism differs from Parkinson's disease in:

- **motor symptoms are generally rapid onset and bilateral**
- **rigidity and rest tremor are uncommon**



Diagnosis: Diagnostic criteria for Parkinson's disease

- **Step 1. Diagnosis of a parkinsonian syndrome**
 - ⇒ Bradykinesia and at least one of the following:
 - Muscular rigidity
 - Rest tremor (4-6 Hz)
 - Postural instability unrelated to primary visual, cerebellar, vestibular, or proprioceptive dysfunction
- **Step 2. Exclusion criteria for Parkinson's disease**
 - ⇒ History of:
 - Repeated strokes with stepwise progression
 - Repeated head injury
 - Antipsychotic or dopamine-depleting drugs
 - Definite encephalitis or oculogyric crises on no drug treatment
 - More than one affected relative
 - Sustained remission
 - Negative response to large doses of levodopa (if malabsorption excluded)
 - Strictly unilateral features after 3 years
 - Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory, or praxis
 - Exposure to known neurotoxin
 - Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

• Step 3. Supportive criteria for Parkinson's disease

- ⇒ Three or more required for diagnosis of definite Parkinson's disease:
 - Unilateral onset
 - Excellent response to levodopa
 - Rest tremor present
 - Severe levodopa-induced chorea
 - Progressive disorder
 - Levodopa response for over 5 years
 - Persistent asymmetry affecting the side of onset most
 - Clinical course of over 10 years.

Feature most strongly suggest idiopathic Parkinson's disease → asymmetry of tremor

Investigations

- Single photon Emission Computed Tomography (SPECT)

- ⇒ The investigation of choice for people with tremor if essential tremor cannot be clinically differentiated from parkinsonism.

Management

General rule of treatment:

- Starting **dopamine agonists** such as ropinirole **for younger patients under 65**.
- **Saving L-dopa for later in the disease** while reducing the long-term risk of motor complications.

Levodopa should be offered for patients with newly diagnosed Parkinson's who have motor symptoms affecting their quality of life

- **First-line treatment**

- ⇒ If the **motor symptoms** are **affecting** the patient's quality of life → **levodopa**
- ⇒ If the motor symptoms are not affecting the patient's quality of life → non-ergot dopamine agonist (e.g., ropinirole, apomorphine), levodopa **or** monoamine oxidase B (MAO-B) inhibitor (e.g., selegiline)
- ⇒ **Patients > 65 years or multimorbid patients of any age** → levodopa PLUS decarboxylase inhibitor (carbidopa): due to inevitable motor complications that is associated with levodopa.
- ⇒ **Patients < 65 years with no significant comorbidities** → Non-ergot dopamine agonists (e.g., pramipexole, ropinirole, apomorphine)

- **Second line**
 - ⇒ **Adjuvant treatment of motor symptoms** (dyskinesia and/or motor fluctuations) if not responded **despite optimal levodopa therapy** → Add **non-ergot-derived dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors** (e.g., entacapone)
- **Third line**
 - ⇒ If dyskinesia is not adequately managed by modifying existing therapy, consider **amantadine**
- **Fourth-line → deep brain stimulation**
 - ⇒ For advanced Parkinson's disease, whose symptoms are not adequately controlled by best medical therapy
 - ⇒ Targets: subthalamic nucleus or internal globus pallidus
 - ⇒ In the context of suicidal behaviour, the patient would not be a candidate for **deep brain stimulation, which for unknown reasons, increases the risk of suicide.**

Comparison between anti-Parkinson drugs

- **Improvement in motor symptoms and activities of daily living.**
 - ⇒ **Levodopa** → **More** improvement
 - ⇒ Other antiparkinsonian medicines (e.g. Dopamine agonists, MAO-B inhibitors & COMT inhibitors) → **Less** improvement
 - ⇒ **Amantadine** → **No evidence of improvement**
- **Off time** (periods of the day between medication doses when the medication is not working well, causing worsening of Parkinsonian symptoms).
 - ⇒ **Dopamine agonists** → **More off-time reduction**
 - ⇒ Amantadine → No studies reporting this outcome
- **Adverse events**
 - ⇒ **Levodopa, MAO-B inhibitors & COMT inhibitors** → **Fewer** adverse events
 - ⇒ **Dopamine agonists** → **Intermediate** risk of adverse events
 - ⇒ Amantadine → No studies reporting this outcome
- **Motor complications**
 - ⇒ **Levodopa** → **More motor complications**
 - ⇒ **Dopamine agonists & MAO-B inhibitors** → **Fewer** motor complications
- **Hallucinations**
 - ⇒ **Levodopa, MAO-B inhibitors & COMT inhibitors** → **Lower** risk
 - ⇒ **Dopamine agonists** → **More** risk
 - ⇒ Amantadine → No studies reporting this outcome

Of the antiparkinson drugs, levodopa is associated with the greatest improvement in symptoms and activities of daily living

Management of non-motor symptoms of Parkinson's disease

- **Excessive daytime sleepiness** → modafinil
- **Rapid eye movement sleep behaviour disorder** → clonazepam or melatonin
- **Nocturnal aknesia** → levodopa or oral dopamine agonists
- **Postural hypotension**
 - ⇒ Review the possible pharmacological causes, e.g: antihypertensives (including diuretics), dopaminergics, anticholinergics, antidepressants.
 - ⇒ First line → **midodrine (alpha agonist)**: monitor for **supine hypertension**.
 - ⇒ Second line → **fludrocortisone** (If midodrine is not tolerated or not effective).

- **Psychotic symptoms (hallucinations and delusions)**
 - ⇒ Do not treat if they are well tolerated.
 - ⇒ Reduce the dosage of any Parkinson's disease medicines
 - ⇒ Consider **quetiapine** (in people without cognitive impairment) or **clozapine**.
 - ⇒ **Do not** offer olanzapine
- **Dementia**
 - ⇒ 1st line: cholinesterase inhibitor (**rivastigmine**, donepezil, or galantamine capsules or rivastigmine patches)
 - ⇒ 2nd line: if cholinesterase inhibitors are not tolerated or contraindicated → **memantine**
- **Drooling**
 - ⇒ 1st line: glycopyrronium bromide (anticholinergic) → reduce excessive saliva (sialorrhea) & does not cross the blood–brain barrier → no central effects.
 - ⇒ 2nd line: If glycopyrronium bromide is not effective → referral for botulinum toxin

Parkinson's medication withdrawal

- Antiparkinsonian medicines **should not be withdrawn abruptly** or allowed to fail suddenly due to poor absorption (for example, gastroenteritis, abdominal surgery) to avoid the potential for acute **akinesia** or **neuroleptic malignant syndrome**.
- The practice of withdrawing people from their antiparkinsonian drugs (so called 'drug holidays') to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome.
- **Parkinsonian malignant syndrome**
 - ⇒ Triggered by abrupt withdrawal from anti-parkinsonian medication.
 - ⇒ The presentation is similar of neuroleptic malignant syndrome (pyrexia, rigidity, tachycardia) but without a history of neuroleptic drug use.
 - ⇒ Re-initiation of Parkinson's therapy is curative.

Anti-Parkinson drugs

Levodopa (L-DOPA)

- **Mode of action**
 - ⇒ **Precursor to dopamine, can penetrate the blood brain barrier** (peripherally administered **dopamine** cannot penetrate the blood brain barrier)
 - ⇒ Converted to dopamine by DOPA decarboxylase at the presynaptic neuron → **direct dopaminergic effect**
- **Indication**
 - ⇒ **First-line treatment for patients > 65 years of age** or patients with comorbidities. Second-line treatment for patients < 65 years of age.
- **Administration**
 - ⇒ Normally combined with a peripheral **decarboxylase inhibitor** (e.g. **carbidopa** or benserazide) to prevent peripheral metabolism of levodopa to dopamine (levodopa alone → peripheral conversion of levodopa to dopamine → significant **GI side effects such as nausea and vomiting**).
- **Advantages**
 - ⇒ Most effective drug for reducing symptoms

- **Disadvantages**

- ⇒ Increased risk of severe motor dysfunction: **levodopa-induced dyskinesia (LID)**
 - **involuntary writhing movements:** choreiform movements, dystonia, myoclonus, and ballism). **Peak-dose dyskinesia** is most common:
 - Due to higher dose of levodopa.
 - Usually involve upper limbs, trunk, and orofacial muscles.
 - Treatment: **reduction of levodopa dose** (use frequent smaller dosage)
 - Amantadine is an NMDA antagonist and considered the most effective drug used for LID.
- ⇒ **Reduced effectiveness with time** (usually by 2 years)
- ⇒ **On/off effect (phenomena)**
 - due to long-standing chronic levodopa therapy and seen when the serum level of levodopa is least.
 - usually manifest as abnormal spasm of body parts, which most commonly affect foot or leg and rarely present on the arm or trunk.
 - Off-period dystonia usually occurs at night or early morning
 - **Treatment**
 - ☞ **may be improved either by the addition of cabergoline (a dopamine agonist) or a subcutaneous infusion of apomorphine.**
 - ☞ Liquid forms of l-dopa may also be helpful as they allow closer titration of dose, and splitting meals into smaller snacks.

- **Side effects**

- ⇒ Nausea & vomiting , dry mouth, anorexia
- ⇒ Cardiac arrhythmias, postural hypotension
- ⇒ Drowsiness
- ⇒ Reddish discolouration of urine upon standing
- ⇒ Psychosis, **hallucinations (usually visual)**
 - usually appear late (more than two years after initiation of treatment).
 - The risk for developing psychiatric symptoms increases with age, other psychiatric conditions, **long duration of levodopa treatment**, and high doses.
- ⇒ **Levodopa can increase intraocular pressure, therefore it is not recommended in patients with glaucoma.**
- Not used in neuroleptic induced parkinsonism

Dopamine receptor agonists

Ropinirole - dopamine receptor agonist

- **Agents**

- ⇒ **Non-ergot dopamine agonists agents:** Ropinirole, apomorphine, pramipexole, rotigotine
- ⇒ **Ergot-derived dopamine agonists:** bromocriptine, cabergoline, pergolide (**not recommended as first-line treatment for Parkinson's disease**).

- **Action:** Act directly at striatal dopamine receptors

- **Indication**

- ⇒ First-line treatment for patients < 65 years of age
- ⇒ Adjunctive treatment for patients of any age

- **Advantage:** Fewer motor side effects
- **Disadvantage:** Less effective than L-DOPA
- **Side effects**
 - ⇒ Nausea, orthostatic hypotension, daytime drowsiness (somnolence)
 - ⇒ **Psychotic symptoms:** **Hallucinations**, psychosis, impulse control disorders
 - **impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating and obsessive shopping).** If modifying dopaminergic therapy is not effective → cognitive behavioural therapy
 - ⇒ **Dopamine agonist withdrawal syndrome**
 - ⇒ **Ergot dopamine agonists:** **fibrosis** (cardiac, pulmonary, retroperitoneal)
 - **retroperitoneal fibrosis → obstruction of both ureters → bilateral hydronephrosis → chronic kidney disease**
 - echocardiogram, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

MAO-B (Monoamine Oxidase-B) inhibitors

- **Agents:** **Selegiline**, Rasagiline, Safinamide.
- **Action:** inhibits the breakdown of dopamine secreted by the dopaminergic neurons
 - ⇒ Selective inhibition of MAO-B → ↓ metabolism of dopamine into DOPAC in the brain → prolonged dopamine availability and effect → ↓ demand for L-DOPA
- **Indication**
 - ⇒ Alternative to L-DOPA or dopamine agonists
 - ⇒ Can also be given in combination with L-DOPA → ↓ motor fluctuations
- **Side effects:** Headache, dyskinesia, psychological disorders (e.g., hallucinations)

NMDA antagonists (Amantadine)

- **Action**
 - ⇒ Acts antagonistically at the glutamate N-methyl-D-aspartate (NMDA) receptor → dopaminergic effect
 - ⇒ ↑ Dopamine release and ↓ dopamine reuptake in central neurons
- **Indication**
 - ⇒ Short-term treatment of mild symptoms
 - ⇒ **Drug of choice during akinetic crisis**
 - ⇒ Reduction of L-DOPA-induced dyskinesia
- **Side-effects**
 - ⇒ **ataxia**, slurred speech, confusion, dizziness
 - ⇒ **livedo reticularis**
 - ⇒ **peripheral edema** (should be avoided in congestive heart failure)

COMT (Catechol-O-Methyl Transferase) inhibitors

- **Agents:** Entacapone, tolcapone
- **Action**
 - ⇒ Inhibition of catechol-O-methyltransferase (COMT) → ↓ peripheral metabolism of L-DOPA to 3-O-methyldopa (3-OMD) → ↑ availability
 - ⇒ Tolcapone also prevents central COMT from breaking down dopamine to 3-methoxytyramine (3-MT) by crossing the blood-brain barrier → ↑ dopamine effect → ↓ demand for L-DOPA and longer therapeutic effect for each dose
- **Indication:** used in conjunction with levodopa. COMT inhibitor monotherapy is ineffective; therefore, it should always be combined with L-DOPA and carbidopa.

Anticholinergic drugs (muscarinic antagonists)

- **Agents:** Procyclidine, Benztropine, Trihexyphenidyl (benzhexol) , Biperiden
- **Action:** Inhibition of excitatory cholinergic neurons → ↓ concentration of acetylcholine
- **Indication**
 - ⇒ Useful as monotherapy in patients < 65 years of age with **tremor as the main symptom**
 - ⇒ Help tremor and rigidity but does not improve bradykinesia.
 - ⇒ Now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
 - ⇒ Usually avoided in patients > 65 years because they are more prone to anticholinergic side effects (e.g., urinary retention, delirium, constipation)

MRCPUK-part-1-January 2017 exam : H/O schizophrenia , developed parkinsonism secondary to his antipsychotic medication. Which drug is most useful in the management of tremor?

→ Benzhexol

MRCPUK-part-1-January 2018 exam: What is the mechanism of action of selegiline in Parkinson's disease?

→ Monoamine Oxidase-B inhibitor

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy:

- the triad of parkinsonism, vertical gaze palsy and cognitive impairment

Overview

- aka **Steele-Richardson-Olszewski syndrome**
- a 'Parkinson Plus syndrome'

Features

- **Impairment of vertical gaze** (especially **downward gaze** - patients may complain of difficulty reading or descending stairs)
- Parkinsonism
- Postural instability leading to **frequent falls** (often first symptom); retropulsion (falling backward on a pull test) is characteristic
- Slurring of speech (pseudobulbar palsy)
- **Cognitive impairment:** frontal lobe abnormalities (apathy, disinhibition, impaired reasoning)
- Dementia

Diagnosis

- **MRI:** "hummingbird sign" showing atrophy of midbrain structures with a relatively intact pons region

Management: poor response to L-dopa

Prognosis: usually fatal within 5–10 years

Multiple system atrophy (MSA)

Multiple system atrophy : a triad of

- Parkinsonism
- **Autonomic disturbance (atonic bladder, postural hypotension)**
- Cerebellar signs (e.g., ataxia, tremor, dysarthria)

Overview

- Shy-Drager syndrome is a type of multiple system atrophy.
- The average age of onset is 50 years (earlier than in Parkinson's disease)
- The median survival six to nine years.
- It runs a briefer course than Parkinson's disease.

Pathology

- Macroscopic: most commonly atrophy of olivopontocerebellar and striatonigral systems
- Microscopic: glial cytoplasmic inclusions

Features

- Parkinsonism
- **Autonomic disturbance (urinary incontinence (atonic bladder), postural hypotension, erectile dysfunction)**
- Cerebellar signs (e.g., ataxia, tremor, dysarthria)
- Myoclonus, dystonia, ocular motility disorders, pyramidal signs

Treatment: Only symptomatic treatment

MRCPUK-part-1-May 2019 exam: A 67-year-old increasing clumsiness + ataxic gait + ↑upper limb tone with cog-wheel rigidity. Blood pressure is 135/80 lying and 95/70 standing. What is the most likely diagnosis?

→ **Multiple system atrophy**

Corticobasal degeneration (a Parkinson-plus syndrome) characterised by:

- Dementia
- Asymmetric motor abnormalities, often initially affecting only one limb
- **Alien limb phenomenon:** involuntary but purposeful movement of the limb PLUS feeling that the affected limb does not belong to the patient and acts on its own.

Differential diagnoses of Parkinson-plus syndromes

Multiple system atrophy	Progressive supranuclear palsy	Corticobasal degeneration	Dementia with Lewy bodies
<ul style="list-style-type: none"> • Autonomic dysfunction with urogenital problems 	<ul style="list-style-type: none"> • Vertical gaze palsy • Frontal lobe disturbances 	<ul style="list-style-type: none"> • Asymmetric motor symptoms • Alien limb phenomenon 	<ul style="list-style-type: none"> • Lewy bodies • Visual hallucinations

Normal pressure hydrocephalus (NPH)

Normal pressure hydrocephalus

- ⇒ Classic triad of urinary incontinence, dementia, and gait apraxia.

Overview

- Normal pressure hydrocephalus is a **reversible cause of dementia** seen in elderly patients.

Mechanism

- It is thought to be secondary to **reduced CSF absorption at the arachnoid villi**.
- ↓ CSF absorption → CSF accumulation → enlargement of the ventricle

Causes

- Idiopathic (most common in adults > 60 years)
- May be secondary to head injury, subarachnoid haemorrhage or meningitis

Features: the triad of

1. urinary incontinence
2. dementia and bradyphrenia
3. gait abnormality (may be similar to Parkinson's disease)

Diagnosis

- **Imaging:** MRI (initial test), CT
 - ⇒ Ventriculomegaly without sulcal enlargement
 - ⇒ Hydrocephalus with an enlarged fourth ventricle
- **CSF tap test:** confirmatory test
 - ⇒ **Opening pressure is normal** or slightly elevated.
 - ⇒ Improvement of symptoms after CSF removal via lumbar puncture or shunt confirms NPH.
 - ⇒ Lumbar puncture is both diagnostic and therapeutic.

Management

- **the most likely helpful initial management steps is CSF drainage via repeated lumbar puncture**
- ventriculo-peritoneal shunting

What is the underlying cause of urinary incontinence in NPH?

- ⇒ **Inability to suppress voiding**

- NPH → compression of the periventricular white matter tracts → functional frontal lobe impairment → loss of central inhibition of the detrusor muscle → strong voiding reflex that cannot be suppressed (**urge incontinence**).

Delirium (Acute confusional state)

Definition

- Delirium: a syndrome of acute confusion characterized by fluctuations in awareness, cognition, and attention

Risk factors

- Age \geq 65 years
- Cognitive impairment (past or present) and/or dementia
- Current hip fracture
- Severe illness: affect up to 30% of all older patients admitted to hospital.

Causes

- **DELIRIUM:** Drugs, Electrolyte abnormalities, Lack of medication (withdrawal), Infection, Reduced sensorial input, Intracranial pathology, Urinary retention or fecal impaction, Myocardial and pulmonary disease
- Delirium is frequently a complication of dementia.

Features

- **Cognitive function:** e.g., worsened concentration, slow responses, confusion, memory disturbances (loss of short term $>$ long term).
- **Perception:** e.g., visual or auditory hallucinations.
- **Physical function:** e.g., reduced mobility, restlessness, agitation, sleep disturbance.
- **Social behaviour:** e.g., lack of cooperation with reasonable requests, withdrawal, mood change

Diagnosis

- The Confusion Assessment Method (**CAM**) is the most effective tool in identifying delirium.
- If there is difficulty distinguishing between the diagnoses of delirium, dementia or delirium superimposed on dementia, treat for delirium first.

Management

- Treatment of underlying cause
- Agitation should initially be managed with nonpharmacologic strategies, verbal and non-verbal techniques to de-escalate the situation (e.g., **modification of environment**).
- Medications should be reserved for refractory agitation.
 - ⇒ the 2019 NICE delirium guidelines recommend short-term **haloperidol** 0.5 mg (usually for \leq 1 week).
 - ⇒ Avoid antipsychotic drugs in Parkinson's disease or dementia with Lewy bodies
- If delirium does not resolve: Re-evaluate for underlying causes, assess for possible dementia

MRCPUK-part-1-January 2011 exam: An elderly patient admitted for UTI, became agitated and aggressive. What is the most appropriate management?

→ **Haloperidol 0.5 mg orally**

Dementia

Overview

- Dementia affect over 700,000 people in the UKT
- **DP43 is a protein that has recently been found to be involved in a multitude of neurodegenerative diseases** including **dementia** and motor neuron disease.

Common causes of dementia

- **Alzheimer's disease** (> 50% of dementia cases)
- Multi-infarct dementia due to **cerebrovascular disease** (20% of dementia cases)
- Lewy body dementia (c. 10-20%)

Rarer causes (5% of cases)

- Huntington's
- CJD
- Pick's disease (atrophy of frontal and temporal lobes)
- HIV (50% of AIDS patients)

Features

- Mini-mental state examination. A score of 24 or less out of 30 suggests dementia
- Short term memory impairment is the commonest clinical presentation of Alzheimer's disease.
- **The best way to test short term memory is to ask the patient to recall new information in the next few minutes.**
- Long term memory is usually intact.
- Usually patients are fully orientated in time, person and place.

Distinguishing between normal aging and dementia

- Memory impairment, occasional difficulties in word finding, and slower cognitive processing are normal effects of aging.
- An important distinguishing factor between normal aging and forms of dementia is the degree to which independence with everyday activities is impaired. In normal aging, **independence in daily activities** is preserved.
- cognitive exams are within normal limits in aging.
- Alzheimer's disease is often accompanied by behavioral changes (such as aggression, depression, insomnia)

Investigations

Neuroimaging is required to diagnose dementia

- **Exclude reversible secondary causes** e.g., hypothyroidism, FBC, U&E, LFTs, calcium, glucose, TFTs, vitamin B12 and folate levels.
- **Neuroimaging** to exclude other cerebral pathologies (e.g. Subdural haematoma, normal pressure hydrocephalus) and to help establish the subtype diagnosis.(CT could be used, but MRI is better)

- Single-photon emission computed tomography (**SPECT**) should be used to differentiate **Alzheimer's disease, vascular dementia and frontotemporal dementia if the diagnosis is in doubt.**
- Cerebrospinal fluid examination should be used if Creutzfeldt–Jakob disease or other forms of rapidly progressive dementia are suspected.

Vascular dementia

- Typically occurs in those with **widespread vascular disease. A history of strokes or the presence of focal neurological signs are very suggestive.**
- CT or MRI will show → multiple lacunar infarcts
- Does not respond to acetylcholinesterase inhibitors such as donepezil.
- Vascular dementia caused by lipohyalinosis or microatheroma formation and **NOT thromboemboli**. Therefore, anticoagulation is not indicated.
- **Memory therapy is the best next step in management for patient's confirmed vascular dementia.**

Presence of the e4 allele of apo-lipoprotein E → Alzheimer's disease

Loss of GABA is seen in → Parkinson's disease.

Peri-vascular mononuclear inflammation is seen in → multiple sclerosis.

Loss of Betz cells is seen in → motor neurone disease.

Alzheimer's disease (AD)

Overview

- Alzheimer's disease is a progressive degenerative disease of the brain and it is the common cause of dementia.
- Typically, first affects the temporal and parietal lobes
 - ⇒ **Temporal lobe** degeneration results in memory loss (misplaced keys, leaving the stove on) and language deficits (word-finding difficulties),
 - ⇒ **whereas parietal** lobe degeneration results in spatial navigation problems (getting lost during walks outside)
- The primary anatomical target of Alzheimer's disease is → the cerebral cortex
 - ⇒ Alzheimer's disease is a form of "**cortical**" type of dementia
 - ⇒ The "**sub-cortical**" type of dementia occurs in Huntington's disease, advanced Wilson's disease, and advanced multiple sclerosis

Genetics

- Most cases are sporadic
- Early-onset (before the age of 65) familial AD represents ~ 10% of all AD cases
- **Mutations in presenilin 1 (PSEN1)**
 - ⇒ **Linked to ~ 50% of familial AD cases**
 - ⇒ **earlier onset compared to AD due to mutations of other genes (median is ~ 43 years)**
- Amyloid precursor protein (APP) gene
 - ⇒ Linked to 10–15% of early-onset familial AD cases
 - ⇒ Since the APP gene is located on chromosome 21, individuals with **trisomy 21 have an increased risk of early-onset AD** (around age 50) due to **APP overexpression**

Pathological changes

- **Macroscopic:** widespread cerebral atrophy, particularly involving the cortex and **hippocampus**
- **Microscopic:** **cortical plaques** due to deposition of type **A-Beta-amyloid protein** and intraneuronal **neurofibrillary tangles** caused by abnormal aggregation of the tau protein
- **Biochemical:** there is a **deficit of acetylcholine** from damage to an ascending forebrain projection
 - ⇒ ↓**production of choline acetyl transferase** → ↓acetylcholine synthesis → ↓cortical cholinergic functioning

Features

- Short-term memory impairment (the most common presentation) of AD dementia (insidious onset, slow progression, episodic memory affected first)
- Language impairment
- Temporal and spatial disorientation (patients are usually not oriented to person, place, time, or events)
- Impairment of executive functions and judgment
- Behavioral changes (apathy, agitation, aggression, irritability)
- Mood disorders (e.g., symptoms of depression)

Investigations

- Screening for B12 deficiency and hypothyroidism
- **MRI or CT to rule out reversible causes of cognitive decline**
 - ⇒ MRI scan in Alzheimer → symmetrically **increased size of the lateral ventricles** along with **cerebral cortical atrophy** in a mainly frontal and parietal distribution.
 - ⇒ Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.
- **FDG-PET** (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable
- **Examining cerebrospinal fluid for:**
 - ⇒ total tau or total tau and phosphorylated-tau 181
 - ⇒ amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40.

Management

- **Non-pharmacological:** should always be attempted prior to resorting to pharmacologic treatment.
 - ⇒ **Memory therapy** for all dementias: involves improving cognitive abilities through image recognition, solving math problems, and past memory recall.
 - ⇒ **Behavioral and environmental regulation**, such as:
 - **adhering to a regular sleep schedule**
 - Maintaining a consistent environment will help orient the patient. Frequent travel has been shown to worsen the symptoms of Alzheimer's disease.
- **Mild to moderate** Alzheimer's disease: **acetylcholinesterase inhibitors** (donepezil, galantamine and rivastigmine)
 - ⇒ **A well-known side effect of rivastigmine is AV block**
 - ⇒ **NICE guidelines recommend discontinuation of cholinesterase inhibitors once the mini mental state examination has fallen below 12.**
 - ⇒ There is no role for cholinesterase inhibitors in advanced Alzheimer's disease.
 - NICE guidelines recommend discontinuation of cholinesterase inhibitors once the mini mental state examination has fallen **below 12**.

- The best option would be to withdraw donepezil and possibly consider memantine, which is licensed for use in moderate to severe dementia.
- ⇒ Side-effects of cholinesterase inhibitors
 - Bradycardia and, rarely, AV block
 - Bladder outflow obstruction
- Moderate to severe Alzheimer's: memantine (a NMDA receptor antagonist)
- Management of aggression in dementia
 - ⇒ 1st line: non-pharmacological: identify and avoid triggers + behavioural techniques.
 - ⇒ 2nd line: pharmacological:
 - Olanzapine or quetiapine for short-term
 - **Risperidone has been tested in this setting and is licensed for 6 weeks treatment of persistent aggression in those with moderate to severe Alzheimer's disease**
 - For patients with dementia with Lewy bodies (DLB), only **very low doses** of certain atypical neuroleptics (eg, quetiapine or clozapine) should be used due to high risk of severe side effects with neuroleptic medications.

Lewy body dementia (LBD)

Lewy body dementia: a triad of: Dementia, parkinsonism, and visual hallucinations

Epidemiology

- Second most common form of neurodegenerative dementia (10–20% of dementia cases)

Pathology

- **Macroscopic:** Cerebral atrophy, particularly of the frontal lobe. Relative sparing of the hippocampi
- **Microscopic:** Lewy bodies: alpha-synuclein-positive, hyaline cytoplasmic inclusions in neurons (mostly cortical) that cause neuronal degeneration. The characteristic pathological feature is **alpha-synuclein** cytoplasmic inclusions (**Lewy bodies**) in the substantia nigra, paralimbic and neocortical areas

Features

- Progressive cognitive impairment
- Parkinsonism
- **Visual hallucinations**
- Intermittent confusion
- Myoclonus
- **Marked sensitivity to neuroleptic treatment.**

Diagnosis

- usually clinical
- Single-photon emission computed tomography (SPECT) is increasingly used. The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%

Differential diagnosis: Parkinson's disease with dementia VS Lewy body dementia

- Lewy body dementia presents with signs similar to Parkinson's Disease, **but cognitive symptoms precede the motor symptoms.**
 - ⇒ Lewy body dementia if the onset of both cognitive and motor symptoms is within 1 year
 - ⇒ Dementia secondary to Parkinson disease if cognitive symptoms occur > 1 year after the onset of motor symptoms

Treatment

Haloperidol is contra-indicated in Lewy body dementia

- The treatment of choice is **rivastigmine**, which improves both the visual hallucinations, and cognitive impairment.
- Neuroleptics should be avoided in Lewy body dementia**, as patients are extremely sensitive and may develop irreversible parkinsonism.
 - ⇒ Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent
 - The most appropriate therapeutic strategy with respect to maintaining his mobility is → **Stop dopamine-blocking drugs (causing significant parkinsonism)** eg: quetiapine

MRCPUK-part-1-September 2018 exam: A 78-year-old man with memory impairment, hallucinations, resting tremor, festinating gait and an expressionless face. He scores 12 / 30 on the mini-mental state examination (MMSE). Which test is most likely to confirm the diagnosis?

→ **SPECT scan (Lewy body dementia)**

MRCPUK-part-1-September 2017 exam: H/O parkinsonian symptoms + agitation. deteriorated after prescribing haloperidol. What is the most likely underlying diagnosis?

→ **Lewy body dementia**

Frontotemporal lobar degeneration (FTLD)**Overview**

- Heterogeneous group of syndromes that involve degeneration of the frontal, insular, and/or temporal cortices
- FTD is sometimes still referred to as Pick disease
- The third most common type of cortical dementia after Alzheimer's and Lewy body dementia.
- Age of onset: typically younger than in Alzheimer disease

Pathology

- Generally associated with pathological intracellular inclusion bodies (Pick bodies) that are caused by mutations in **tau** (main protein component of Pick bodies) or progranulin (precursor of granulin, which regulates cell growth) proteins.

The inclusions found histologically in frontotemporal dementia, or Pick's disease are hyperphosphorylated tau proteins.

Features

- Onset before 65
- Insidious onset
- **Personality change and social conduct problems** (apathy, disinhibited behavior)
- Relatively **preserved memory and visuospatial skills**
- Changes in cognitive functioning: Aphasia
- CT/MRI: atrophy of the frontal and/or temporal lobes

Types: There are three recognised types of FTLD

- **Frontotemporal dementia (Pick's disease)**
 - ⇒ This is the most common type of frontotemporal dementia
 - ⇒ characterised by personality change and impaired social conduct.
- **Progressive non-fluent aphasia (chronic progressive aphasia, CPA)**
 - ⇒ Here the chief factor is non-fluent speech. They make short utterances that are agrammatic.
 - ⇒ Comprehension is relatively preserved.
- **Semantic dementia**
 - ⇒ Here the patient has a fluent progressive aphasia. The speech is fluent but empty and conveys little meaning.
 - ⇒ Unlike in Alzheimer's memory is better for recent rather than remote events.

Patients with FTD display changes of personality and social behavior, but their memory generally remains intact.

Treatment

- No curative treatment.
- Dementia: Cholinesterase inhibitors and memantine are usually not effective
- Agitation, hallucinations, insomnia: Atypical antipsychotics

Creutzfeldt-Jakob disease (CJD)

Rapidly progressive dementia and myoclonic jerks are the hallmarks of Creutzfeldt-Jakob disease.

Definition

- Creutzfeldt-Jakob disease (CJD) is **rapidly progressive** neurological condition caused by prions that are resistant to degradation by proteases due to misfolding into beta-pleated sheets. **prion** is an **incorrectly folded protein** that causes misfolding of other proteins.

Epidemiology

- CJD is the most common prion disease in humans.

Causes and types

- Sporadic (~ 85%): no identifiable cause
- Familial (~ 10–15%): various mutations in the PRNP gene
- Acquired (< 1%)
 - ⇒ **Iatrogenic CJD**: transmission during medical procedures (e.g., via organ transplantation, blood transfusion)

- ⇒ **Variant CJD (vCJD):** by ingestion of beef infected with bovine spongiform encephalopathy (BSE)
 - BSE is a transmissible prion disease occurring in cattle. Infection leads to vCJD in humans.)

Pathophysiology

- Conversion of normal cellular prion proteins with alpha-helical structure (PrP^c) to prions that demonstrate an increase in beta-pleated sheet structure (PrP^{Sc}) (insoluble, misfolded prions resistant to proteases) → PrP^{Sc} accumulation → plaque formation → neuronal cell death → progression to spongiform encephalopathy

What is the agent responsible for variant Creutzfeldt-Jakob disease (CJD)?

→ Proteinaceous infectious particle (prion protein)

Features

- Rapidly progressing dementia (weeks to months)
- **Myoclonus**
- Cerebellar disturbances (e.g., gait instability, ataxia)
- Pyramidal weakness
- Behavioural abnormality
- Akinetic mutism.

Investigation

- **CSF analysis :** ↑ 14-3-3 protein → useful in confirming a diagnosis of sporadic CJD.
- **MRI:** shows high-signal abnormalities (**hyperintense signals**) in caudate nucleus and putamen or at least 2 cortical regions (temporal-parietal-occipital)
- **EEG:**
 - ⇒ **biphasic, high amplitude sharp waves** (only in sporadic CJD)
 - ⇒ EEG is usually normal in new variant CJD.
- **Brain biopsy**
 - ⇒ Diagnosis can only be confirmed by biopsy'autopsy
 - ⇒ Microscopic findings include spongiform degeneration , **amyloid plaques (vCJD)**

Types

Form	Features
Sporadic caused by (Unknown cause)	<ul style="list-style-type: none"> • Account for 85% of cases • Occur at middle-age (mean age of onset is 65 years) • Median duration of disease is 5 months
Genetic caused by (Mutation in PRNP gene)	<ul style="list-style-type: none"> • Can occur at younger ages • Family history can be negative • Dementia usually occur late in the course of the disease • Often no detectable 14-3-3 protein in CSF • Median duration of disease is several years
Iatrogenic caused by (Transmission of prion protein by invasive medical treatment)	<ul style="list-style-type: none"> • Similar as sporadic form
Variant caused by (Ingestion of contaminated products with bovine spongiform encephalopathy)	<ul style="list-style-type: none"> • Occurs at a young age (median age 25 years) • Psychological symptoms such as anxiety, withdrawal and dysphonia are the most common initial presenting features • Ataxia, myoclonus appear late (6 months after psychological symptoms) • EEG is usually normal • MRI brain typically shows bilateral pulvinar (posterior thalamic nuclei) high signals. • Median duration of disease is 13 months

The rapidly progressive neurological impairment, with myoclonus and hyper-reflexia coupled with EEG abnormality and MRI changes in the caudate and putamen, is most consistent with **sporadic CJD**.

Treatment

- No curative therapy available
- Symptomatic treatment and eventually palliative care

Prognosis

Following disease manifestation, most individuals with sporadic CJD die within 12 months, usually from complications such as pneumonia.

Transient global amnesia

Definition

- Transient loss of memory function

Pathophysiology

- Aetiology is unknown, thought to be due to transient ischaemia to the thalamus (in particular the amygdala and hippocampus)

Risk factors

- Usually affects people over the age of 50
- Psychological and physical stress

Diagnostic criteria

- **Abrupt onset** of amnesia (anterograde or partial retrograde)
- Patients may appear anxious and **repeatedly ask the same question**
- Episodes last between 1–24 h, but never > 24 h
- Patients are usually disoriented in time and place, but not usually person.
- **Normal perception**, preserved personal identity
- Absence of other cognitive or neurological impairments.
- Patients have no recall of events after the attack

Investigations

- If the diagnosis is clear, further diagnostic procedures are not necessary.
- If the diagnosis is uncertain:
 - ⇒ MRI: evidence of typical focal, hyperintense lesions in the hippocampus
 - ⇒ EEG: exclude differential diagnoses (e.g., epileptic amnesia attacks)

Differential diagnosis

- Epilepsy can present with discreet episodes of amnesia. This syndrome is called **transient epileptic amnesia**. Features that suggest epilepsy are:
 - ⇒ shorter duration (should be less than 1 hour)
 - ⇒ multiple attacks
 - ⇒ onset on waking from sleep
 - ⇒ accompanying epileptic features - e.g. motor automatism, stereotyped behaviour, limb shaking.

Management

- No treatment is needed except observation until recovery.
- Most patients recover within 24 hours and do not get further such episodes.
- Imaging is considered if amnesia does not resolve after 24 hours.

Transient global amnesia

- **The best line of management → Admit for observation**

Prognosis

- Resolves spontaneously within 24 h
- Recurrence is unusual.

Restless legs syndrome (RLS)

Restless leg syndrome - management includes dopamine agonists such as ropinirole

Definition

- Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia.

Epidemiology

- It is extremely common, affecting between 2-10% of the general population.

- Males and females are equally affected and a family history may be present

Pathophysiology

- Studies suggest that abnormal dopamine pathways in the brain and impaired iron homeostasis (leading to iron deficiency in the substantia nigra) are the most prominent pathophysiological mechanisms involved.

Features

- Uncontrollable urge to move legs (akathisia).
 - initially occur at night but as condition progresses may occur during the day.
 - movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)
 - Begins and/or worsened with rest**
 - Typically relieved by movement**
- Paraesthesiae e.g. 'crawling' or 'throbbing' sensations

Investigations

- Iron studies (best initial test)**
- Polysomnogram: quantification of periodic limb movements of sleep (PLMS)

Causes

- Primary (common): idiopathic, but is familial in up to 77% of cases
- Secondary
 - Chronic conditions
 - Iron deficiency** with or without anaemia, vitamin deficiency
 - Drugs : H1 antihistamines, Antidepressants, Dopamine antagonists (neuroleptics, metoclopramide, MDMA), Lithium, Beta blockers
 - Pregnancy

A low serum ferritin is most likely to be a cause of secondary restless legs syndrome

Diagnosis criteria

- Exclude iron deficiency anaemia
- The international restless legs syndrome study group four basic criteria for diagnosing RLS:
 - A desire to move the limbs, often associated with paraesthesiae or dysaesthesiae
 - Symptoms that are worse or present only during rest and are partially or temporarily relieved by activity
 - Motor restlessness, and
 - Nocturnal worsening of symptoms.

Management

- Lifestyle changes (e.g. avoid stimulants in the evening such as caffeine, tobacco and alcohol), regular daily exercise (but avoid exercising close to bedtime)
- Simple measures: walking, stretching, massaging affected limbs
- Treat the underline cause: **Treat any iron deficiency**
- 1st line:** pregabalin, gabapentin **or** dopamine agonist (e.g. **ropinirole**, pramipexole and rotigotine skin patch)

Essential tremor

Essential tremor is an AD condition that is made worse when arms are outstretched, made better by alcohol and propranolol

Causes

- positive family history (50–70%; **autosomal dominant inheritance**) or sporadic; benign form

Epidemiology

- Most common form of tremor
- Bimodal distribution: teens and 6th decade of life (common in elderly patients)

Features

- Mostly bilateral postural tremor with a frequency of 5–10 Hz
- Postural tremor: worse if arms outstretched
- Localization: hands (~ 90%), head (~ 30%; "yes-yes" or "no-no" motion), voice (~ 15%)
- Most common cause of titubation (head tremor)
- Worse with sustained voluntary movement, stress or anxiety.
- Improved by alcohol and rest

Diagnostics: usually a clinical diagnosis of exclusion

Consider an essential tremor in a patient presenting with chronic bilateral hand tremors without further neurological deficits and positive family history.

Management

- propranolol is first-line**
- primidone (a barbiturate) is sometimes used
- In drug-resistant cases
 - ⇒ Deep brain stimulation (DBS)
 - ⇒ Thalamotomy

MRCPUK-part-1-January 2019 exam: H/O involuntary movements of the head, worse on movement and during stress and relieved by alcohol and sleep. What is the most likely diagnosis? **Essential tremor** (Essential tremor is the most common cause of titubation (head tremor).

MRCPUK-part-1-January 2020 exam: H/O tremor of the arms, which is worse when arms are outstretched. His father suffered from a similar complaint. What is the most suitable first-line treatment? **Propranolol**

Holmes tremor

Holmes tremor → lesion in the red nucleus

Overview

- Holmes tremor or rubral tremor is caused by a lesion in the red nucleus.

Causes

- Previous stroke of the red nucleus (the most common cause), head trauma, and demyelinating diseases.

Pathophysiology

- It is assumed that a double lesion is required to develop HT, including the dopaminergic nigrostriatal system and the cerebello-thalamo-cortical or dentate-rubro-olivary pathways

Features

- **Irregular low frequency (< 4.5 Hz) tremor**, mostly of the upper extremities and affecting both proximal and distal muscles.
- It **presents at rest** and is **aggravated by positioning and movement (combination of resting, postural and action tremor)**.
- Signs of ataxia and weakness can occur.

Differential diagnosis: Holmes tremor VS Parkinson

- In contrast to Holmes tremor, Parkinsonian resting tremor (4-6 Hz) improves with voluntary activity and involves distal muscles.

Treatment

- Initial medical therapy: levodopa
- For refractory cases: thalamotomy or chronic thalamic stimulation

Friedreich's ataxia

Friedreich's ataxia: most common cause of death → heart failure due to hypertrophic cardiomyopathy

Pathophysiology

- **Autosomal recessive, trinucleotide repeat disorder**
- **Trinucleotide repeat expansion** (of the nucleotide triplet GAA) in the **FXN gene** on **chromosome 9**; → deficiency of frataxin (an iron-binding protein) → intramitochondrial accumulation of iron and ; mitochondrial dysfunction → oxidative damage and degeneration of CNS and PNS
- Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in **not demonstrating the phenomenon of anticipation**.

Epidemiology

- The most common early-onset hereditary ataxias.
- Peak incidence: 10–15 years

Features

- **Neurological**
 - ⇒ Gait ataxia: due to damage to the **spinocerebellar tracts** (**often a presenting feature**)
 - ⇒ Impaired **proprioception** and **vibration** sense due to damage to the **dorsal columns**
 - ⇒ **Loss of deep tendon reflexes** due to degeneration of the **dorsal root ganglia**
 - **Absent ankle jerks/extensor plantars**
 - ⇒ Spastic paralysis due to degeneration of the **lateral corticospinal tract**
 - ⇒ Nystagmus, dysarthria and dysphagia
 - ⇒ Sensory-motor peripheral neuropathy
- **Other features**
 - ⇒ Hypertrophic obstructive cardiomyopathy (90%, **most common cause of death**)
 - ⇒ **Diabetes mellitus** (10-20%)
 - ⇒ Bilateral **pes cavus** (high-arched palate)
 - ⇒ Kyphoscoliosis

Diagnosis

- Definitive diagnosis → Genetic testing for **expansion of the GAA triplet repeat** in the **FXN gene**
- MRI brain and spinal cord: cervical spine atrophy (minimal cerebellar atrophy)
- Nerve conduction studies
 - ⇒ Sensory: absent or reduced sensory nerve action potentials (SNAP)
 - ⇒ Motor: normal until advanced stages

Friedreich's ataxia VS Ataxic-telangiectasia

Friedreich's ataxia versus Ataxia-telangiectasia		
	Friedreich's ataxia	Ataxia-telangiectasia
Epidemiology	The most common autosomal recessive ataxia in children	The second most common autosomal recessive ataxia in children, after Friedreich's ataxia
Affected chromosome	Chromosome 9	Chromosome 11
Affected gene	FXN gene	ATM gene
Age of presentation	Late childhood (10-15 years old)	Early childhood (1 – 5 years old)
Similarities	<ul style="list-style-type: none"> ▪ Autosomal recessive ▪ cerebellar ataxia ▪ onset in childhood 	<ul style="list-style-type: none"> ▪ Autosomal recessive ▪ Cerebellar ataxia ▪ Onset in childhood
Associations	Kyphoscoliosis and pes cavus (high-arched palate)	Immunodeficiency & risk of developing malignancy
Cause of death	Hypertrophic cardiomyopathy (HCM)	Bronchiectasis or malignancy
Average life expectancy	37 years	25 years

Ataxic telangiectasia

The 4 A's of ataxia telangiectasia: **ATM gene, Ataxia, spider Angiomas, and IgA deficiency.**

Overview

- Autosomal recessive disorder
- Caused by a defect in the **ATM gene** which encodes for **DNA repair enzymes**.
- It is one of the inherited combined immunodeficiency disorders.
- It typically presents in early childhood with abnormal movements, oculomotor apraxia and choreoathetosis developing later.

Features

- Cerebellar ataxia
- Telangiectasia (spider angiomas)
- **IgA deficiency** resulting in recurrent chest infections → **bronchiectasis**
- Increased risk of malignancy (10%), lymphoma or leukaemia, gastric carcinoma

Diagnosis

- Elevated **serum alpha-fetoprotein**, at least two standard deviations above the normal range, is diagnostic of ataxia-telangiectasia
- Confirmed by the identification of mutations on the ATM gene.

Prognosis

- Death in the late teens or 3rd decade from **bronchiectasis** is typical.

Avoid x-ray exposure because of high sensitivity to radiation and increased risk of malignancy.

Sleep

Sleep Stage	Description	EEG Waveform
	<ul style="list-style-type: none"> • Awake and alert • Awake and eyes closed 	<ul style="list-style-type: none"> • Beta • Alpha • Theta
Stage N1	• Light sleep	
Stage N2	• Deeper sleep	<ul style="list-style-type: none"> • Sleep spindles and K complexes
Stage N3	<ul style="list-style-type: none"> • Deepest non-REM sleep • Sleep walking • Night terrors • Bed wetting 	<ul style="list-style-type: none"> • Delta
REM	• Dreaming	<ul style="list-style-type: none"> • Beta

- **REM Sleep:**
 - ⇒ **Physiology**
 - rapid eye movement
 - same EEG pattern as when awake
 - erection
 - ↑ and variable pulse and blood pressure
 - loss of muscle tone
 - ⇒ **Timing**
 - occurs every 90 min
 - duration ↑ with every cycle
 - amount of REM sleep ↓ with age
 - ⇒ Acetylcholine is the principle neurotransmitter
 - ⇒ Norepinephrine, serotonin, and histamine suppress REM sleep
 - therefore, certain antidepressants (eg, SSRI, SNRI) can pharmacologically suppress REM sleep

Sleep paralysis

Overview

- Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep.
- It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye movement) sleep.
- Mechanism is believed to involve a dysfunction in REM sleep.
- Males and females are affected equally.

Feature

- **aware but unable to move.**
- may include: hallucinations, fear.
- **feeling of suffocation may present** (although the respiratory muscles are only ever mildly affected in comparison with the limbs).
- Episodes generally last less than a couple of minutes.

Associations

- May occur in those who are otherwise healthy
- Narcolepsy
- Familial
- Can be triggered by sleep deprivation, psychological stress, or abnormal sleep cycles

Treatment

- reassured that the condition is common and not serious.
- Other options that may be tried including sleep hygiene, cognitive behavioral therapy, and antidepressants.
- if troublesome clonazepam may be used

Narcolepsy

Definition

- Daily periods of excessive daytime sleepiness for ≥ 3 months

Pathophysiology

- Narcolepsy type 1: Loss of **lateral hypothalamic** neurons, which produce hypocretin-1 and hypocretin-2 (i.e. orexin A and orexin B) → severe hypocretin (orexin) deficiency → dysregulation of sleep-wake cycles
 - ⇒ Orexin (Hypocretin) is a neuropeptide that is released to increase the activity of brain regions involved in wakefulness, including the raphe nuclei and tuberomammillary nucleus and locus coeruleus.
- Narcolepsy type 2: Idiopathic

Features

- **Triad of:**
 1. **Sleep paralysis**
 2. **Excessive daytime somnolence and**
 3. **Cataplexy.** About 5% of patients with narcolepsy have cataplexy.
- Sleep hallucinations
 - ⇒ hypnagogic hallucinations: just before sleep
 - ⇒ hypnopompic hallucinations: just before awakening

Hypnagogic hallucinations occur while going to sleep.

Diagnosis

- Diagnosis is a clinical one, supported by an **overnight polysomnogram** and **multi sleep latency test**.
- Lumbar puncture: decreased CSF hypocretin-1 (orexin A) levels due to a loss of orexinergic neurons in the lateral hypothalamus

Treatment

- Non-amphetamine-based stimulants, such **modafinil**, are the treatment of choice.

Cataplexy

- Cataplexy describes the sudden and transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened).
- Features range from buckling knees to collapse.
- Longer episodes can be associated with hallucinations.
- Around two-thirds of patients with narcolepsy have cataplexy.

Head injury

CT head immediately (within the one hour)

- GCS < 13 on initial assessment
- **GCS < 15 at 2 hours post-injury**
- suspected open or depressed skull fracture.
- any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- post-traumatic seizure.
- focal neurological deficit.
- more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- age 65 years or older
- any history of bleeding or clotting disorders
- dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs)
- more than 30 minutes' retrograde amnesia of events immediately before the head injury
- **If a patient is on warfarin perform a CT head scan within 8 hours of the injury regardless of whether he have risk factors for an intracranial injury.**

Head injury: types of traumatic brain injury

Type of injury	Notes
Extradural (epidural) haematoma	<ul style="list-style-type: none"> ⌚ Bleeding into the space between the dura mater and the skull. ⌚ Often results from acceleration-deceleration trauma or a blow to the side of the head. ⌚ The majority of epidural haematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery. <p>Features</p> <p>Epidural haematoma - lucid interval</p> <ul style="list-style-type: none"> ⌚ features of raised intracranial pressure ⌚ lucid interval (apparent recovery from the initial concussion, but deterioration is usually within 15-30 minutes).
Subdural haematoma	<ul style="list-style-type: none"> ⌚ Bleeding into the outermost meningeal layer. ⌚ Most commonly occur around the frontal and parietal lobes. ⌚ Risk factors include old age, alcoholism and anticoagulation. ⌚ Slower onset of symptoms than epidural haematoma.
Subarachnoid haemorrhage	<ul style="list-style-type: none"> ⌚ Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury

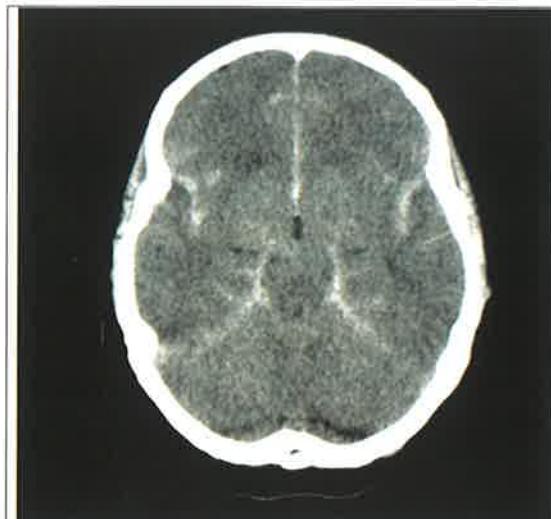
Comparison of Intracranial Haemorrhage

Feature	Subarachnoid	Subdural	Extradural
Location	The inner most layer around the brain tissue	Between the dura mater and arachnoid mater	The outermost layer, between the skull and dura mater
Mechanism	Usually due to rupture of a blood vessel (e.g. berry aneurysm or AVM). Pain typically felt at the back of the head	Usually due to trauma causing damage to one of the bridging veins . Trauma may be minor and could be many months ago. Can be acute or chronic.	Due to direct moderate / severe head trauma. Typically around the eye, causing fracture of the temporal or parietal bone, resulting in laceration of the middle meningeal artery and/or vein
Pain	Sudden onset, painful	Possible dull headache	Likely, and often severe, but not sudden onset
Consciousness	May become impaired quickly – if so, a very bad prognostic indicator	Fluctuates, often over weeks or even months	Classically, an initial lucid period, followed by impaired consciousness
Neurological signs	May be present; are a poor prognostic indicator	Often insidious. May involve memory impairment, epilepsy , drowsiness, dizziness . Often occur weeks / months after injury	Typically after a lucid period , severe headache, impaired consciousness. Vomiting, seizures, drowsiness, confusion , and later, coma .
Investigations	CT – should show irregular shaped bleed. If absent, and still suspicious, do LP to confirm (blood in CSF, CSF turn yellow when left to stand – xanthochromia)	CT / MRI – classically shows a crescent of blood around the brain tissue, and midline shift	CT / MRI – described as a lens Shaped lesion – meaning it is biconvex . LP is contraindicated! X-ray may show skull fracture
Management	If few symptoms, surgical clipping of platinum coiling of aneurysm, or if AVM then balloon therapy and stenting are beneficial. Give Nimodipine to reduce risk of vasospasm (and ↑ survival) as long as BP can be maintained.	Burr hole or craniotomy	Surgery to evacuate blood and ligate bleeding vessels

Which vessel is involved?

subdural haematomas	Bridging veins
subarachnoid haemorrhage	anterior and posterior communicating arteries
extradural haematoma	middle meningeal artery

Acute extradural and subdural haematomas would both be high attenuation and anatomically located next to the skull - **extradural haematomas have a convex border whilst subdural haematomas have a concave border.**

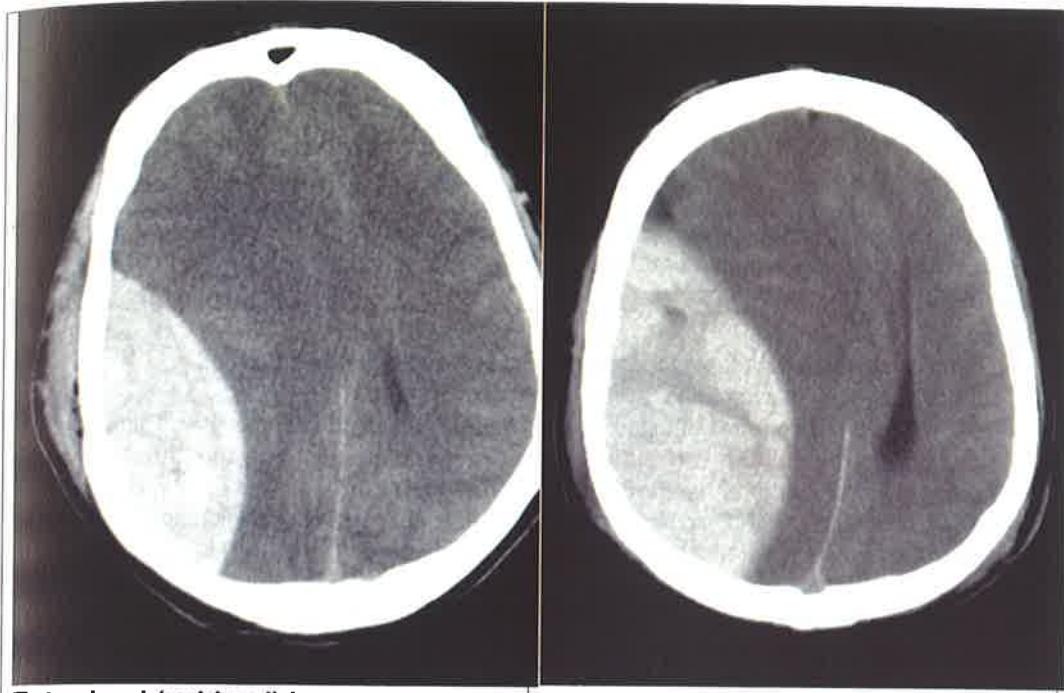
**Subarachnoid haemorrhage**

CT image shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the inter-hemispheric fissure.

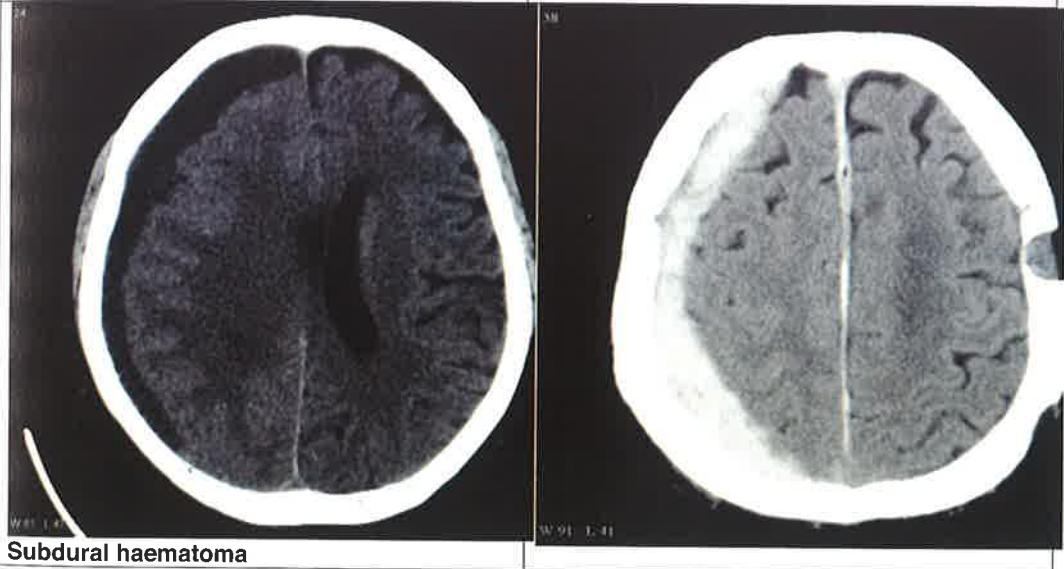
This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.

Post-concussion syndrome :features

- headache and neck discomfort
- changes in memory
- Poor concentration span and Subjects are easily distracted.
- dizziness
- irritability
- depression or anxiety
- sleep disturbance
- **Anxiety is common**



Extradural (epidural) haematoma:



Subdural haematoma

Subdural haemorrhage

Fluctuating consciousness = subdural haemorrhage

The history of progressive 'confusion' and unsteadiness for some weeks followed by an acute exacerbation is a typical presentation of a subdural haematoma in the elderly population.

Basics

- most commonly secondary to trauma e.g. old person/alcohol falling over
- initial injury may be minor and is often forgotten
- caused by bleeding from damaged bridging veins between cortex and venous sinuses
- **The phrase 'fluctuating conscious level' is common in questions and should always bring to mind subdural haemorrhage**
- The combination of falls, alcohol excess, fluctuating episodes of confusion and focal neurology points towards a diagnosis of subdural haemorrhage.

Features

- headache (The most common presenting symptom , seen in up to 80% of patients)
- classically fluctuating conscious level
- raised ICP → bilateral papilloedema
- **Other common symptoms** are:
 - ⇒ Fatigue
 - ⇒ memory impairment
 - ⇒ confusion
 - ⇒ nausea and vomiting
 - ⇒ impaired vision
 - ⇒ seizures
 - ⇒ Hemiparesis, or paralysis is also possible.

Treatment

- needs neurosurgical review ? burr hole

Acute subdural haematoma

- usually results from acute head trauma
- The haematoma accumulates between the surface of the brain and the dura mater.
- The mortality rate ranges between 50% and 90%.
- A good outcome is most likely if surgical evacuation of the haematoma is prompt and secondary brain injury is prevented.
- Mortality is less likely in:
 - ⇒ younger adults
 - ⇒ patients with a GCS score above 6 or 7
 - ⇒ those with pupil reactivity, and
 - ⇒ those without cerebral contusions or uncontrolled rises in intracranial pressure.

Subarachnoid haemorrhage (SAH)

Overview

- **Vascular malformations and aneurysms typically bleed in the subarachnoid space.**

Causes

- 85% are due to rupture of berry aneurysms
 - ⇒ conditions associated with berry aneurysms include:
 - **adult polycystic kidney disease,**
 - Ehlers-Danlos syndrome and
 - coarctation of the aorta
 - ⇒ occur most frequently in the anterior half of the circle of Willis.
 - ⇒ The most common site of aneurysm rupture causing SAH is at the junction of the anterior communicating artery and anterior cerebral artery.
- AV malformations
- trauma
- tumours

Features

- headache
 - ⇒ sudden onset.
 - ⇒ typically described as the worst headache experienced.
- Meningism :
 - ⇒ neck stiffness,
 - ⇒ photophobia,
 - ⇒ nausea and vomiting,
 - ⇒ meningeal stretch signs (e.g., Kernig's sign and Brudzinski's sign)

Hunt and Hess scale: grades SAH: Severity and mortality increase with grade:

1. grade-1: Asymptomatic or minimal headache & slight neck stiffness
2. grade-2: Moderate or severe headache with neck stiffness, but no neurological deficit other than cranial nerve palsy
3. **grade-3: Drowsiness with confusion or mild focal neurology**
4. grade-4: Stupor with moderate to severe hemiparesis or mild decerebrate rigidity
5. grade-5: Deeply comatose with severe decerebrate rigidity.

Complications

- rebleeding (in 30%)
- obstructive hydrocephalus (due to blood in ventricles)
- **vasospasm leading to cerebral ischaemia**
 - ⇒ Cerebral ischemia may be delayed as a result of **delayed cerebral ischaemia (DCI)** or cerebral vasospasm.
 - ⇒ **It is the most common cause of death and disability following aneurysmal (SAH).**
 - ⇒ It may lead to death or permanent neurologic deficits in over 17-40% patients following SAH.
 - ⇒ The clinical diagnosis of DCI is made when the patient experiences an altered level of consciousness or a **new focal neurologic deficit following an initial bleed.**

- ⇒ Typically, the development of **DCI starts on day 3 after the initial SAH** and is maximal at days 5-14, resolving on day 21.
- ⇒ This can cause serious morbidity or death in up to 30% of patients with SAH.
- ⇒ Treatment for DCI includes prophylactic administration of nimodipine and current neurointensive care.

Investigations

- If SAH is suspected, obtain a head CT without contrast.
- If CT is \ominus , LP is mandatory.

- Non-contrast CT-scan:
 - ⇒ **the most appropriate initial investigation**
 - ⇒ negative in 5%
- **Lumbar puncture (LP):**
 - ⇒ **done after 12 hrs (allowing time for xanthochromia to develop)**
 - (presence of oxidized RBCs)
 - ⇒ (LP) is not usually required unless the history is suggestive, and the **CT is normal**.
 - ⇒ **CSF examination with spectrophotometry for haemoglobin breakdown products**, particularly CSF bilirubin, which proves the presence of prior recent bleeding.
 - This is now recommended instead of measuring the CSF red cell count or xanthochromia, as the procedure of lumbar puncture itself can introduce red cells into the CSF sample and thus give an uninterpretable result.
 - (spectrophotometry remains positive for 2 weeks with 100% sensitivity, sensitivity drops thereafter).
- **CT cerebral angiography**
 - ⇒ If CT image shows blood in the subarachnoid space, the most appropriate next investigation is → **CT cerebral angiography**
 - ⇒ to look for an underlying aneurysm or vascular malformation which may be amenable to neurosurgical intervention.

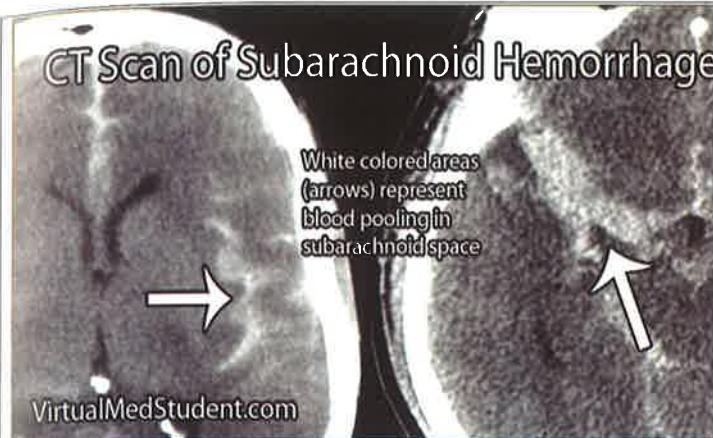
Intracranial hemorrhage ECG changes:

- Deep symmetrical T- wave inversion
- Prolonged QT interval

Management

- Neurosurgical opinion
 - ⇒ no clear evidence over early surgical intervention against delayed intervention
- Nimodipine (a calcium channel blocker)
 - ⇒ SAH → cerebral vasospasm (in 30% of patients) → result in further ischemia due to a reduction in distal blood flow.
 - ⇒ All patients are prescribed a calcium channel blocker (eg Nimodipine) to prophylactically prevent this.
 - ⇒ **reduces cerebral vasospasm** (hence maintaining cerebral perfusion) → reduce the incidence and severity of neurological deficits.
 - post-operative nimodipine (e.g. 60mg / 4 hrly, if BP allows) has been shown to reduce the severity of neurological deficits but doesn't reduce rebleeding

What is the most appropriate minimum interval between neurological observations in the first instance? Answer → 30 min



Conditions associated with berry aneurysms that can MAKE an SAH more likely:

Marfan's syndrome
Aortic coarctation
Kidney disease
 (autosomal dominant, polycystic)
Ehlers-Danlos syndrome
Sickle cell anemia
Atherosclerosis
History (familial)

Brain stem herniation

The sudden onset of headache, ataxia and vomiting suggest → an intracranial haemorrhage, which leads to → mass effect and → subsequent **brain stem herniation**.

- Brain herniation often causes false localising signs due to compression of various areas of the brain.
- it usually follows two patterns:
 1. **uncal herniation** : presented with:
 - **third nerve paresis**
 - ❖ (ipsilateral dilated pupil, abnormal external ocular movements, including nystagmus)
 - ❖ The third nerve paresis occurs due to compression of the parasympathetic fibres around the third nerve, which results in unopposed sympathetic response.
 - **contralateral hemiparesis**
 - ❖ which can lead to ipsilateral hemiparesis.
 - ❖ Contralateral hemiparesis occurs with compression of the cerebral peduncle.
 - ❖ Ipsilateral hemiparesis and third nerve palsy occur late when the lateral translation is so great that it compresses the contralateral third nerve and peduncle.
 2. **Central herniation**: presents with:
 - confusion and drowsiness,
 - followed by impaired vertical gaze,
 - small pupils,
 - impaired oculocephalic reflexes
 - Bilateral corticospinal tract signs including increased tone and Babinski signs.

- signs of raised intracranial pressure:
 - ❖ bradycardia,
 - ❖ hypertension,
 - ❖ irregular breathing (Cushing response)
 - ❖ and a sixth-nerve palsy.
- The sixth nerve is usually the first to be compressed due to its long extracerebral intracranial course.
- Diplopia from either a third or sixth nerve palsy can cause nystagmus.
- Treatment
 - ⇒ immediate intensive care support, with intubation and hyperventilation.
 - ⇒ The case should be discussed urgently with neurosurgeons, and their advice sought regarding the possibility of operative intervention.
 - ⇒ Intravenous mannitol and other hyperosmolar solutions are often indicated, and should be considered.

Brain stem death tests include:

- Pupillary light response - CN II and III
- Corneal reflex, response to supraorbital pressure - CN V and VII
- Vestibulo-ocular reflex - CN III and VIII
- Gag reflex - CN IX and X
- **Cough reflex - CN X**
- Absence of respiratory effort.

Encephalitis

Causes

- **Direct invasion** by a neurotoxic virus (encephalitis).
 - ⇒ most commonly caused by enteral viruses, herpes simplex virus (HSV) 1 and 2, varicella, cytomegalovirus (CMV), and Epstein-Barr virus (EBV).
 - ⇒ occasionally caused by respiratory viruses, human herpes virus 6 (HHV6), rubella, or mumps.
- **Post-infectious** encephalopathy: delayed brain swelling because of an immunological response to the antigen, i.e. a neuroimmunological response.
 - ⇒ **caused by measles** or varicella zoster (cerebellar ataxia).
- **Slow virus infection**, for example, human immunodeficiency virus (HIV) or subacute sclerosing panencephalitis (SSPE).
- **limbic encephalitis**
 - ⇒ In 60% of cases, limbic encephalitis is a **paraneoplastic disorder** and indicates the presence of an underlying cancer; **the most common underlying malignancy is small cell lung carcinoma (SCLC)**, followed by testicular cancer, thymoma, and Hodgkin's lymphoma.
 - Among patients with SCLC, the **anti-Hu antibody is present in about 50%** of those with predominant or isolated symptoms of limbic encephalitis
 - ⇒ In contrast to patients with other paraneoplastic neurologic syndromes, in whom magnetic resonance imaging (MRI) is of limited usefulness in helping to establish the diagnosis, patients with limbic encephalitis may present with early MRI changes suggestive of the disorder.⁵
 - ⇒ Typically, the MRI shows hyperintense abnormalities in the medial aspect of the temporal lobes.⁶
 - These MRI abnormalities should be differentiated from those in patients with herpes simplex encephalitis, in whom the MRI usually shows signs of

oedema, mass effect, contrast enhancement, and, sometimes, areas of haemorrhage.

Differential diagnosis of acute/subacute encephalopathy is etiologically wide and includes:

- Neurodegenerative (for example sporadic Creutzfeldt-Jakob disease [CJD])
- Endocrine (hypothyroidism)
- Toxicological (lead, arsenic poisoning)
- Nutritional (vitamin B1 deficiency)
- Infective (HSV, HIV), and
- Autoimmune causes.

Paraneoplastic neurological syndromes

- uncommon but important because they frequently present before the malignancy, and because they cause severe neurological disability.
 - ⇒ **Limbic encephalitis**
 - ⇒ Cerebellar degeneration
 - ⇒ Opsoclonus-myoclonus
 - ⇒ Sensory neuronopathy
 - ⇒ Lambert-Eaton myasthenic syndrome
 - ⇒ Myasthenia gravis
 - ⇒ Dermatomyositis, and
 - ⇒ Polymyositis.
- Most paraneoplastic syndromes respond poorly to immunomodulatory treatment although occasional improvement is seen when the underlying tumour is treated.

Herpes simplex encephalitis (HSE)

HSE: behavioral changes and CT head showing temporal lobe changes

Overview

- Herpes simplex (HSV) encephalitis is a common topic in the exam.
- The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe **temporal lobe signs** e.g. aphasia.
- **Temporal lobe involvement is common (limbic encephalitis), in particular the anterior temporal lobes. These abnormalities are visible on CT or MRI.**
- Winter is the peak incidence.
- It has peaks of presentation in the young and old.

Types

- Both herpes simplex virus type 1 and type 2 can cause encephalitis:
 - ⇒ **Herpes simplex type 1** is the virus associated with encephalitis in older children and adults.
 - HSV-1 responsible for 95% of cases in adults
 - typically affects temporal and inferior frontal lobes
 - ⇒ **Herpes simplex type 2** is characterised by generalised brain involvement, but is almost exclusively seen in neonates who acquire the virus during delivery.

Herpes simplex encephalitis presents with:

- Behavioural changes or psychiatric disturbance
- Focal seizures
- Fever and
- Alteration in consciousness.

Features

- fever, headache, **psychiatric symptoms, seizures**, vomiting
- focal features e.g. aphasia
- peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis

Investigation

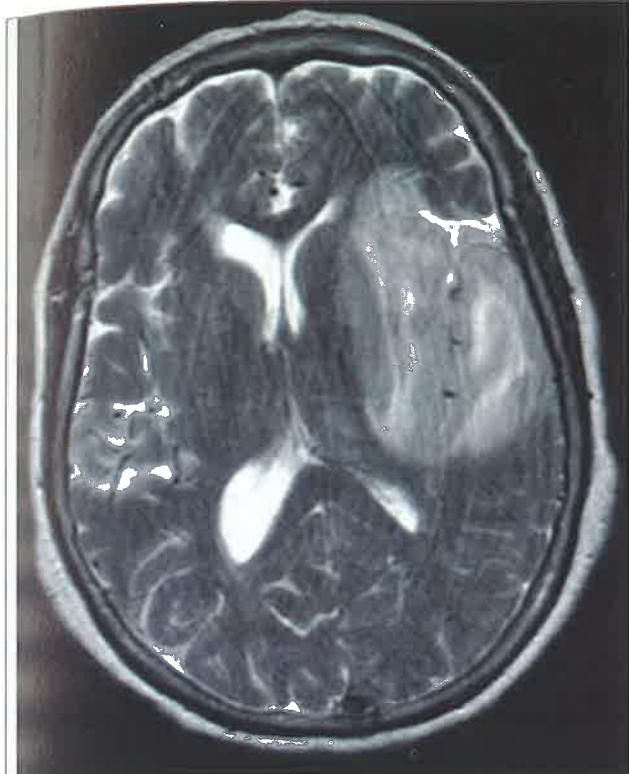
- CSF: **lymphocytosis**, elevated protein, mildly raised red cells and a normal or low glucose.
- **PCR for HSV on (CSF) is a highly specific test.**
- **MRI brain is the investigation of choice** initially, which should demonstrate temporal lobe changes, although often CT only is available out of hours.
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) - normal in one-third of patients
 - ⇒ CT scan of the brain may be normal, but MRI may reveal the diagnosis.
- **EEG pattern: lateralised periodic discharges at 2 Hz**

Treatment

- intravenous aciclovir
 - ⇒ Immediate treatment is required on clinical suspicion - do not wait
 - ⇒ continued until CSF PCR is negative, or for at least 14 days.
 - ⇒ **Intravenous fluids and aciclovir is the best option here.**

Prognosis

- The prognosis is dependent on whether aciclovir is commenced early.
 - ⇒ If treatment is started promptly the mortality is 10-20%.
 - ⇒ Left untreated the mortality approaches 80%



MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

MRCPUK-part-1-January 2012: H/O Confusion, headache and fever + seizure. MRI shows patchy haemorrhagic changes in the temporal lobe. Given the likely diagnosis, what is the treatment of choice?

→ **Supportive treatment + intravenous acyclovir.** (Δ Herpes simplex encephalitis)

HIV: neurocomplications

Focal neurological lesions

Toxoplasmosis

HIV - multiple ring enhancing lesions = toxoplasmosis

- the **most common** neurological infection seen in HIV,
- occurring in up to 10% of patients
- accounts for around **50%** of cerebral lesions in patients with HIV
- occurring at CD4 counts of less than 100 cells/mm³.
- constitutional **symptoms**, headache, confusion, drowsiness
- **CT:** usually single or multiple ring enhancing lesions, mass effect may be seen
- **management:** sulfadiazine and pyrimethamine



Cerebral toxoplasmosis; CT scan with contrast showing multiple ring enhancing lesions



Cerebral toxoplasmosis; MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

The differential diagnosis of ring-enhancing lesions on CT in a patient with AIDS include:

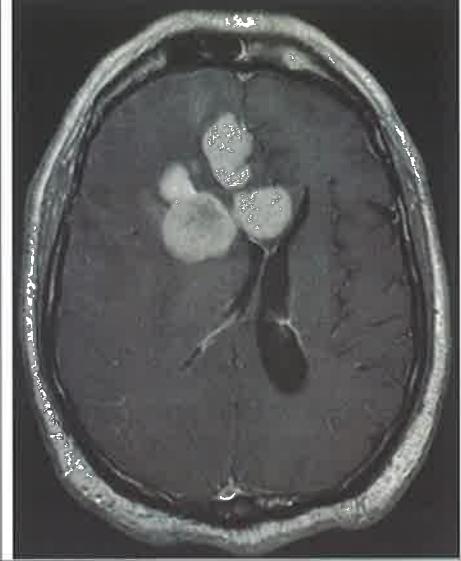
- Cerebral toxoplasmosis
- Abscesses
- Metastases
- Atypical CNS lymphoma.

Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. The table below gives some general differences.

Condition	CT finding
Toxoplasmosis	<ul style="list-style-type: none"> ▪ Multiple lesions ▪ Ring or nodular enhancement ▪ Thallium SPECT negative
Lymphoma	<ul style="list-style-type: none"> ▪ Single lesion ▪ Solid (homogenous) enhancement ▪ Thallium SPECT positive
Tuberculosis	single enhancing lesion
Encephalitis	oedematous brain
Cryptococcus	meningeal enhancement, cerebral oedema
Progressive multifocal leukoencephalopathy (PML)	single or multiple lesions, no mass effect, don't usually enhance
AIDS dementia complex	cortical and subcortical atrophy

Given the more limited availability of SPECT compared to CT many patients are treated empirically on the basis of **scoring systems**, for example there is a 90% likelihood of toxoplasmosis if all of the following criteria are met:

- toxoplasmosis IgG in the serum
- CD4 < 100 and not receiving prophylaxis for toxoplasmosis

- multiple ring enhancing lesions on CT or MRI

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

Generalised neurological disease

Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

Cryptococcus

- most common fungal infection of CNS
- typically there is a sub-acute onset of symptoms and the disease is associated with raised intracranial pressure (leading to the papilloedema and the falsely localising 6th nerve palsy).
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion
- raised intracranial pressure (ICP) is thought to be caused by the yeast cells and fungal polysaccharides forming microscopic plugs and blocking CSF resorption in the subarachnoid villi.
- management**
 - The best management would be intravenous anti-fungal agents, such as amphotericin B and flucytosine.
 - Therapeutic lumbar puncture is also advocated to reduce ICP.
 - Anti-retroviral (ARV) therapy should not be started immediately, as there is a very high risk of the patient developing IRIS (immune reconstitution inflammatory syndrome). Instead, ARVs should be delayed for several weeks or months after initiating treatment.

Progressive multifocal leukoencephalopathy (PML)

Overview

- widespread demyelination
- rare and fatal opportunistic infection of the central nervous system caused by **(JC) virus**.
 - (JC) virus is a papovavirus (polyoma DNA virus) found latent in most healthy adults.

Risk factors

- seen in advanced HIV/AIDS**
 - With CD4 counts of less than 100 this virus becomes active leading to progressive neurological deterioration.
- Natalizumab has a black-box warning of increased risk of developing (PML),**
- Three risk factors have been clearly identified in patients with multiple sclerosis which predispose them to the future developing PML:
 - positive anti-JC viral serum antibodies,
 - prior use of immunosuppressants, and
 - increased duration of **natalizumab treatment** and its number of infusions (25-49 infusions).

Features

- subacute onset:
- Behavioural changes, speech, motor, visual impairment
- Ataxia
- Head tremor
- Focal neurology progressing over a period of months to paresis and even coma.

Diagnosis

- CT: single or multiple lesions, **no mass effect, don't usually enhance**.
- MRI is better - **high-signal demyelinating white matter lesions are seen**
- It can be diagnosed via **CSF PCR for the JC virus**.
- **Brain biopsy**
 - ⇒ **the definitive diagnostic test**
 - ⇒ (showing asymmetric foci of demyelination and intranuclear inclusions containing the JC virus).

Treatment

- There is no effective treatment, but progression can be slowed by initiation of antiretroviral therapy.

AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy
- progresses over a longer time period than progressive multifocal leukoencephalopathy (PML).
- **Differential diagnosis**
 - ⇒ Patients with **cryptococcal meningitis** present with headache, fever, vomiting and few neurological signs.
 - ⇒ **PML** can present at any CD4 count with ataxia, behavioural changes and focal neurological signs, often progressing over a period of months to paresis or even coma.
 - ⇒ **Toxoplasmosis** presents with headache, fever and seizures. It has a typical CT head scan with ring enhancing lesions.

January 2019 exam: H/O HIV positive, admitted following a seizure + headaches, night sweats and poor appetite. CD4=89 u/l. CT head =Single homogenously-enhancing lesion in the right parietal lobe . What is the most likely diagnosis?

→ Primary CNS lymphoma

January 2016 exam: HIV positive, admitted with confusion, drowsiness and headache. temperature is 37.2°C. CT brain (with contrast): Multiple hypodense regions predominantly in the basal ganglia which show ring enhancement. Minimal surrounding oedema. No mass effect. What is the most likely diagnosis?

→ Cerebral toxoplasmosis (HIV - multiple ring enhancing lesions = toxoplasmosis)

Motor neuron disease (MND)

Progressive motor weakness and pseudo-bulbar palsy + normal sensations + normal brain imaging → always think of amyotrophic lateral sclerosis.

Electromyography is the best investigation to carry out next.

Overview

- The primary defect is in the anterior horn cells

Epidemiology

- Sex: ♂ > ♀
- Rarely presents before 40 years

Types

1. Amyotrophic lateral sclerosis (50% of patients)

- Lower motor neuron (LMN) signs in arms and upper motor neuron (UMN) in legs
 - anterior motor horn degeneration leads to lower motor neuron signs.
 - lateral corticospinal tract degeneration leads to upper motor neuron signs.
- Causes
 - unknown in 90 % (sporadic)
 - inherited (10%)
 - polygenic inheritance
 - A defect on chromosome 21, which codes for superoxide dismutase 1 (SOD1), is associated with about 20% of familial cases of ALS, or about 2% of ALS cases overall.

2. Primary lateral sclerosis

- UMN signs only

3. Progressive muscular atrophy

- LMN signs only
- affects distal muscles before proximal
- carries best prognosis

4. Progressive bulbar palsy

- Accounts for ~ 0.2% of all motor neuron diseases
- Age: 75–80 years
- palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
- carries worst prognosis
- Most common cause of death is respiratory complications secondary to recurrent aspiration(e.g., pneumonia).

Features

• Clues, which point towards a diagnosis of motor neuron disease:

- fasciculation
- Absence of sensory signs/symptoms
- Lower motor neuron signs in arms and upper motor neuron signs in legs
- Wasting of the small hand muscles/tibialis anterior is common

- Other features
 - ⇒ Asymmetric limb weakness
 - ⇒ Dysarthria, dysphagia, and tongue atrophy
 - ⇒ **20% of patients present with bulbar onset (late feature and suggests a poor prognosis).**
 - ⇒ Pseudobulbar palsy
 - ⇒ **Onuf nucleus** (of spinal cord segments S1-S4) is preserved, thus **the bladder and rectal sphincters remain normal** through the course of the disease.
 - ⇒ Abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature
 - ⇒ **Fronto-temporal dementia** (10 %)
 - ⇒ **Respiratory involvement** (present in up to **50%** of MND cases at presentation).
 - Bilateral **diaphragmatic weakness causing orthopnea and exertional dyspnoea**
 - Respiratory failure is the commonest cause of death in this condition.
- Features **NOT compatible with MND**
 - ⇒ Sensory impairment. **Note it may be present due to concomitant diabetic peripheral neuropathy.**
 - ⇒ Optic atrophy
 - ⇒ External ocular muscles palsy
 - ⇒ Cerebellar signs
 - ⇒ Bladder dysfunction.

Diagnosis

- **Electromyography** shows: Denervation: indicated, e.g., by fibrillations
 - ⇒ reduced number of action potentials
 - ⇒ increased amplitude.
- Nerve conduction studies: **usually normal**, to **exclude** a neuropathy.
- MRI: to **exclude** the differential diagnosis of cervical cord compression and myelopathy
- Creatine kinase → increased
- Nerve conduction studies: usually normal

Management

Motor neuron disease - treatment: NIV is better than riluzole

Motor neuron disease - riluzole

- **Riluzole** (glutamate antagonist)
 - ⇒ prevents stimulation of glutamate receptors → **decreasing presynaptic glutamate release** (thereby limiting cytotoxic effects of this neurotransmitter)
 - ⇒ prolongs life by about **3 months**
 - ⇒ Common side effects: nausea, asthenia, abdominal pain, dizziness, asymptomatic elevation in liver enzymes.
 - ⇒ Rare life-threatening side effects: **pancreatitis**, hepatitis, and neutropenia

- **Respiratory care**
⇒ Non-Invasive Ventilation (NIV) (usually BIPAP) is used at night
 - **have the greatest effect on survival** → survival benefit of around **7 months**
- **Radiologically inserted gastrostomy feeding** (in case of dysphagia)

Prognosis

- Poor: Median survival time from onset of symptoms is three to five years.
- Poor prognostic factors include: low forced vital capacity (FVC) and older age.

Bulbar VS Pseudobulbar palsy**Comparison of bulbar and pseudobulbar palsy**

Pseudobulbar Palsy	Bulbar Palsy
⌚ Bilateral damage or injury of corticobulbar tracts to nerve nuclei of cranial nerves V, VII, IX, X, XI, and XII	⌚ Bilateral damage or injury of the nerve nuclei of cranial nerves IX, X, XI, and XII
⌚ Upper motor neuron palsy of the respective muscles	⌚ Lower motor neuron palsy of the respective muscles
Lower motor neurone signs absent	Lower motor neurone signs present
Spastic tongue (no wasting/fasciculations)	Wasted tongue, fasciculations
Spastic dysarthria	Nasal speech
Labile emotions	Normal emotions
Facial expressions: absent	Facial expression: normal
Gag reflex: brisk (exaggerated)	Gag reflex: absent
Jaw jerk: exaggerated	Jaw jerk: normal

Multiple sclerosis (MS)

Multiple sclerosis' diagnosis that requires demyelinating lesions that are separated in space and time

Definition

- Demyelinating CNS condition clinically defined by 2 episodes of neurological dysfunction (brain, spinal cord, or optic nerves) that are separated in space and time.

Pathophysiology

- Pathophysiology of MS is characterized by autoimmune inflammation, demyelination, and axonal degeneration.
- Exact cause remains unknown
- Most commonly accepted theory: Activation of autoreactive T-lymphocytes → inflammatory processes → focal demyelination with partial preservation of axons (acute plaques) → loss of axons and atrophy of oligodendrocytes (chronic plaques) → gliosis → inadequate remyelination
- Genetic susceptibility → **Associated with HLA-DR2**
- Environmental risk factors → **Low vitamin D levels**, smoking , EBV, HHV 6
- Most common sites of demyelination in MS

- ⇒ Periventricular areas
- ⇒ Brainstem
- ⇒ Cerebellum
- ⇒ Spinal cord

Epidemiology

- Sex: ♀ > ♂ (2:1) (MS is more common in women)
- Age of onset: 20–40 years of age
- Ethnicity: ↑ prevalence among the white population

Classification and clinical course

- Relapsing-remitting MS (90%, the most common clinical course)
 - ⇒ Lesions developed at different times and in different anatomical locations
 - ⇒ Symptoms remit almost completely between exacerbations
- Primary progressive MS (10%):
 - ⇒ Progressive neurological deterioration over 1 year or more
 - ⇒ Continuous worsening of symptoms from the first onset of the disease
- Secondary progressive MS : Continuous worsening of symptoms in between exacerbations

Features

- Non-specific features: eg: lethargy (75%). .
- Optic neuritis
 - ⇒ Most often the earliest manifestation
 - ⇒ Typically unilateral
 - ⇒ Can be painful
 - ⇒ Impaired vision and color blindness
 - ⇒ Relative afferent pupillary defect (Marcus Gunn pupil)
 - ⇒ Any patient with isolated optic neuritis → refer to a neurologist for further assessment
 - ⇒ The cumulative probability of developing MS by 15 years after onset of optic neuritis is 50%
- Internuclear ophthalmoplegia (INO)
 - ⇒ Result from a lesion in the medial longitudinal fasciculus (MLF)
 - ⇒ Ipsilateral medial rectus weakness but an intact convergence reflex
 - ⇒ Disconjugate, lateral gaze nystagmus in the contralateral eye
 - ⇒ More frequently bilateral than unilateral
- Demyelination of spinal cord tracts
 - ⇒ Lhermitte sign: a shooting electric sensation that travels down the spine upon flexion of the neck
 - ⇒ Pyramidal tract lesion: upper motor neuron weakness (spasticity, hyperreflexia, positive Babinski sign)
 - ⇒ Involvement of the dorsal spinal column
 - Loss of vibration and fine-touch sensation
 - Numbness, paresthesias
 - Sensory ataxia usually involving the trunk or one or more limbs
 - ⇒ Neuropathic pain
- Cerebellar involvement: Charcot neurological triad
 - ⇒ Scanning speech
 - ⇒ Nystagmus
 - ⇒ Intention tremors

- **Cranial nerve palsies** (diplopia, trigeminal sensory neuralgia, facial palsy)
- Autonomic dysfunction (bowel and bladder neurogenic disorders, impaired sexual function)
- **Uhthoff's phenomenon:** a reversible exacerbation of neurological symptoms following an increase in body temperature, e.g., physical exertion, a warm bath, or fever (**worsening of vision following rise in body temperature**)

Uhthoff phenomenon triggered by a viral infection may mimic an exacerbation of MS.

Fundoscopy is normal in 60% of cases of optic neuritis. Neither the patient nor the doctor are able to see anything.

Multiple sclerosis (MS): presentation

- Loss or reduction of vision in 1 eye with painful eye movements
- Double vision
- Ascending sensory disturbance and/or weakness
- Problems with balance, unsteadiness or clumsiness
- Altered sensation travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's symptom).

Investigations

- **Plain MRI** (brain and spine): **investigation of choice**
 - ⇒ Multiple sclerotic plaques (**most commonly seen in periventricular white matter**); related to demyelination and reactive gliosis
 - ⇒ Contrast MRI (with gadolinium): enhancement of active lesion during and up to 6 weeks after the exacerbation
- **Visual evoked potentials (VEPs)**
 - ⇒ **Highly sensitive for detecting demyelination of the optic nerve** and central visual pathways
 - ⇒ **May demonstrate abnormality when the MRI is normal**, because the optic nerves are often involved early and may be asymptomatic
- **Lumbar puncture**
 - ⇒ Lymphocytic pleocytosis
 - ⇒ Oligoclonal bands (\uparrow production of IgG subfractions): the presence of multiple oligoclonal bands in CSF and their absence in the blood is highly suggestive of MS.
 - **The appearance of oligoclonal bands in the early stages of the disease indicates a poor prognosis**
 - ⇒ \uparrow myelin basic protein

Diagnostic criteria (Revised McDonald criteria 2017): used to diagnose MS based on the dissemination of the CNS lesions in time and space.

- **Dissemination in time (DIT):** appearance of new lesions over time
 - ⇒ Criterion met (≥ 2 exacerbations) occurring at least 30 days apart
 - ⇒ Criterion not met (1 exacerbation) → diagnosis requires confirmation of DIT by **one of the following:**
 - An additional exacerbation

- MRI that demonstrates the presence of both gadolinium-enhancing and nonenhancing lesions at any time or a new hyperintense T2 or enhancing lesion on follow-up MRI
- Oligoclonal bands in the CSF
- **Dissemination in space (DIS) on MRI :** presence of lesions in different regions of the CNS
 - ⇒ Criterion met (≥ 2 lesions with objective clinical evidence) of the 4 MS-typical regions of CNS (periventricular, juxtacortical, infratentorial, or spinal cord).
 - ⇒ Criterion not met (1 lesion with objective clinical evidence) → diagnosis requires confirmation of DIS by one of the following:
 - An additional exacerbation with presence of one more lesion with objective clinical evidence involving a different CNS region
 - Presence on MRI of ≥ 1 T2-hyperintense lesion in at least 2 of the following regions: periventricular, juxtacortical, infratentorial, spinal

If the MRI of the brain is inconclusive, what is the most appropriate next investigation?

⇒ **MRI spinal cord**

- Small ischaemic lesions in the brain may be difficult to distinguish from demyelination.
- Spinal cord lesions are more specific than brain for inflammatory disorders such as MS rather than ischaemic lesions. Thus, **cord imaging is useful when there is diagnostic difficulty.**

Management

• **Treatment of acute exacerbations**

- ⇒ First line: high-dose glucocorticoid therapy for 3–5 days
 - Oral methylprednisolone 0.5 g daily for 5 days (If not admitted to hospital)
 - IV methylprednisolone 1 g daily for 3–5 days (if oral steroids have failed or not tolerated or need admission to hospital)
 - **Steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)**
- ⇒ Second line: plasmapheresis

• **Disease-modifying MS therapy** (prevention of future attacks)

⇒ **Beta-interferon**

- **Action:** Suppresses T cell activity → ↓ proinflammatory cytokines and ↓ lymphocyte invasion of the CNS
- **Indication:** Criteria from the Association of British Neurologists (ABN) for commencing beta-interferon therapy:
 1. Has had more than two separate episodes within the last two years
 2. Is more than 18-years-old, and
 3. Can walk more than 100 metres.
- **Benefits:** Reduces number of relapses by one third (30%) and MRI changes, however, doesn't reduce overall disability
- **When to stop it?: Stop beta interferon if three or more relapses occurred per year** (as the objective behind using them is to reduce relapse frequency).
- **Side effects**
 - ⇒ Flu-like symptoms
 - ⇒ Liver dysfunction
 - ⇒ Thrombotic microangiopathy

- ☞ Depression
- ☞ **Risk of thyroid disease** (both, hyper- and hypothyroidism) **during the first year only, Keep thyroid function tests under review**
- **Contraindications**
 - ☞ History of severe clinical depression
 - ☞ Uncontrolled epilepsy
 - ☞ **Hepatic dysfunction**
 - ☞ Myelosuppression.
- ⇒ **Glatiramer acetate:**
 - Action:
 - ☞ Immunomodulating drug, acts as a decoy for T cells instead of neuronal myelin
 - ☞ Decreases activity of proinflammatory Th1 lymphocytes
 - **Safe in pregnancy**
 - **Save in liver dysfunction**
 - Side effects: Chest pain, Lipoatrophy
- ⇒ **Natalizumab:**
 - **Action:** An antibody against Alpha-4 Beta-1-integrin (decreases lymphocyte invasion of the CNS) → inhibits the migration of leucocytes into the CNS, hence reducing inflammation and demyelination.
 - **Side effects: Risk of progressive multifocal leukoencephalopathy (PML) in patients with (latent) JC virus infection**
 - ☞ MRI scan is recommended before starting treatment
 - ☞ Testing for serum anti-JCV antibodies before starting natalizumab is recommended and should be repeated every 6 months.
 - Commenced as monthly IV infusions
- ⇒ **Alemtuzumab**
 - **Action:** Anti-CD52 antibody.
 - **Side effects:** Secondary, B-cell mediated autoimmune phenomena (e.g., formation of autoantibodies, ITP, glomerulonephritis)
- ⇒ **Ocrelizumab**
 - **Action:** An antibody against CD20 that depletes premature and mature B-cells.
 - **Side effects:**
 - ☞ Hepatitis B virus reactivation
 - ☞ Immune suppression
- ⇒ **Fingolimod:**
 - **Action:**
 - ☞ sphingosine-1-phosphate analog that decreases lymphocyte invasion of the CNS (**sphingosine 1-phosphate receptor modulator**)
 - ☞ prevents lymphocytes from leaving lymph nodes. It is an immunomodulator, which sequesters lymphocytes in lymph nodes.
 - **Reduce the rate of relapses in relapsing-remitting MS by over half.**
 - **Side effects**
 - ☞ increased incidence of varicella zoster, tumour formation and progressive multifocal leukoencephalopathy (PML)
 - **Reserved for patients who fail 1st line therapies.**
 - **An oral formulation is available**

- **Symptomatic treatments**

- ⇒ **Spasticity** → **Baclofen** and gabapentin are first-line.
- ⇒ **Oscillopsia** (loss of natural image stabilization)
 - Consider **gabapentin** as a first-line
 - Consider **memantine** as the second-line
- ⇒ **Bladder dysfunction**
 - May take the form of urgency, incontinence, overflow etc
 - Guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
 - ❖ if significant residual volume → intermittent self-catheterisation
 - ❖ if no significant residual volume → anticholinergics may improve urinary frequency
- ⇒ **MS-related fatigue**
 - Usually described as physical exhaustion that is unrelated to the amount of activity performed.
 - Seen in 78% of patients.
 - Often aggravated by heat and humidity.
 - Offer **amantadine** to treat **fatigue in people with MS**.
 - Consider mindfulness-based training, cognitive behavioural therapy
 - Exercises including yoga may be helpful.

Multiple sclerosis in pregnancy

⇒ Only glatiramer acetate is thought to be safe in pregnancy.

Modifiable risk factors for relapse or progression of MS

- Exercise may have beneficial effects on MS
- Live vaccinations may be contraindicated in people with MS who are being treated with disease-modifying therapies.
- Flu-vaccination: possible benefits and possible risk of relapse after flu vaccination.
- **Pregnancy**
 - ⇒ Decreased relapse rate of MS during pregnancy
 - ⇒ Increased relapse rate in the postpartum period (3–6 months after childbirth)
 - ⇒ The long-term clinical course of MS remains unchanged.

Prognostic features

- **Good prognosis features**
 - ⇒ female sex
 - ⇒ young age of onset
 - ⇒ relapsing-remitting disease
 - ⇒ sensory symptoms
 - ⇒ long interval between first two relapses
- **Ways of remembering prognostic features**
 - ⇒ the typical patient carries a better prognosis than an atypical presentation

The episode of poor co-ordination followed a few months later by unilateral optic neuritis raises the possibility of a demyelinating disease. An MRI and LP are next steps confirming the diagnosis.

Internuclear ophthalmoplegia (INO)

Internuclear ophthalmoplegia (INO)

- Impaired adduction of the eye ipsilateral to the lesion and Nystagmus on the Opposite side.
- When covering one eye, unilateral movements will be normal. But when together, the adducting eye will not move past the midline.

Definition

- **Damage to the medial longitudinal fasciculus** (the connection between the abducens nucleus, **CN VI**, on one side and the oculomotor nucleus, **CN III**, on the other), which leads to impaired lateral gaze.
- Manifests primarily with impaired adduction of the eye ipsilateral to the lesion (ipsilateral to the medial longitudinal fasciculus lesion)

Causes

- Multiple sclerosis (MS): **characteristic of MS**, typically bilateral
- Tumour of the brainstem (eg: glioma)
- Brainstem vascular lesions
- Wernicke's encephalopathy.

Pathophysiology

- Normally, CN VI receives a signal from the ipsilateral paramedian pontine reticular formation and sends a signal to the contralateral CN III via the medial longitudinal fasciculus.
- Activation of the CN VI ipsilateral to the lesion → activation of the ipsilateral lateral rectus → abduction of the ipsilateral eye
- Activation of the CN III contralateral to the lesion → activation of the contralateral medial rectus → adduction of the contralateral eye
- Disruption of the medial longitudinal fasciculus fibers linking the **CN VI** ipsilateral and the **CN III** contralateral to the lesion → failure of signal transmission from CN VI to CN III → the ipsilateral lateral rectus is activated while the contralateral medial rectus is not → abduction of the ipsilateral eye, no adduction of contralateral eye
- Firing from CN VI which fails to be transmitted to CN III is instead partially transmitted to the lateral rectus ipsilateral to the lesion → nystagmus of the ipsilateral abducting eye

Clinical findings

- Adduction limited in horizontal eye movements
- Adduction is retained in convergence reaction
- The patient may complain of horizontal diplopia.
- Dissociated nystagmus: gaze to the opposite side → nystagmus of the abducted contralateral eye

INO - Internuclear Ophthalmoplegia

Patient looks to the left...



Right eye does not adduct past the midline

Patient looks to the right...



Left Eye does not adduct past the midline

Chronic progressive external ophthalmoplegia (CPEO)

Overview

- Patients with CPEO typically develop a slowly progressive paresis of extraocular muscles along with bilateral ptosis in the fourth decade of life
- Often associated with **mitochondrial disease** (inherited only from the mother)
- Most common manifestation of mitochondrial myopathy (in two-thirds of all cases).

Diagnosis

- ↑ Lactate in serum and cerebrospinal fluid
- Muscle biopsy → accumulation of enlarged mitochondria "**red ragged fibers**"
- PCR → mutation of mitochondrial DNA.

Differential diagnosis

- Other causes external ophthalmoplegia must be ruled out, like Graves' disease, myasthenia gravis and glioma
- Kearns-Sayre syndrome: combination of CPEO with pigmentary retinopathy and onset before age 20 (Ophthalmoplegia + retinitis pigmentosa + AV block)

Treatments

- no specific treatment currently, surgery can be used to correct ptosis

Ptosis, Miosis and Mydriasis

Ptosis + dilated pupil → Third nerve palsy

Ptosis + constricted pupil → Horner's

Ptosis

- Causes of bilateral ptosis:

- ⇒ Myotonic dystrophy
- ⇒ Myasthenia gravis (ptosis is much less common in Lambert-Eaton syndrome than myasthenia gravis)
- ⇒ Syphilis
- ⇒ Congenital

- Causes of unilateral ptosis, as above plus:

- ⇒ Third nerve palsy
- ⇒ Horner's

Miosis

- Causes of miosis (small pupil)

- ⇒ Horner's syndrome
- ⇒ Argyll-Robertson pupil
- ⇒ senile miosis
- ⇒ pontine haemorrhage
- ⇒ congenital
- ⇒ Drugs causes
 - Opiates
 - parasympathomimetics: pilocarpine
 - organophosphate toxicity

Mydriasis

- Causes of dilated pupils include:

- ⇒ Holmes-Adie (myotonic) pupil
- ⇒ Third nerve palsy
- ⇒ Drugs, and Poisons (atropine, CO, ethylene glycol).

Horner's syndrome

Horner's syndrome : triad of ptosis, miosis and anhydrosis

Horner's syndrome: anhydrosis determines site of lesion:

- Head, arm, trunk → central lesion : stroke, syringomyelia
- Just face → pre-ganglionic lesion : Pancoast, cervical rib
- Absent → post-ganglionic lesion : carotid artery

Overview

- Horner's syndrome develops following disruption of the sympathetic chain.
- Sweat glands are controlled by the sympathetic nervous system, for example, anhydrosis in Horner's syndrome.

Features

- Miosis (small pupil)
- Ptosis
- Anhydrosis (loss of sweating one side)
- Enophthalmos (sunken eye): in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos
- Facial flushing due to vasodilatation

Types: there are three separate forms of Horner's syndrome, depending on what level the sympathetic fibres are affected at:

- **First-order sympathetic fibres**
 - ⇒ Originate in the hypothalamus and descend through the brainstem to their synapse with the preganglionic sympathetic fibres at C8-T2.
 - ⇒ Caused by: strokes, multiple sclerosis and basal meningitis.
- **Second-order (preganglionic) fibres**
 - ⇒ Leave the cord at T1 and ascend in the sympathetic chain over the lung apex. They synapse in the superior cervical ganglion at the level of C3-C4, at the bifurcation of the common carotid artery.
 - ⇒ Caused by: apical lung tumours, lymphadenopathy and lower brachial plexus trauma.
- **Third-order (postganglionic) fibres**
 - ⇒ Pass along the **internal carotid artery**, with branches passing to the blood vessels and sweat glands of the face. They pass through the cavernous sinus and superior orbital fissure, where they joint the long ciliary nerves to supply the iris dilator and Muller's muscle.
 - ⇒ Caused by: **internal carotid artery dissection** or herpes zoster infection.

Because the sympathetic plexus accompanying the internal carotid artery innervates sweat glands only to the medial forehead, facial anhydrosis is only partial when Horner's syndrome is caused postganglionic lesions.

Distinguishing between causes

- **Heterochromia (difference in iris colour)** is seen in congenital Horner's
- Anhydrosis: see the table below

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the face	No anhydrosis
<ul style="list-style-type: none"> ⌚ Stroke ⌚ Syringomyelia ⌚ Multiple sclerosis ⌚ Tumour ⌚ Encephalitis 	<ul style="list-style-type: none"> ⌚ Pancoast's tumour ⌚ Thyroidectomy ⌚ Trauma ⌚ Cervical rib 	<ul style="list-style-type: none"> ⌚ Carotid artery dissection ⌚ Carotid aneurysm ⌚ Cavernous sinus thrombosis ⌚ Cluster headache

Orbital apex syndrome

- The combination of optic neuropathy, proptosis, chemosis, Horner syndrome, ophthalmoplegia and involvement of the first branch of the trigeminal nerve is typical of orbital apex syndrome
- The presence of proptosis, with swelling of eyelids and chemosis (swelling of the ocular surface membranes), indicates significant mass extension within the orbit
- The orbital apex syndrome (involvement of cranial nerves II, III, IV and V1) is a superior orbital fissure syndrome with loss of vision

Myasthenia gravis (MG)**Overview**

- Myasthenia gravis is an autoimmune disorder caused by autoantibodies directed against acetylcholine receptors (AChR).
- More common in women (2:1)
- **Associated conditions**
 - ⇒ Other autoimmune diseases: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
 - ⇒ Thymic hyperplasia (50-70%)
 - ⇒ Thymoma (15%)

Feature

- **Extraocular muscle weakness:** Ptosis, **Diplopia**, Blurred vision (**most common initial symptom**)
- **Bulbar muscle weakness**
 - ⇒ Slurred speech
 - ⇒ Difficulty chewing and/or swallowing: (dysphagia that is **worse with liquids than solids** in contrast to achalasia which typically affects solids more than liquids, or solids and liquids equally)
- **Muscle fatigability** (**the key feature**)
 - ⇒ Symptoms worsen with **increased muscle use** throughout the day and **improve with rest**.
- **Proximal muscle weakness**
 - ⇒ Rising from a chair
 - ⇒ Climbing stairs
 - ⇒ Brushing hair
 - ⇒ Deep tendon reflexes are not affected.
- **Respiratory muscle weakness:** causes dyspnea

Exacerbating factors

- **Exertion** (the most common exacerbating factor)
- **Pregnancy:** has a variable effect on the course of myasthenia:
 - ⇒ Women with myasthenia that is stable prior to pregnancy are likely to remain stable throughout pregnancy, although a small proportion may have post-partum worsening.
 - ⇒ In poorly controlled myasthenia before pregnancy, flares are most likely to occur in the first trimester and the postpartum period.
- **Infection**

- Drugs:

- ⇒ **Penicillamine**
 - penicillamine toxicity → nephrotic syndrome and myasthenic syndrome.
- ⇒ Quinidine, procainamide
- ⇒ **Beta-blockers**, calcium channel blockers, verapamil, propafenone,.
- ⇒ Lithium, Tricyclic antidepressants
- ⇒ Phenytoin
- ⇒ Antibiotics: **gentamicin**, macrolides, quinolones, tetracyclines
 - **Aminoglycoside-induced neuromuscular blockade**
 - ☞ Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis.
 - ☞ **large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function.**

Investigations

- Autoantibodies (most specific test)
 - ⇒ **Antibodies to acetylcholine receptors** are seen in 80-90% of cases.
 - ⇒ 100% of patients with thymoma have antibodies
 - ⇒ Antibodies are less commonly seen in disease limited to the ocular muscles
 - ⇒ Seronegative MG (10-20%): negative for AChR antibodies, may be positive for **muscle-specific tyrosine kinase antibodies** (MuSK antibodies)
 - patients with (**MuSK**) antibodies are much less likely to have thymic hyperplasia or a thymoma, less responsive to anticholinesterase drugs, and may require more aggressive early immunotherapy than patients who have AChR antibodies.
- Single fibre electromyography (EMG) (most sensitive test)
 - ⇒ **High sensitivity** (92-100%)
 - ⇒ It simultaneously records the variability in potentials of two muscle fibres innervated by an individual axon: jitter.
 - ⇒ shows decremental response following repetitive nerve stimulation
 - ⇒ **Electrical recordings of single motor unit activity commonly reveal variation in the latency of the various muscle fibre responses (abnormal jitter)**
 - ⇒ **Jitter is the most sensitive EMG index in MG but is not specific of the condition.**
- CT thorax to exclude thymoma
- CK normal
- Edrophonium test (Tensilon test)
 - ⇒ Used to diagnose MG before AChR antibody test became the common method
 - ⇒ Symptoms improve rapidly after administration of a short-acting acetylcholinesterase inhibitor

Management

- In mild cases : long-acting anticholinesterase e.g. **pyridostigmine**
 - ⇒ Pyridostigmine → cholinesterase inhibitors → ↑ ACh at neuromuscular junctions.
- In more severe disease (with limb weakness or bulbar dysfunction) → immunosuppression
 - ⇒ Prednisolone initially

- ⇒ Addition of steroid-sparing agents such as mycophenolate mofetil, cyclosporin or azathioprine if necessary.
- In patients with **congenital myasthenia**, anticholinesterase drugs and immunomodulating treatments are not beneficial and **should be avoided**.
- **Thymectomy**
 - ⇒ Can be beneficial even if a thymoma is not present
 - ⇒ **Thymectomy is the following cases:**
 1. Patients with MuSK antibody-associated MG without a thymoma
 2. Late onset disease or
 3. Purely ocular disease

Myasthenic crisis

- **Definition:** acute, life-threatening exacerbation of myasthenic symptoms that leads to respiratory failure
- **Epidemiology:** affects 15–20% of patients with MG
- **Aetiology**
 - ⇒ Infection
 - ⇒ Surgery, anesthesia
 - ⇒ Pregnancy
 - ⇒ Medications
- **Differential diagnosis: cholinergic crisis**
 - ⇒ Overuse of pyridostigmine → **cholinergic crisis** (like organophosphate poisoning)
 - bradycardia, hypotension, bronchospasm, abdominal cramping, diarrhea, and **flaccid paralysis of the extremities**.
 - ⇒ **Edrophonium test is your clue** (a short-acting acetylcholinesterase inhibitor).
 - In myasthenia gravis, this will lead to a temporary relief of symptoms.
 - **In a cholinergic crisis, this will have no effect (or worsen the situation).**
 - ⇒ Managed with **Atropine to antagonize cholinergic activity**.
- **Treatment**
 - ⇒ Intravenous immunoglobulins (IVIg 400mg/kg for 5 days)
 - ⇒ Plasmapheresis: usually works quicker but involves more expensive equipment
 - ⇒ Early endotracheal intubation: **Elective intubation should be considered if the vital capacity show values are less than 20 mL/kg.**

Myasthenic crisis: The patient has marked respiratory weakness with reduced breath count, reduced oxygen saturation, chest expansion and forced vital capacity.

Myasthenic crisis VS Cholinergic crisis

	Myasthenic crisis	Cholinergic crisis
Pupil	Normal	Miosis (constricted pupil)
Fasciculations	None	Present
Heart rate	Tachycardia	Bradycardia
Skin	Cold and faint	Warm and flushed
Bronchial secretion	Normal	Increased

Lambert-Eaton myasthenic syndrome (LEMS)

Definition

- Rare autoimmune disease that reduces neuromuscular transmission, leading to muscle weakness

Prevalence

- Occurs in males more often than females (5:1).

Aetiology

- Paraneoplastic: associated with small-cell lung carcinoma (in 2/3 of LEMS cases)
- May also occur independently as an autoimmune disorder.

Pathophysiology

- Autoantibodies directed against presynaptic voltage-gated calcium channels (anti-VGCC antibodies)** → ↓ Ca²⁺ influx → ↓ presynaptic vesicle fusion → impaired acetylcholine release in the neuromuscular junction (NMJ)

Features

- Proximal muscle weakness
- Repeated muscle contractions lead to increased muscle strength** (in contrast to myasthenia gravis)
- Reduced or absent reflexes** (in contrast to myasthenia gravis where the reflexes are normal or brisk)
- Autonomic symptoms:** dry mouth, impotence, difficulty micturating.
- Ophthalmoplegia and ptosis are not common (unlike in myasthenia gravis)

Diagnostics

- Active muscle contraction or repeated muscle tapping increases reflex activity.
- Lambert sign: **a patient's muscle strength improves with repetitive or ongoing use**
- EMG: Repetitive nerve stimulation results in incremental responses.**
- Confirmatory test:** serologic detection of anti-VGCC antibodies

Treatment

- First-line to improve neuromuscular transmission: amifampridine

Myasthenia gravis VS Lambert-Eaton

	Myasthenia gravis	Lambert-Eaton
Muscle weakness	Proximal muscle weakness: face, neck, limb girdle	Affects lower limbs first
Muscle power following exercise	Becomes weaker	Temporary increase
Reflexes	Normal or brisk	Absence or hyporeflexia
Autonomic dysfunction	None	Common
Antibodies	Antibodies to acetylcholine receptors	Antibody directed against pre-synaptic voltage gated calcium channel
Commonly associated tumor	Thymomas or thymic hyperplasia	Small cell lung cancer

MRCPUK-part-1-May 2019 exam: A patient of small cell lung carcinoma presents with muscle weakness, spreading from legs to arms + hyporeflexia . C/O dry mouth & erectile dysfunction. Antibodies to which one are most likely to be responsible for these findings?
Voltage gated calcium channels

Neurofibromatosis (NF)

NF1: chromosome 17 - as neurofibromatosis has 17 characters

NF2: chromosome 22 - all the 2's

Lisch nodules are seen in neurofibromatosis

Aetiology

- Inherited (50%) Autosomal dominant
- Sporadic mutations (50%): no family history

Pathophysiology

- Mutation of tumor suppressor gene → loss of function → uninhibited cell growth → neurofibroma development
 - ⇒ NF type 1: NF1 gene mutation (100% penetrance)
 - Encodes **neurofibromin** protein
 - Located on chromosome **17**
 - Inhibition of cell growth and proliferation via inhibition of the Ras signal transduction pathway (Ras activity is inhibited by the stimulation of GTPase)
 - ⇒ NF type 2: NF2 gene mutation
 - Encodes **merlin** protein
 - Located on chromosome **22**

Features

NF1	NF2
<ul style="list-style-type: none"> More common (affects 1 in 4,000) Café-au-lait spots (\geq 6 spots, 15 mm in diameter) Axillary/groin freckles Peripheral neurofibromas Iris hamartomas (Lisch nodules) in > 90% Seizures and/or focal neurologic signs due to brain lesions (especially meningiomas) Scoliosis Pheochromocytomas 	<ul style="list-style-type: none"> Less common (Affects around 1 in 100,000) Bilateral vestibular schwannomas (acoustic neuromas) → affecting the vestibulocochlear nerve → tinnitus, hearing loss, or vertigo Early-onset cataracts, usually bilateral Multiple cerebral and spinal tumors (especially meningiomas and ependymomas)



café-au-lait spots

Multiple light brown macules with irregular borders (café-au-lait spots) is highly suggestive of neurofibromatosis type 1.



Lisch nodules

Pigmented hamartomas on the iris, which are pathognomonic of neurofibromatosis type 1.

Complications

- increased lifetime cancer risk

Diagnostics

- MRI of the brain and spine with contrast
- Ophthalmological exam
- Auditory testing
- Genetic testing

Treatment

- Excision or resection of tumors (e.g., meningiomas)
- Surgery for kyphoscoliosis in NF type 1
- Drugs targeting the mTOR pathway (e.g., sirolimus) to reduce tumor growth

Tuberous sclerosis (TS)

Overview

- **Autosomal dominant** condition, variable expression
- TS affects about 1 in 10,000 people in the general population
- It is the second most frequent neurocutaneous syndrome after neurofibromatosis.
- Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

Pathophysiology

- Mutation of tumor suppressor genes → loss of function → unchecked cell growth → tumor development
- Tumor suppressor genes
 - ⇒ TSC1 gene on chromosome **9** encodes hamartin protein
 - ⇒ TSC2 gene on chromosome **16** encodes tuberin protein

Tuberous sclerosis: presentation

- Cigarettes and coffee with a rough stupid person with a butterfly on his nose while he is dancing

Features

- **Cutaneous**
 - ⇒ **Adenoma sebaceum** (facial angiofibroma): benign tumor composed of blood vessels and fibrous connective tissue, located around the nose and cheeks (butterfly distribution)
 - ⇒ **Ash-leaf spots**: hypopigmented (white) macules on the trunk and extremities
 - ⇒ **Shagreen patch**: flesh-colored papule in the lumbosacral region with an orange-peel appearance
 - ⇒ fibromata beneath nails (subungual fibromata)
- **Neurological**
 - ⇒ Developmental delay
 - ⇒ Epilepsy (infantile spasms is most common form)
 - ⇒ Autism
 - ⇒ intellectual impairment
 - ⇒ Fibromas may also develop within the central nervous system, where they calcify typically in the periventricular area.
- **Cardiac rhabdomyoma**
 - ⇒ Present in > 50% of affected individuals
 - ⇒ May cause symptoms of mitral regurgitation and/or congestive heart failure
- Renal disease: Renal cysts, Angiomyolipoma, Renal carcinoma

Diagnostics

- ECG: cardiac rhabdomyoma can cause ventricular hypertrophy and arrhythmias
- EEG: seizure activity
- Echocardiography: rhabdomyoma (common in the apex of the left ventricle)
- Abdominal MRI: renal cyst, angiomyolipoma, and/or carcinoma
- Contrast cerebral CT/MRI
 - ⇒ Tumors (e.g., giant cell astrocytomas)
 - ⇒ Enlarged ventricles (tumors in the periventricular area commonly cause obstructive hydrocephalus)
- Genetic testing

Treatment

- Seizure control
- mTOR inhibitors: to treat renal angiomyolipoma and inoperable giant cell astrocytoma
- Removal of angiofibroma (laser treatment or electrosurgery)
- Surgery in the case of:
 - ⇒ Obstructive hydrocephalus (with ↑ ICP)
 - ⇒ Drug-resistant seizures

MRCPUK-part-1-January 2018 exam: Generalised seizure + patches of hypopigmented skin + fibromata under finger nails. What is the most likely diagnosis? **Tuberous sclerosis**

MRCPUK-part-1-May 2017 exam: H/O hypovolaemic shock. CT abdomen reveals a haemorrhagic lesion in the right kidney. biopsy shown it to be an angiomyolipomata. What is the most likely underlying diagnosis? **Tuberous sclerosis**

Paraneoplastic syndromes affecting nervous system

Lambert-Eaton myasthenic syndrome

- associated with small cell lung cancer (also breast and ovarian)
- antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system
- can also occur independently as autoimmune disorder

Anti-Hu

- associated with small cell lung carcinoma and neuroblastomas
- sensory neuropathy - may be painful
- cerebellar syndrome
- encephalomyelitis

Anti-Yo

- associated with ovarian and breast cancer
- cerebellar syndrome

Anti-GAD antibody

- associated with breast, colorectal and small cell lung carcinoma
- stiff person's syndrome or diffuse hypertension

Anti-Ri

- associated with breast and small cell lung carcinoma
- ocular opsoclonus-myoclonus

Anti-Purkinje cell antibodies

- subacute cerebellar degeneration
- peripheral neuropathy due to a remote (autoimmune) effect of gynecologic or breast carcinoma.

GM1 antibodies (Glycolipid ganglioside-monosialic acid) associated with

- Lower motor neuron syndromes
- Amyotrophic lateral sclerosis
- Multiple sclerosis
- Other multifocal neuropathies and
- Systemic lupus erythematosus (SLE) with central nervous system involvement.

MRCPUK-part-1-May- 2019 exam: Ovarian cancer + unsteadiness, nystagmus and past-pointing. Which antibody is most likely to be present?

→ Anti-Yo

Brain tumours

The majority of adult tumours are supratentorial, whereas the majority of childhood tumours are infratentorial.

Type of tumour	Features
Glioblastoma multiforme	<ul style="list-style-type: none"> The most common primary brain tumour in adults, accounts for about 20% of all cerebral tumours. Histology: Pleomorphic tumour cells border necrotic areas <u>Pseudopalisading tumor cells on brain biopsy are a characteristic</u>
Meningioma	<ul style="list-style-type: none"> The second most common primary brain tumour in adults Histology: Spindle cells in concentric whorls and calcified psammoma bodies
Schwannoma	<ul style="list-style-type: none"> Often seen in the cerebellopontine angle: acoustic neuroma Bilateral schwannomas are seen in neurofibromatosis Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)
Pilocytic astrocytoma	<ul style="list-style-type: none"> The most common primary brain tumour in children Histology: Rosenthal fibres (corkscrew eosinophilic bundle)
Medulloblastoma	<ul style="list-style-type: none"> More common in children Found exclusively in the posterior fossa Metastases through the CSF Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures
Ependymoma	<ul style="list-style-type: none"> Commonly seen in the 4th ventricle May cause hydrocephalus Histology: perivascular pseudo rosettes
Oligodendroma	<ul style="list-style-type: none"> Benign, slow-growing tumour common in the frontal lobes Histology: Calcifications with 'fried-egg' appearance
Haemangioblastoma	<ul style="list-style-type: none"> Vascular tumour of the cerebellum Associated with von Hippel-Lindau syndrome Histology: foam cells and high vascularity
Pituitary adenoma	<ul style="list-style-type: none"> Most common type is a prolactinoma May present with bitemporal hemianopia
Craniopharyngioma	<ul style="list-style-type: none"> Most common paediatric supratentorial tumour The commonest presentation in young patients is growth failure and delayed puberty. CT: suprasellar calcified cyst Histology: Derived from remnants of Rathke pouch
Metastases	<ul style="list-style-type: none"> Most common type of brain tumour The most common sites that metastasise to the brain is Lung (44%), therefore, a chest x ray would be the initial investigation of choice. Initial treatment: Start dexamethasone immediately



Meningioma - MRI showing the typical well-circumscribed appearance. A dural tail can be seen where the tumour 'connects' to the dura. It is seen in around 65% of meningiomas.



The CT shows a well defined spherical mass in the right posterior falk cerebri consistent with a **meningioma**. There is mild oedema and mass effect on the right lateral ventricle. The tumour is straddling the inferior surface of the falx.



Glioblastoma multiforme - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the more homogenous meningioma above.

Von Hippel-Lindau syndrome (VHL)

Early age SAH occur in Von Hippel Lindau

Overview

- Autosomal dominant condition
- VHL gene is tumor suppressor gene on the short arm of **chromosome 3**
- Deletion of VHL gene → loss of function → tumor and cyst development

Features

- **Vascular tumors (hemangioblastoma):** Common in retina, cerebellum, brainstem, and/or spine
 - ⇒ **Cerebellar haemangiomas:** neurological deficits
 - ⇒ Retinal haemangiomas: vitreous haemorrhage → vision loss
 - ⇒ Hemangioblastomas are highly vascularized lesions whose cells have **hyperchromatic nuclei.**
- **Renal cysts** (premalignant), renal cell carcinoma
- **Phaeochromocytoma**
- Extra-renal cysts: epididymal, pancreatic, hepatic
- Endolymphatic sac tumours → hearing loss, tinnitus, and/or vertigo (bilateral disease is a pathognomonic feature)

Cerebrospinal fluid (CSF)

Overview

- CSF Produced by **ependymal cells** of choroid plexuses in the lateral, third, and fourth ventricles by filtration of plasma.
- Approximately 500ml of cerebrospinal fluid is produced each day.
- It is absorbed into the circulation via the arachnoid villi.
- CSF is largely similar to plasma in composition, but has much lower levels of protein.

What type of cells produce cerebrospinal fluid?

⇒ **Ependymal cells**

Normal values of cerebrospinal fluid (CSF)

- Pressure = 60-150 mm (patient recumbent)
- Protein = 0.2-0.4 g/l
- Glucose = > 2/3 blood glucose (60% of serum levels)
- Cells: red cells = 0, white cells < 5/mm³

Conditions associated with raised lymphocytes

- Viral meningitis/encephalitis
- TB meningitis
- Partially treated bacterial meningitis
- Lyme disease
- Behcet's, SLE
- Lymphoma, leukaemia

Conditions associated with raised protein levels

- Guillain-Barre syndrome
- Tuberculous, fungal and bacterial meningitis
- Spinal block (Froin's syndrome): ↑CSF protein below a spinal canal blockage (e.g. tumour, disc, infection)
- Viral encephalitis

Disruption of the blood-brain barrier (i.e., infections, autoimmune diseases, CNS malignancies) or intrathecal production of IgG (i.e., multiple sclerosis, CNS infections such as Lyme disease) → increased immunoglobulins (oligoclonal bands) → increased CSF protein

Vertebral level and corresponding structure

- C4 → Hyoid bone, **Bifurcation of common carotid**
- C5 → Thyroid cartilage, Carotid pulse palpated
- C6 → Cricoid cartilage, Beginning of trachea, Beginning of esophagus
- T2 → Sternal notch, Arch of aorta
- **T12 → aortic opening**
- T4 → Sternal angle, Junction of superior and inferior mediastinum, Bifurcation of trachea
- **T8 → Inferior vena caval hiatus** (opening in the diaphragm)
- T9 → Xiphisternal joint
- **T10 → Esophageal hiatus** (opening in the diaphragm)
- T11 → Upper pole of left kidney
- T12 → Upper pole of right kidney, **Aortic hiatus** (opening in the diaphragm)
- L3 → Umbilicus
- L4 → Iliac crest, Bifurcation of aorta
- **L1 → End of spinal cord**
- S1 → Beginning of sigmoid colon
- S2 → End of dural sac (and CSF)
- S3 → End of sigmoid colon

The spinal cord terminates at lower border of L1 vertebra

Post-lumbar puncture headache

Epidemiology

- Headache following lumbar puncture (LP) occurs in approximately **one-third** of patients.
- More common in **young females** with a **low body mass index**

Pathophysiology

- **Leaking of cerebrospinal fluid from the dura** is the most likely explanation.

Typical features

- Usually develops within 24-48 hours following LP but may occur up to one week later
- May last several days
- Worsens with upright position
- Improves with recumbent position

Factors which may contribute to headache	Factors which do not contribute to headache
<ul style="list-style-type: none"> ⌚ Increased needle size ⌚ Direction of bevel ⌚ Not replacing the stylet ⌚ Increased number of LP attempts ⌚ Use of a Quincke (sharp) needle 	<ul style="list-style-type: none"> ⌚ Increased volume of CSF removed ⌚ Bed rest following procedure ⌚ Increased fluid intake post procedure ⌚ Opening pressure of CSF ⌚ Position of patient

What is the most appropriate type of needle to use in lumbar puncture?

- ⌚ **20G Sprotte® (atraumatic) needle**
- ⌚ Studies show that smaller atraumatic needles reduce the risk of post-lumbar puncture headache.

Management

- Supportive initially (analgesia, rest)
- If pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma
- Treatment options include: blood patch, **epidural saline** and intravenous caffeine

Spinal cord lesions

Disorder	Tracts affected	Clinical notes
Brown-Séquard syndrome (spinal cord hemisection)	1. Lateral corticospinal tract 2. Dorsal columns 3. Lateral spinothalamic tract	1. Ipsilateral spastic paresis below lesion 2. Ipsilateral loss of proprioception and vibration sensation 3. Contralateral loss of pain and temperature sensation
Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency)	1. Lateral corticospinal tracts 2. Dorsal columns 3. Spinocerebellar tracts	1. Bilateral spastic paresis 2. Bilateral loss of proprioception and vibration sensation 3. Bilateral limb ataxia
Friedreich's ataxia	Same as subacute combined degeneration of the spinal cord (see above)	Same as subacute combined degeneration of the spinal cord (see above)
Anterior spinal artery occlusion	1. Lateral corticospinal tracts 2. Lateral spinothalamic tracts	1. Bilateral spastic paresis 2. Bilateral loss of pain and temperature sensation
Syringomyelia	1. Ventral horns 2. Lateral spinothalamic tract	1. Flaccid paresis (typically affecting the intrinsic hand muscles) 2. Loss of pain and temperature sensation
Multiple sclerosis	Asymmetrical, varying spinal tracts involved	Combination of motor, sensory and ataxia symptoms
Neurosyphilis (tabes dorsalis)	Dorsal columns	Loss of proprioception and vibration sensation

Metastatic spinal cord compression

Metastatic spinal cord compression:

- **Dexamethasone should be given immediately (to reduce inflammation around the cord)**
- **Then Urgent radiotherapy is the definitive treatment.**

Epidemiology

- Spinal cord compression is an oncological emergency and affects up to **5% of cancer patients**.

Causes

- Extradural compression accounts for the majority of cases, usually due to vertebral body metastases.

- It is more common in patients with lung, breast and prostate cancer

Features

- back pain
 - ⇒ the earliest and most common symptom
 - ⇒ may be worse on lying down and coughing
- lower limb weakness
- sensory changes: sensory loss and numbness
- neurological signs depend on the level of the lesion.
 - ⇒ **Lesions above L1** usually result in upper motor neuron signs in the legs and a sensory level.
 - ⇒ **Lesions below L1** usually cause lower motor neuron signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion

Diagnosis

- **The definitive investigation in this case is an MRI** of the vertebral column to look for vertebral collapse or other vertebral disease.

Management

- high-dose oral **dexamethasone**
 - ⇒ **Corticosteroids should be started immediately**, even before the diagnosis is confirmed radiologically,
 - ⇒ usually with dexamethasone 16 mg STAT followed by 8mg BD (either oral or IV is acceptable).
 - ⇒ **Dexamethasone given for spinal cord compression can be given via any available route. Giving it intravenously offers no significant advantage over giving it orally.**
 - ⇒ temporarily reduce oedema related to the underlying tumour and thus have a positive impact on neurological deficit,
 - ⇒ the response to steroids predicts neurological response to subsequent definitive treatment which should be started within 24 hours.
- urgent oncological assessment for consideration of **radiotherapy** or surgery
 - ⇒ **Urgent radiotherapy is the definitive treatment**, although neurosurgical opinion should be sought in order to ensure that surgical decompression is not required.
 - ⇒ Treatment is effective in 90% of patients if the diagnosis is made early.
 - ⇒ As L1 is being affected, this can be arranged urgently, rather than immediately. Immediate radiotherapy is necessary for lesions above L1.
- **Spinal stabilisation surgery**
 - ⇒ should be urgently considered for:
 - Patients with spinal metastases and imaging evidence of structural spinal failure with spinal instability.
 - Patients with spinal metastases and mechanical pain resistant to conventional analgesia, even if they have been completely paralysed.
 - ⇒ **Preoperative radiotherapy should not be performed**, although postoperative radiotherapy can be offered to patients with a satisfactory outcome, once the wound has healed.

Prognosis

- **Pre-treatment ambulatory function is the best determinant of post treatment gait function**
 - ⇒ 80% of patients will maintain mobility if ambulatory function is good at presentation.

Disc prolapse

Loss of sensation in the upper outer thigh is consistent with nerve root compression caused by a prolapsed vertebral disc.

pathophysiology

- The intervertebral disk consists of a dense outer ring (annulus fibrosus) and a gelatinous core (nucleus pulposus).
- disk protrusion or herniation through the annulus fibrosus into the central canal → adjacent nerve root impingement → sensorimotoric deficits in affected nerve root
- The herniation of the nucleus pulposus is most commonly in the **posteriorlateral direction** as it is the weakest part of the surrounding annulus fibrosus.
- **The affected nerve root is typically the one below the level of disc herniation**

Intervertebral discs usually protrude/herniate posterolaterally, as the posterior longitudinal ligament is thinner than the anterior longitudinal ligament.

Common sites of prolapse

- **Most often occurs in the lumbar spine**
 - ⇒ (95% of disc herniations occur at the L4-L5 and L5-S1 level).
 - ⇒ L5-S1 (most common site)
 - ⇒ L4-L5 (second most common site)
- Cervical and thoracic disc herniations are rare

Causes

- **Disc degeneration (the most common cause)**
- Trauma

Features

- **Acute onset of severe neck or back pain**
 - ⇒ Radicular pain: pain that radiates to the legs (sciatic pain) or arms
 - ⇒ The pain is either stabbing in nature or resembles an electric shock
- **Features of radiculopathy:** lower motor neuron signs of the affected nerve root (typically unilateral)
 - ⇒ Paresthesia of the affected dermatome
 - ⇒ Muscle weakness
 - ⇒ Absent or diminished deep tendon reflexes
- **Character of pain**
 - ⇒ Pain increases with pressure (e.g., from coughing or sneezing)
 - ⇒ Pain is typically better with rest: if it is **unremitting or worse on resting** you should **consider other causes** such as bony **metastases** or infection.
 - ⇒ Changing position reduces the pain

Management

- **Gentle mobilisation and physiotherapy (the management of choice):** most patients will make a spontaneous improvement within 4–6 weeks.
- Surgery (Microdiscectomy or open discectomy)
 - ⇒ is a potential treatment options for patients with radiologically proven nerve root compression and severe symptoms or symptoms that do not resolve with conservative measures.
- Local corticosteroid injection: symptomatic relief if not fit for surgery

This table demonstrates the expected features according to the level of compression

Level of compression	Features
L3 nerve root compression	<ul style="list-style-type: none"> ⇒ Sensory loss from anterior thigh to medial aspect of lower leg ⇒ Weak quadriceps ⇒ ↓ knee reflex ⇒ Positive femoral stretch test
L4 nerve root compression	<ul style="list-style-type: none"> ⇒ Caused by L3/4 disc prolapse ⇒ Sensory loss over the thigh and anterior aspect of knee ⇒ Weak quadriceps ⇒ ↓ knee reflex ⇒ Positive femoral stretch test
L5 nerve root compression	<ul style="list-style-type: none"> ⇒ Caused by L4/5 disc prolapse ⇒ Sensory loss dorsum of foot and lateral aspect of leg ⇒ Weakness in foot and big toe dorsiflexion ('foot drop') ⇒ Reflexes intact ⇒ Positive sciatic nerve stretch test
S1 nerve root compression	<ul style="list-style-type: none"> ⇒ Caused by L5/S1 disc prolapse ⇒ Sensory loss posterolateral aspect of leg (posterior calf and the plantar surface of the foot) and lateral aspect of foot ⇒ Weakness in plantar flexion of foot ⇒ ↓ ankle reflex ⇒ Positive sciatic nerve stretch test

Prolapsed cervical disc (Cervical radiculopathy)

Overview

- Most commonly affects the C5/C6 and C6/C7 vertebrae.
- Central protrusions can lead to symptoms of spinal cord compression.
- **Posterolateral protrusions can cause a stiff neck, pain radiating to the arm, weakness of the muscles affected by the nerve root and depressed reflexes.**
- X-ray may show narrowing of the disc space between the C5 and C6 vertebrae.

Differential diagnosis

- **Cervical spondylosis**
 - ⇒ occurs as a result of osteoarthritis.
 - ⇒ **Muscle weakness is uncommon**
 - ⇒ X-ray changes:
 - Disc spaces can be narrowed
 - **Osteophytes** seen in the central and posterior intervertebral joints.
- **Cervical rib**
 - ⇒ can present with similar symptoms but the X-ray would be diagnostic (showing the presence of a cervical rib).

- **Spasmodic torticollis**

- ⇒ sudden onset of a stiff painful neck with torticollis can occur in adults due to spasm of the trapezius and sternocleidomastoid muscles.
- ⇒ X-ray of the cervical spine is usually normal.

Common cervical radiculopathies

	Sensory deficits	Motor deficits	Reduction of reflexes
C5 radiculopathy	Anterior shoulder	Biceps and deltoid	Biceps
C6 radiculopathy	From upper lateral elbow over radial forearm up to thumb and radial side of index finger	Biceps and wrist extensors	Biceps Brachioradialis
C7 radiculopathy	<ul style="list-style-type: none"> ⇒ Palmar: fingers II–IV (II ulnar half, III entirely, IV radial half) ⇒ Dorsal: medial forearm up to fingers II–IV (II ulnar half, III entirely, IV radial half) 	Triceps and wrist flexors, finger extensors	Triceps
C8 radiculopathy	Dorsal forearm up to dorsal and palmar area of fingers IV (ulnar half)	Finger flexors	None

Conus medullaris syndrome

Conus medullaris syndrome is caused by compression of the T12-L2 cord and nerve roots, and therefore results in a mix of upper and lower motor neuron signs.

- **Mixed upper and lower motor neurone signs.**
 - ⇒ These include bilateral distal weakness with increased tone and hyper-reflexia, fasciculation, positive Babinski sign and clonus.
 - Cauda equina would give just LMN signs,
- **Sensory loss is most marked in the perianal region.**
 - ⇒ In Amyotrophic lateral sclerosis (the commonest form of motor neurone disease), there would be a mixture of UMN and LMN signs; however, they do not have any sensory signs or incontinence.
- It is much rarer than cauda equina syndrome.

Conus medullaris syndrome VS Cauda equina syndrome

	Conus medullaris syndrome	Cauda equina syndrome
Presentation	Sudden and bilateral	Gradual and may be unilateral leg signs initially
Reflexes	Knee jerk preserved Ankle jerk affected	Both knee and ankle jerk affected
Radicular pain	Less severe	More severe
Sensory	Numbness often localised peri-anal area (often bilateral)	Numbness often localised saddle area (often unilateral)
Motor	Symmetrical Upper motor signs (hyperreflexic distal paresis, less than cauda equina, may be fasciculation)	May be asymmetrical Lower motor signs (areflexic paraplegia, atrophy, fasciculations is rare)
Impotence	Frequent	Often less marked
Sphincter dysfunction	Urinary retention and atonic anal sphincter present early in disease (can cause overflow urinary incontinence)	Urinary retention usually present later in course of disease
Low back pain	More marked	Less marked

Conus medullaris syndrome and cauda equina syndrome are medical emergencies requiring immediate surgical intervention.

Cauda equina syndrome

Cauda equina syndrome is caused by compression of the lumbosacral roots, from L1 down to S5, and therefore results in only lower motor neuron signs.

Causes

- herniation of a lumbar disc (at L4/L5 and L5/S1)
- tumour (metastases, lymphoma, primary spinal tumours)
- trauma
- infection (epidural abscess).
- Others: ankylosing spondylitis, Paget's disease, and congenital spinal stenosis.

Features

- lower motor neuron signs: **flaccid paraplegia**, areflexia, flexor plantar reflexes
- unilateral or bilateral lower limb motor and/or sensory abnormality
- low back pain
- Whilst classically patients present with a sensory level, this is variable in clinical practice.
- bladder retention and **overflow incontinence** (bowel and/or bladder dysfunction with saddle and perineal anaesthesia)
- Saddle anesthesia.
 - ⇒ Patients usually describe numbness and/or "pins-and-needles" sensations of the groin and inner thighs which would contact a saddle when riding a horse. This reflects involvement of the S3-S5 roots.

Diagnosis

- **MRI is the investigation of choice**

Autonomic dysreflexia

Definition

- A clinical syndrome occurs in patients who have had a spinal cord injury at, or above T6 spinal level (85% of patients).

Mechanism

- A strong sensory input (most commonly urine retention or constipation) → travels up the spinal cord → massive reflex sympathetic surge from the thoracolumbar sympathetic nerves → widespread vasoconstriction, most significantly in the subdiaphragmatic (or splanchnic) vasculature → **hypertension** crisis
- The brain detects this hypertensive crisis through intact baroreceptors in the neck delivered to the brain through cranial nerves IX and X.
- The brain attempts two maneuvers to decrease BP:
 1. by sending descending inhibitory impulses of sympathetic surge which are unable to travel because of the spinal cord injury at T6 or above.
 2. by slowing the heart rate through an intact vagus (parasympathetic) nerve; however, this compensatory bradycardia is inadequate, and hypertension continues.
- In summary, the sympathetics prevail below the level of neurologic injury, and the parasympathetic nerves prevail above the level of injury.

Triggers

- urinary retention (cystitis, retention of urine or a blocked catheter): most common
- constipation (faecal impaction)

Features

- unbalanced physiological response, characterised by :
 - ⇒ extreme hypertension, may leads to complications
 - ⇒ flushing and sweating above the level of the cord lesion
 - ⇒ Agitation
 - ⇒ **Bradycardia**

Treatment

- recognition and removal of the triggers.
- Vasodilators such as calcium antagonists may be used to treat the hypertension.

Spastic paraparesis

Definition

- Spastic paraparesis describes an upper motor neuron pattern of weakness in the lower limbs

Causes

- demyelination e.g. multiple sclerosis
- cord compression: trauma, tumour
- parasagittal meningioma (**Spinal meningioma**)
 - ⇒ progressive symptoms (not acute), well-defined sensory level
 - ⇒ MRI of the spine with gadolinium contrast is the investigation of choice
- **tropical spastic paraparesis**
 - ⇒ classic presentation → **HTLV-1 positive patient presenting with paraparesis and urinary retention due to Adult T-cell lymphoma (ATL) caused by human T-lymphotropic virus type 1 (HTLV-I)**

- transverse myelitis e.g. HIV
- syringomyelia
- hereditary spastic paraparesis
- osteoarthritis of the cervical spine

Sudden onset	Progressive onset
<ul style="list-style-type: none"> ⇒ Anterior spinal artery infarct ⇒ Osteoporotic thoracic spine collapse ⇒ Prolapsed thoracic disc 	<ul style="list-style-type: none"> ⇒ demyelination e.g. multiple sclerosis ⇒ Metastatic carcinoma ⇒ Spinal meningioma

Absent ankle jerks, extensor plantars

Overview

- Typically caused by lesion producing both upper motor neuron (extensor plantars) and lower motor neuron (absent ankle jerk) signs
- **Mixture of UMN and LMN signs**

Causes

- subacute combined degeneration of the cord
- motor neuron disease
- Friedreich's ataxia (usually presents by age 30)
- Syringomyelia
- taboparesis (syphilis)
- HIV
- Spinal AVM
- **conus medullaris lesion**

Which neurological finding is most helpful in differentiating subacute combined degeneration of the cord from multiple sclerosis?

→ Absent ankle jerk

Subacute combined degeneration of spinal cord (SACDC)

Basics

- due to vitamin B12 deficiency
- vitamin B12 deficiency → **increased levels of methylmalonic acid** → impairs spinal cord myelinization.
- dorsal + lateral columns affected
- if untreated stiffness and weakness persist

Features

- **joint position and vibration sense lost first** then distal paraesthesia
- upper motor neuron signs typically develop in the legs, classically:
 - ⇒ extensor plantars,
 - Plantars are initially flexor, and later extensor.
 - ⇒ brisk knee reflexes,
 - (but may be increased, normal or absent)
 - ⇒ **absent ankle jerks**

- On presentation, 50% of patients have absent ankle reflexes with hyper-reflexia at the knees.
- Spastic paresis
- Gait abnormalities (spinal ataxia, positive Romberg's test)
- Lhermitte's phenomenon is typically present in multiple sclerosis, but may also occur in subacute combined degeneration of the cord.

Diagnosis

- MRI typically shows **increased signal on T2-weighted imaging** in the dorsal columns

Transverse myelitis

Overview

- inflammation across the entire width of one level, or segment of the spinal cord.
- Characterised by acute or subacute motor, sensory and autonomic spinal cord dysfunction.
- the thoracic region of the spinal cord is most commonly affected.

Causes

- Acute infection
 - ⇒ Viral: most commonly
 - ⇒ Bacterial infections: syphilis, Lyme disease
- Post-infections or vaccination (immune mediated)
- Autoimmune (SLE, MS)

Features

- **Course of the disease:** develop over hours to days, and are usually bilateral
- **Motor dysfunction** (e.g., paresis, paraplegia)
- **Sensory dysfunction**
 - ⇒ Sensory level is characteristic.
 - ⇒ Midline or dermatomal neuropathic pain can be present.
- **Autonomic dysfunction**
 - ⇒ Sphincter dysfunction
 - Urinary incontinence or retention
 - Bowel incontinence or constipation
 - ⇒ Sexual dysfunction is common but vary in severity.

Investigation

- **MRI**
 - ⇒ to rule out the presence of structural lesions,
 - ⇒ to determine the presence of myelitis, which enhances with gadolinium in the acute phase.
 - Evidence of inflammation can be confirmed via gadolinium-enhanced MRI.
 - ⇒ There may be more than one area of myelitis, and the lesions usually span at least two vertebral segments.
 - ⇒ there is variable enlargement of the spinal cord
 - ⇒ In the acute phase the MRI may be normal.
- **CSF analysis:** pleocytosis and/or elevated IgG index

Treatment

- First-line: immediate high-dose IV corticosteroids
- Plasma exchange can be given to those who fail to respond.
- Patients with demyelinating disease can be started on long term immunosuppression.

Prognosis

- **Predictors of poor prognosis**
 - ⇒ rapidly progressive course
 - ⇒ severe weakness
 - ⇒ hypotonia
 - ⇒ areflexia
- **Improvement chances**
 - ⇒ time frame: improvement can take three months and longer to develop
 - ⇒ percentage: 50 - 70% of patients have **partial or complete recovery**.
 - One-third of patients **recover with little or no sequelae**
 - One-third are left **with a moderate degree of permanent disability**
 - One-third are left **with severe disabilities**
- **Risk of future MS:** Depends on the pattern of transverse myelitis:
 - ⇒ complete transverse myelitis: only 5-10% will be diagnosed with MS
 - ⇒ incomplete transverse myelitis: 60-90% will be diagnosed with MS within 5 years.

Syringomyelia

Syringomyelia - spinothalamic sensory loss (pain and temperature)

Syringomyelia typically causes loss of reflexes, spinothalamic sensory loss (pain and temperature), and weakness. It can be asymmetrical initially

Definition

- Syringomyelia is a **degenerative** disease of the spinal cord that is characterized by a fluid-filled cavity within the cervical spinal cord.

Pathophysiology

- development of cavity (syrinx) within the spinal cord
- Syrinx (fluid-filled cavitation) in the central spinal cord, usually cervical. This can elongate and enlarge, causing → compression of the corticospinal and spinothalamic tracts and anterior horn cells.
- if extends into medulla then termed syringobulbia
- Most of the cavities in syringomyelia lie between the **second cervical** and the **ninth thoracic** vertebrae.
 - ⇒ most commonly affecting the cervical region
- collection of fluids within the central canal of the spinal cord → enlargement spinal canal, leading to damage of the crossed fibers (anterior white commissure) of the spinothalamic tract → loss of pain and temperature sensation in the upper extremities

Epidemiology

- more common in men than women
- usually presents in the 20s and 30s although it can present later in life.

Causes

- Arnold-Chiari malformation type I → impaired cerebrospinal fluid circulation
 - ⇒ **The most common cause**
- arachnoiditis,
- meningeal carcinomatosis,
- space-occupying lesions
- **Post-traumatic syringomyelia**

- ⇒ complicate up to 4% of spinal cord injury
- ⇒ often presents with pain, which spreads upwards from the initial injury site.
- idiopathic.

Features

- maybe asymmetrical initially
- **slowly progressive** sensory and motor symptoms, possibly over years
- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
 - ⇒ bilateral loss of pain and temperature sensation in the upper extremities.
 - ⇒ fine touch sensation, vibration and proprioception are preserved
- loss of reflexes, bilateral upgoing plantars
- Horner's syndrome,
 - ⇒ seen in advanced syringomyelia due to disruption of sympathetic trunk neurons.
- Bladder, bowel and sexual dysfunction can develop

Investigations

MRI is the investigation of choice

- MRI of the spinal cord
 - ⇒ **the diagnostic modality of choice.**
 - ⇒ MRI enhanced with gadolinium has more sensitivity than regular MRI.
- Myelography
 - ⇒ used to confirm the diagnosis but was associated with more deterioration

Localization of the lesion

- At syrinx (there is anterior horn cell involvement) → lower motor neuron pattern of weakness.
- At central decussating fibres (spinothalamic tract) → dissociated sensory loss with late development of neuropathic arthropathy.
- At corticospinal tracts below the level of the syrinx results in spastic paraparesis.

Differential diagnosis

- Amyotrophic lateral sclerosis → NO sensory deficits.
- Anterior spinal artery thrombosis
 - ⇒ characterised by loss of motor function below the level of injury, loss of pain and temperature sensations, and preservation of proprioception, fine touch and vibration.
- Post-traumatic spinal stenosis
 - ⇒ result in neurological changes below the level of stenosis.

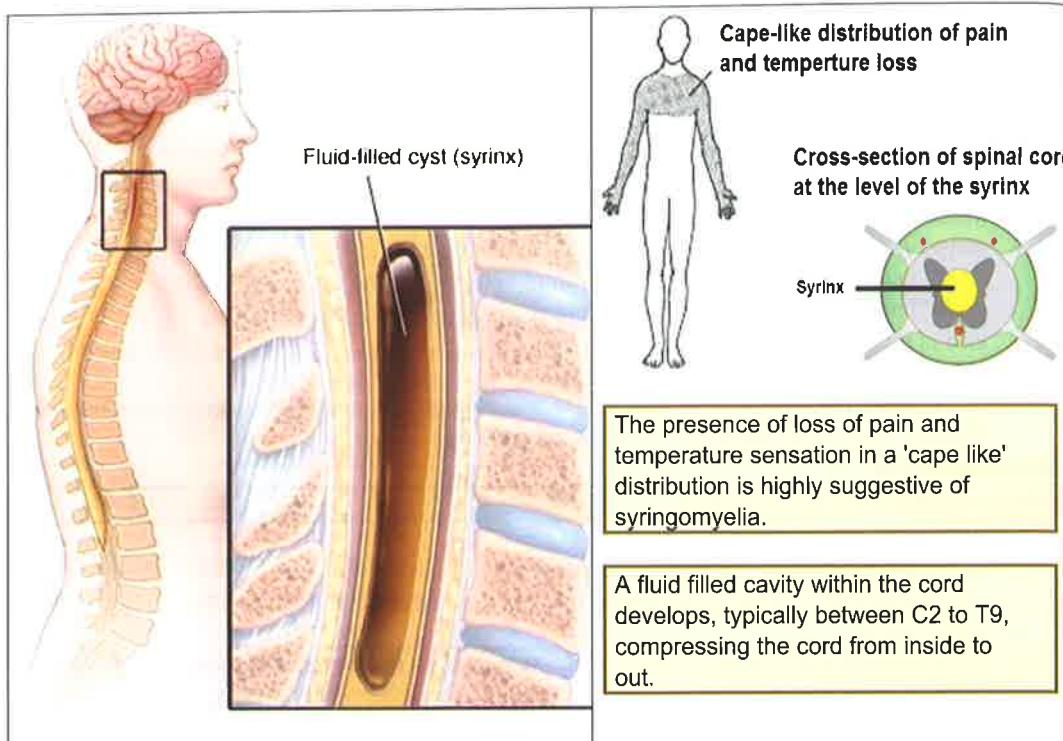
Management

- The mainstay of the treatment is surgery.

MRCPUK-part-1-May 2010: feature of weakness & wasting of the small muscles of the hand.

Which one of the following features would most support a diagnosis of syringomyelia?

→ **Loss of temperature sensation in the hands**



Arnold-Chiari malformation (CM)

Definition

- Arnold-Chiari malformation describes the downward displacement, or herniation, of the cerebellar tonsils through the foramen magnum.

Causes

- may be congenital or acquired through trauma.

Pathophysiology

- Symptoms of Arnold-Chiari malformation, type I develop as a result of **three pathophysiological consequences** of the disordered anatomy:
 - compression of the medulla and upper spinal cord,
 - compression of the cerebellum,
 - disruption of cerebrospinal fluid flow through the foramen magnum.

Classification

- classified by extent with which parts of the brain protrude into the spinal canal.
 - ⇒ **Chiari I malformation**,
 - the only type that can be acquired or can remain asymptomatic until late childhood or early adulthood.
 - characterized by:
 - the time of onset (late childhood/early adulthood) and
 - the downward herniation of cerebellar tonsils, without the involvement of brainstem tissue.

- symptoms due to obstruction of cerebrospinal fluid flow.
- ⇒ more severe types of Chiari malformations would involve additional herniation of brainstem tissue (Types II and III) or incomplete development of the cerebellum as a whole (Type IV).

Features

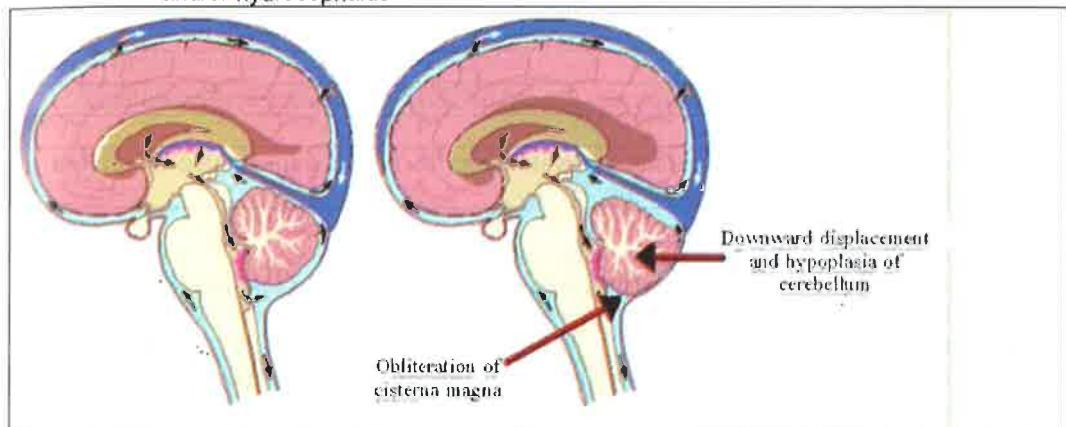
- non-communicating hydrocephalus may develop as a result of obstruction of cerebrospinal fluid (CSF) outflow
- neck pain
- Occipital headache
 - ⇒ exacerbated by cough, valsalva maneuver and exercise.
- **syncope due to intermittent obstructive hydrocephalus.**
- changes in balance, and poor hand coordination
- Syringomyelia
- **Downbeat nystagmus is classically associated with lesions at the foramen magnum (Arnold-Chiari malformation)**

Investigations

- MRI brain: → Narrow posterior fossa

Treatment

- type II and III CM and in symptomatic type I CM
 - ⇒ Surgery
- asymptomatic type I CM :
 - ⇒ Surveillance: annual MRI of the brain to look for development of syringomyelia and/or hydrocephalus





MRI showing herniation of the cerebellar tonsils through the foramen magnum consistent with a Chiaria I malformation

Anterior spinal artery thrombosis

Anterior spinal artery thrombosis → Sudden paralysis and loss of pain and temperature sensation and preservation of fine touch, vibration, and proprioception below the level of the lesion.

Vibration and proprioception are typically spared because of an intact dorsal column

Anterior spinal artery infarct occurs at the 'watershed' T4-T6 and would cause symptoms primarily in the lower limb and a sensory level.

- it supplies, roughly the anterior 2/3 of the cord.
- segments of the cord in the watershed area between the branches (around T2–T4) are vulnerable to ischaemia.

Sequelae

- Occlusion of the anterior spinal artery infarcts the ventral portion of the cord.
- affects the structures found at the front of the spine
 - ⇒ corticospinal tracts (motor neurons)
 - ⇒ spinothalamic tracts (pain/temperature sensation).

Feature

- Acute (within hours)
 - ⇒ Back or chest pain
 - ⇒ Spinal shock
 - Bilateral loss of temperature and pain sensation , motor function (**flaccid paraparesis or quadriplegia**) , and autonomic function (bladder, bowel, and sexual dysfunction, orthostatic hypotension) below the level of the lesion
 - reflexes are diminished

- Absent Bulbocavernosus reflex: squeezing the glans penis or pulling on a Foley catheter while digitally palpating the contraction of the anal sphincter
- Late (after days or weeks)
 - ⇒ Continued sensory and autonomic dysfunction
 - Power is reduced below the hips
 - Pain and temperature sensation are lost to the waist.
 - ⇒ **Spastic** paraparesis or quadriplegia (increased muscle tone)
 - ⇒ Hyperreflexia
- **Light-touch sensation, vibration and proprioception** (joint-position sense) are normal because these are carried in the dorsal columns that are **supplied by the posterior spinal artery**.
- **Injury level**
 - ⇒ Anterior spinal cord lesions above **cervical vertebra 6** will result in **tetraplegia** with involvement of the upper and lower extremities.
 - ⇒ injuries from **T1-T6** have normal upper extremity, although abdominal and chest muscles may be affected with diminished respiratory excursion.
 - ⇒ The region of **thoracic vertebra 6** is the thoracic watershed zone; lesions below this level result in loss of bowel, bladder, and sexual functions.

Anterior spinal arteries supply corticospinal and spinothalamic tracts, and anterior horns of the grey matter.

What are the diagnostic possibilities of a lesion involve the anterior two thirds of the spinal cord which **spares light touch, vibration and position sense**, but causes loss of pain and temperature sensation distally?

The diagnostic possibilities include :

- 1- anterior spinal artery occlusion → **sudden onset**
- 2- intramedullary spinal cord metastasis

Types of incomplete spinal cord syndromes

- All types present with dissociated sensory loss: a pattern of selective sensory loss ("dissociation of modalities"); suggests a focal lesion of a single tract within the spinal cord

	Affected spinal tracts	Etiology	Clinical features
Central cord syndrome (most common)	Bilateral central corticospinal tracts and lateral spinothalamic tracts	<ul style="list-style-type: none"> Hyperextension injury (e.g., car crash) associated with chronic cervical spondylosis Spinal cord compression 	<ul style="list-style-type: none"> Bilateral paresis: upper > lower extremities
Anterior cord syndrome	Corticospinal and spinothalamic tracts	<ul style="list-style-type: none"> Trauma (e.g., penetrating injury, burst fracture of vertebra) Occlusion of anterior spinal artery 	<ul style="list-style-type: none"> Bilateral motor paralysis, loss of pain and temperature sensation, and autonomic dysfunction below the level of the lesion
Posterior cord syndrome	Bilateral posterior columns	<ul style="list-style-type: none"> Trauma (e.g., penetrating injury) Occlusion of the posterior spinal artery Multiple sclerosis 	<ul style="list-style-type: none"> Ipsilateral loss of proprioception, vibration, and touch sensation below the level of the lesion
Brown-Séquard syndrome (hemisection syndrome)	Hemisection of the cord	<ul style="list-style-type: none"> Trauma (e.g., penetrating injury) Spinal cord compression 	<ul style="list-style-type: none"> Ipsilateral: <ul style="list-style-type: none"> Loss of proprioception, vibration, and tactile discrimination below the level of the lesion Segmental flaccid paresis at the level of the lesion, spastic paralysis below the level of the lesion, and ipsilateral Babinski sign Contralateral: <ul style="list-style-type: none"> loss of pain and temperature sensation one or two levels below lesion

Diagnosis

- Spinal MRI** (best confirmatory test): excludes soft-tissue lesions (e.g., tumors, hematomas), bone lesions, and detects spinal cord parenchyma abnormalities (e.g., infarction)

Brown-Séquard's syndrome

Definition

- Thoracic spinal cord lesion produced by a hemisection of the spinal cord.

Causes

- trauma, (most commonly)
- tumours, and
- multiple sclerosis.

Features

- Ipsilateral**
 - ⇒ **Weakness** (paralysis)
 - ⇒ loss of position and vibration below the lesion (dorsal column dysfunction)
 - ⇒ Horner syndrome,
 - If the lesion is above the spinal cord level T1, due to damage of the oculosympathetic pathway.
- Contralateral**
 - ⇒ **loss of pain and temperature.**

Diagnosis

- MRI is the imaging of choice in spinal cord lesions

Management

- Steroids may decrease cord swelling.

Lower back pain

Overview

- Lower back pain (LBP) is one of the most common presentations seen in practice.
- Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	<p>May be acute or chronic Pain worse in the morning and on standing On examination there may be pain over the facets. The pain is typically worse on extension of the back</p>
Spinal stenosis	<p>Usually gradual onset Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. pain is worse with walking downhill and less with walking uphill. Resolves when sits down. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis</p>
Ankylosing spondylitis	<p>Typically, a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if female)</p>
Peripheral arterial disease	<p>Pain on walking, relieved by rest Absent or weak foot pulses and other signs of limb ischaemia Past history may include smoking and other vascular diseases</p>

Wernicke's encephalopathy

Wernicke's encephalopathy: classic **triad of:**

1. nystagmus,
2. ophthalmoplegia
3. ataxia

Definition

- Wernicke's encephalopathy is a neuropsychiatric disorder caused by **thiamine deficiency**, which is most commonly seen in alcoholics.

Causes

- **Most common: alcohol**
- **Rarer causes include:**
 - ⇒ persistent vomiting,
 - ⇒ stomach cancer,
 - ⇒ dietary deficiency.

Features

- nystagmus (the most common ocular sign)
- ophthalmoplegia
- ataxia
- confusion, altered GCS
- peripheral sensory neuropathy
- Sometimes bilateral wrist drop but more frequently bilateral foot drop with pain or pressure over the long nerves.

- petechial haemorrhages occur in a variety of structures in the brain including the mamillary bodies and ventricle walls

Investigations

- **1st investigations to order → therapeutic trial of parenteral thiamine**
- decreased red cell transketolase
- MRI

Treatment is with urgent replacement of **thiamine (Pabrinex (Intravenous))**

Korsakoff syndrome

Korsakoff's syndrome: Inability to acquire new memories and confabulation

Definition

- a late neuropsychiatric manifestation of Wernicke encephalopathy.

Pathophysiology

- alcohol → vitamin B1 (thiamine) deficiency → damage to mammillary bodies (structures of the limbic system)

Feature

- Wernicke's encephalopathy + antero- and retrograde **amnesia** and **confabulation**.
 - ⇒ confabulation (false memories) is a disturbance of memory, defined as the production of fabricated memories without the conscious intention to deceive.
 - ⇒ dementia is typically not reversible.

Investigations

- MRI finding → **mammillary body degeneration**

Treatment

- maintenance thiamine and rehabilitation

Anti-NMDA receptor encephalitis (Autoimmune encephalitis)

Definition

- It is a type of brain inflammation due to antibodies. (a paraneoplastic syndrome), presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability.
- might be misdiagnosed as a primary psychiatric illness.

Mechanism

- **autoimmune** with the primary target the N-methyl D-aspartate receptors (NMDAR) in the brain

Epidemiology

- 80% are female
- particularly prevalent in Afro-Caribbean patients.

Associations

- Ovarian teratomas are detected in up to half of all female adult patients,

Investigations

- CSF
 - can be normal initially.

- may demonstrate pleocytosis
- **antibodies against NMDA receptors**
- CSF titers of anti-NMDA receptor antibodies correlate with clinical illness
- MRI head
 - ⇒ can be normal in 50%
 - ⇒ abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures.
- evaluation for an ovarian teratoma by MRI, CT scan, or ultrasound

Treatment

- immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination.
- Resection of teratoma is also therapeutic.

CADASIL

Overview

- **Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)**
- A family history is almost always present, as it is an autosomal dominant condition, **located to chromosome 19**.
- the most common genetic form of vascular dementia.

Features

- **What is the pathophysiology of this condition?**
 - ⇒ **NOTCH3 mutation**
- strokes at a young age and
- early vascular (subcortical) dementia (multi-infarct dementia)
- **patients often present with migraine**
- Recurrent ischaemic events (transient or permanent) & Severe mood disorders

Diagnosis

- Characteristic MRI changes include T2 weighted hyperintensity of the periventricular white matter.
- **DNA testing** for the **notch-3 gene mutation** confirms the diagnosis.

Treatment

- the **oral contraceptive pill should be stopped**, given its association with stroke in migraine.

Myotonic dystrophy

Definition

- Myotonic dystrophy (also called dystrophia myotonica) is an inherited myopathy results in a **selective atrophy of type I muscle fibers** affects skeletal, cardiac and smooth muscle.

Genetics

- autosomal dominant, trinucleotide repeat disorder. Patients have between 50 to 1,000 CTG trinucleotide repeats in the myotonin protein kinase gene (normal is less than 30 repeats).

Types: There are two main types of myotonic dystrophy, DM1 and DM2.

	DM1	DM2
Genetics	DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome 19	ZNF9 gene on chromosome 3
Onset	Congenital, juvenile, or adult-onset	Adulthood
Features	Distal weakness more prominent	Proximal weakness more prominent
Severity	Severe disease	Mild disease

Features

- features developing at around 20-30 years old.
- myotonic facies (long, 'haggard' appearance), frontal balding, atrophy of temporalis, masseters and facial muscle, bilateral ptosis
- cataracts
- myotonia (tonic spasm of muscle), **slow-relaxing grip** may be noticed on initial hand-shake with the patient and is **typical** of myotonic dystrophy.
- weakness of arms and legs (distal initially)
- mild mental impairment
- diabetes mellitus (Insulin resistance)
- testicular atrophy
- Dysarthric speech secondary to myotonia of the tongue and pharynx
- cardiac involvement: heart block, cardiomyopathy
- dysphagia

Diagnosis

- Serology → increased serum CK
- **Electromyogram (EMG)** → the most appropriate next step to confirm the diagnosis
 - ⇒ EMG changes → **Waxing and waning of potentials**, termed the "dive bomber effect"
- Muscle biopsy
- Genetic testing: the gold standard for confirming the diagnosis

Treatment: mostly symptomatic

- for weakness which is the main cause of disability → there is no treatment
- for myotonia → phenytoin, quinine or procainamide may be useful , mexiletine is a sodium channel blocker often used for myotonic symptoms.
- for cardiac abnormalities → pacemaker
- for obstructive sleep apnea → CPAP
- **Foot drop** can be managed with → ankle-foot orthosis and **splints**.
- For ptosis : lid-lifting surgery has no place except in severe cases
- may need cataract extraction.
- Genetic counseling and testing

Prognosis

- The course is chronic progressive.
- **Cardiac complications reduce life expectancy.**

Top Tips

Dystrophia myotonica - DM1

- distal weakness initially
- autosomal dominant
- diabetes
- dysarthria



Dystrophinopathies

Overview

- **X-linked recessive**
 - ⇒ Affected father (Y, X):
 - All sons will not be affected and not carriers (His sons will get the X chromosome from their mother)
 - All his daughters will be carriers
 - ⇒ Carrier mother (X, X):
 - **50% of sons will be affected** (there is a 1 in 2 chance (50:50) of passing the gene on to their sons.)
- due to mutation in the gene encoding dystrophin, **dystrophin gene on Xp21**

- dystrophin is a protein in muscle which connects the muscle membrane to actin, part of the muscle cytoskeleton

Diagnostic investigations

- 1st investigations to order**
 - ⇒ serum CK
 - 50 to 100 times normal level consistent with Duchenne muscular dystrophy
 - ⇒ genetic testing
 - DNA analysis → **Xp21 mutation** → may present in both Duchenne and Becker muscular dystrophies
- Investigations to consider
 - ⇒ EMG
 - EMG can distinguish between neuropathic and myopathic pathology.
 - **myopathic reading** with **fast firing, short duration** but **polyphasic** and **decreased amplitude** motor units with **early recruitment** in the affected muscles
 - ⇒ **muscle biopsy**
 - absence of dystrophin → Duchenne muscular dystrophy
 - diminished quantity or quality of dystrophin → Becker muscular dystrophy

Duchenne muscular dystrophy (DMD)

- most common and most rapidly progressive muscular dystrophy
- there is a **frameshift mutation** resulting in one or both of the binding sites are lost leading to a **severe form**
- progressive proximal muscle weakness **from 5 years**
 - ⇒ Usually, there is severe progression with wheelchair dependence by the age of 12 on average
 - ⇒ Death usually occurs as a teenager or in the early 20s from respiratory failure.
- calf pseudohypertrophy
- Gower's sign: child uses arms to stand up from a squatted position
- intellectual impairment (30%)
- urinary and bowel incontinence (common)
- DMD patients tend to be hyperactive and have difficulty in focusing attention.

Becker muscular dystrophy

- there is a **non-frameshift insertion** in the dystrophin gene resulting in both binding sites being preserved leading to a **milder form**
- develops after the age of 10 years
- Similar type of disease to Duchenne's, with a later onset (average age at presentation 12 years), milder phenotype and longer life expectancy**
- intellectual impairment much less common
- Occasionally, patients present with CHF and cardiac arrhythmias before complaining of muscle weakness and before diagnosis.

Facio-scapulo-humeral muscular dystrophy (FSHMD)

- autosomal dominant form of muscular dystrophy.
- As the name suggests it typically affects the face, scapula and upper arms first.
- Symptoms typically presents by the age of 20 years.
- may go unrecognised until later life

- The presence of distal wasting and **pes cavus** (indicates a very **chronic neuromuscular disorder** with axonal loss)

Oculopharyngeal muscular dystrophy

- ptosis
- weakness of the extraocular muscles
- dysphagia
- tongue atrophy

Foster-Kennedy syndrome

Foster Kennedy's syndrome is a combination of optic atrophy and central scotoma, contralateral papilloedema and anosmia.

Overview

- Foster-Kennedy syndrome describes a series of symptoms and signs associated with frontal lobe lesions.
- It is caused by optic and olfactory nerve compression and raised intracranial pressure.
- This is **often secondary to a mass such as an olfactory groove meningioma**.

Features

- optic atrophy in the ipsilateral eye**
- central scotoma in the ipsilateral eye
- papilloedema in the contralateral eye
- anosmia
- symptoms of raised intracranial pressure such as nausea and vomiting,
- frontal symptoms such as emotional lability and memory loss.

The presence of optic atrophy on one side with contralateral papilloedema is characteristic of Foster Kennedy syndrome as it is usually due to frontal tumour or tumour within the olfactory bulb compressing the ipsilateral optic nerve and causing raised intracranial pressure.

Hypokalaemic periodic paralysis and thyrotoxic periodic paralysis

Epidemiology

- Most commonly seen in Asian** men in their third to fifth decades
- The prevalence is much higher in patients with thyrotoxicosis of Chinese origin versus Caucasians, (13-14% vs. 0.1-0.2%).
- occurs in 10% of young Latin American or Asian men **with thyrotoxicosis** (of whatever aetiology).

Pathophysiology

- autosomal dominant** disorder
- The underlying defect is a mutation in muscle voltage-gated calcium channels.
- Increase Na^+/K^+ -ATPase activity → shift of potassium into tissues

Features

- **Episodes of paralysis:** sudden onset of complete weakness with speedy recovery.
 - ⇒ Attacks of focal or generalized flaccid muscle weakness (periodic paralysis)
 - ⇒ Proximal muscles are more prominently affected; respiratory and facial muscles are generally spared
 - ⇒ Variable duration (hours to days)
 - ⇒ Concomitant fatigue, muscle pain, and/or altered state of consciousness during the attacks
 - ⇒ Neurological examination is usually normal between attacks.
- **Attacks may be precipitated by:**
 - ⇒ Carbohydrate-rich meals
 - ⇒ **Exercise**
 - ⇒ Stress
- May associate with thyrotoxicosis
 - ⇒ **With thyrotoxicosis called → Thyrotoxic hypokalaemic periodic paralysis**
 - ⇒ Without thyrotoxicosis called → hypokalaemic periodic paralysis.

Diagnosis

- ↓ K+, documentation of hypokalaemia during an attack
- ↓ TSH, ↑ T3, T4 hormones (Thyrotoxic periodic paralysis)

Management

- **Potassium infusion → provide immediate relief from symptoms**
- Continuous cardiac monitoring
- Lifelong potassium supplementation
- The periodic paralysis resolves when the thyrotoxicosis is treated.
- Non-selective beta-blocker such as propranolol blunts the hyperadrenergic stimulation of Na⁺/K⁺-ATPase and thus prevents intracellular shift of potassium and phosphate.

Neuromyelitis optica (NMO)

The classic antibody associated with neuromyelitis optica is NMO-IgG or antibodies against aquaporin-4.

Definition

- demyelinating disease involving the **optic nerves and spinal cord** but sparing the brain.

Features

- monophasic or relapsing-remitting
- particularly prevalent in Asian populations
- Vomiting is also a common presenting complaint.

Diagnostic criteria: bilateral optic neuritis, transverse myelitis and 2 of the following 3 criteria:

1. Spinal cord lesion involving 3 or more spinal levels
2. Initially normal **MRI** brain
3. **Aquaporin 4 positive serum antibody**

Vertigo

Overview

- Vertigo is a sensation of spinning while you're actually stationary.
- Vertigo is caused most often by inner ear disease but can also be caused by disease of the vestibular nerve, brainstem, or cerebellum.
- Inner ear causes of vertigo include benign paroxysmal positional vertigo (BPPV), labyrinthitis, and Ménière disease.
- Horizontal-rotational nystagmus is associated with peripheral vertigo, whereas vertical nystagmus is associated with central vertigo.

Common causes of vertigo

Disorder	Notes
Labyrinthitis	<ul style="list-style-type: none"> ⌚ Recent viral infection or head trauma ⌚ Sudden onset ⌚ Nausea and vomiting ⌚ Typically has associated tinnitus and a history of infection. ⌚ Hearing may be affected
Vestibular neuritis	<ul style="list-style-type: none"> ⌚ Recent viral infection ⌚ Recurrent vertigo attacks lasting hours or days ⌚ No hearing loss
Benign paroxysmal positional vertigo	<ul style="list-style-type: none"> ⌚ Gradual onset ⌚ Triggered by change in head position ⌚ Each episode lasts 10-20 seconds
Meniere's disease	<ul style="list-style-type: none"> ⌚ Associated with hearing loss, tinnitus and sensation of fullness or pressure in one or both ears
Vertebrobasilar ischaemia	<ul style="list-style-type: none"> ⌚ Elderly patient ⌚ Dizziness on extension of neck
Acoustic neuroma	<ul style="list-style-type: none"> ⌚ Hearing loss, vertigo, tinnitus ⌚ Absent corneal reflex is important sign ⌚ Associated with neurofibromatosis type 2

Distinguishing vertigo of brainstem and cerebellar ischemia from peripheral causes

The **HINTS** exam is a three-part, rapid bedside oculomotor test used to help differentiate central from peripheral vertigo. **HINTS** stands for **H**ead **I**mpulse, **N**ystagmus and **T**est of **S**kew. The test consists of **three** parts:

1 – Patients with peripheral vertigo will have abnormal (positive) head impulse testing, while patients with central vertigo typically have a normal (negative) head impulse test.

2 – Patients with peripheral vertigo will have unidirectional, horizontal nystagmus, while patients with **central** vertigo can have **rotatory or vertical** nystagmus, or direction-changing horizontal nystagmus.

3 – Alternate eye cover testing may reveal skew deviation in patients with central vertigo, and should be absent in peripheral vertigo.

Any of the following, whether present or untestable, suggest a brainstem or cerebellar lesion:

- Normal head impulse test on both sides
- Direction-changing nystagmus
- Skew deviation

The presence of all of the following suggests a peripheral lesion:

- An abnormal head impulse test on one side
- Unidirectional, horizontal, torsional nystagmus that increases in intensity with gaze toward the fast phase
- Absent skew

The importance of these oculomotor tests is that brain imaging with either CT or MRI may be normal during the acute phase of ischemic symptoms. In this regard, the HINTS test appears to be more sensitive for the diagnosis of acute stroke than even brain MRI within the first two days after symptom onset

Benign paroxysmal positional vertigo (BPPV)

Overview

- vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards)
- may be associated with nausea
- each episode typically lasts 10-20 seconds

Features

Vertigo and nausea, with nystagmus, fit best with benign paroxysmal positional vertigo, which occurs due to otolith detachment into the semicircular canals of the inner ear.

Diagnosis

- **Positive Dix-Hallpike manoeuvre**
 - ⇒ First-line test for suspected BPPV
 - ⇒ Positive Dix-Hallpike test: positional vertigo and nystagmus triggered during the maneuver
 - ⇒ Further steps for positive test: Perform Epley repositioning maneuver.

Treatment

- Symptomatic relief may be gained by Epley manoeuvre (successful in around 80% of cases)
- Medication is often prescribed (e.g. Betahistine) but it tends to be of limited value.

Prognosis

- BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months.

MRCPUK-part-1-May 2017 exam: H/O vertigo and dizziness precipitated by a change in head position. What is the most appropriate next step to confirm the diagnosis?

→ Dix-Hallpike manoeuvre

Meniere's disease

Definition

- Meniere's disease is a **disorder of the inner ear** of unknown cause.
- characterised by excessive pressure and progressive dilation of the endolymphatic system.

Epidemiology

- more common in middle-aged adults but may be seen at any age.
- similar prevalence in both men and women.

Features

- Recurrent episodes of vertigo, (the prominent symptom)
- Tinnitus and **hearing loss (sensorineural)**.
- Sensation of aural fullness or pressure
- Nystagmus
- Positive Romberg test
- Episodes last minutes to hours
- Typically, symptoms are unilateral but bilateral symptoms may develop after a number of years

Natural history

- symptoms resolve in the majority of patients after 5-10 years
- the majority of patients will be left with a degree of hearing loss
- psychological distress is common

Management

- patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- Acute attacks: buccal or intramuscular prochlorperazine.
- Restriction of salt and fluid may hasten resolution.

MRCPUK-part-1-May 2013 exam: H/O recurrent attacks of 'dizziness' + 'roaring' sensation in the left ear. Weber's test localises to the right ear. What is the most likely diagnosis?

→ Meniere's disease

Vestibular neuritis

Definition

- Vestibular neuritis is a cause of vertigo that often develops following a viral infection.

Features

- recurrent vertigo attacks lasting hours or days
- nausea and vomiting may be present
- horizontal nystagmus is usually present**
- no hearing loss or tinnitus

Management

- vestibular rehabilitation exercises are the preferred treatment for patients who experience chronic symptoms
- betahistidine is often used although the evidence base suggests it is less effective than vestibular rehabilitation

Tinnitus

Causes of tinnitus

Meniere's disease	Associated with hearing loss, vertigo, tinnitus and sensation of fullness or pressure in one or both ears
Otosclerosis	<ul style="list-style-type: none"> ⌚ Onset is usually at 20-40 years ⌚ Conductive deafness ⌚ Tinnitus ⌚ Normal tympanic membrane (10% of patients may have a 'flamingo tinge', caused by hyperaemia) ⌚ Positive family history
Acoustic neuroma	<ul style="list-style-type: none"> ⌚ Hearing loss, vertigo, tinnitus ⌚ Absent corneal reflex is important sign ⌚ Associated with neurofibromatosis type 2
Hearing loss	Causes include excessive loud noise and presbycusis
Drugs	<ul style="list-style-type: none"> ⌚ Aspirin ⌚ Aminoglycosides ⌚ Loop diuretics ⌚ Quinine

The combination of sensorineural deafness, facial nerve palsy and cranial nerve V involvement suggests a cerebellopontine angle tumour, for example, acoustic neuroma.

Other causes include

- impacted ear wax
- chronic suppurative otitis media

Clinical physiology of the ear

- The **scala media** contains the organ of Corti, which produces nerve impulses in response to sound vibrations.
- **High-frequency waves** are detected in the **scala vestibuli**.
- **Low-frequency** waves are detected in the **scala tympani**.
- Normal hearing frequency ranges from 20 to 20 000 Hz.

Hearing loss

	Conductive hearing loss	Sensorineural hearing loss
Age of Onset	<ul style="list-style-type: none"> commonly in childhood or young adulthood 	<ul style="list-style-type: none"> commonly in middle or late age
Aetiology	<ul style="list-style-type: none"> Otosclerosis Otitis media Ear barotrauma Cerumen Impaction External auditory canal atresia 	<ul style="list-style-type: none"> Ménière's disease Acoustic neuroma Noise-induced hearing loss Internal ear infections Presbycusis
Pathophysiology	<ul style="list-style-type: none"> External or middle ear pathology that disrupts conduction of sound into the inner ear 	<ul style="list-style-type: none"> Inner ear, cochlear, or auditory nerve pathology that impairs neuronal transmission to the brain
Clinical Features	<ul style="list-style-type: none"> Hearing improves in noisy environments Volume of voice remains normal because inner ear and auditory nerve are intact Sound normally is not distorted Features of external auditory canal pathology (e.g., cerumen impaction) 	<ul style="list-style-type: none"> Hearing worsens in noisy environments Volume of voice may be loud because nerve transmissions are impaired Tend to lose higher frequencies preferentially, such that sounds may be distorted Absent features of external auditory canal pathology
Weber Test(unilateral hearing loss)	<ul style="list-style-type: none"> Lateralization to impaired ear (cannot hear ambient room noise well, so detection of vibration is greater) 	<ul style="list-style-type: none"> Lateralization to good ear (sound is not transmitted by damage inner ear or auditory nerve)
Rinne Test(unilateral hearing loss)	<ul style="list-style-type: none"> Bone conduction > air conduction (vibrations bypass blockage to reach the cochlea) 	<ul style="list-style-type: none"> Air conduction > bone conduction (the inner ear or auditory nerve cannot transmit sound information well regardless of how vibrations reach the cochlea)

Down syndrome : Hearing loss

- 60%-70 develop conductive deafness **due to glue ear**
- 10%-15% develop sensorineural deafness

Rinne's and Weber's test

- Performing both Rinne's and Weber's test allows differentiation of conductive and sensorineural deafness.
- **Rinne's test**
 - ⇒ tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus
 - ⇒ air conduction (AC) is normally better than bone conduction (BC)
 - ⇒ if BC > AC then conductive deafness
- **Weber's test**
 - ⇒ tuning fork is placed in the middle of the forehead equidistant from the patient's ears
 - ⇒ the patient is then asked which side is loudest
 - ⇒ in unilateral sensorineural deafness, sound is localised to the unaffected side
 - ⇒ in unilateral conductive deafness, sound is localised to the affected side

Motion sickness

Motion sickness - hyoscine > cyclizine > promethazine

Overview

- Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement

Management

- the BNF recommends hyoscine (e.g. transdermal patch) as being the most effective treatment.
 - ⇒ Use is limited due to side-effects
- non-sedating antihistamines such as cyclizine or cinnarizine are recommended in preference to sedating preparation such as promethazine

Peripheral neuropathy

Definitions

- **Allodynia:** pain caused by a stimulus that does not normally cause pain (e.g. light touch, contact with clothing)
- **Dysesthesia:** abnormal spontaneous sensations (burning, stinging, stabbing) from activities that do not normally cause pain)
- **Paresthesia:** an abnormal skin sensation in the absence of a stimulus (described as burning, prickling, itching, tingling)
- **Hyperesthesia:** increased sensitivity to sensory stimuli
- **Hypoesthesia:** decreased sensitivity to sensory stimuli

Classifications

- neuropathy is classified into:
 - ⇒ mononeuropathy commonly due to entrapment or trauma;
 - ⇒ mononeuropathy multiplex commonly due to leprosy and vasculitis; and
 - ⇒ polyneuropathy due to systemic, metabolic or toxic etiology.
- Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss	Predominately sensory loss
<ul style="list-style-type: none"> • Guillain-Barre syndrome • porphyria • lead poisoning • hereditary sensorimotor neuropathies (HSMN) - Charcot-Marie-Tooth • chronic inflammatory demyelinating polyneuropathy (CIDP) • diphtheria 	<ul style="list-style-type: none"> • diabetes • uraemia • leprosy • alcoholism • vitamin B12 deficiency • amyloidosis • Sjogren's syndrome

Types

- **Large-fibre neuropathy**
 - ⇒ the earliest clinically identifiable feature of peripheral sensory motor neuropathy.
 - ⇒ Reduced light pressure sensation and vibration sensation are the earliest clinically identifiable manifestations of large fibre neuropathy.
 - ⇒ **Features**
 - **paraesthesia**
 - glove and stocking sensory loss
 - increased risk of charcot arthropathy, particularly in association with autonomic nerve dysfunction.
 - **reduced vibration and proprioception sensation,**
 - **loss of reflexes** (diminished ankle jerks),
 - muscle wasting
 - increased blood flow.
- **Small-fibre neuropathy**
 - ⇒ typically presents with pain and loss of temperature sensation, with relative preservation of other sensory modalities and muscle strength.
 - General neurological examination and reflexes are usually normal
 - ⇒ not detectable on conventional nerve conduction studies, which can only investigate large fibres.
 - ⇒ **Causes** of small fiber neuropathy
 - **Diabetes**
 - ❖ is a **common** cause and should be excluded in any patient with a painful peripheral neuropathy.
 - ❖ Conditions in which the small fibres are preferentially affected in the early stages include **diabetes** and **amyloidosis**. In the later stages however the neuropathy in these conditions also affects large fibres.
 - **Amyloidosis**
 - **Fabry's disease**
 - ❖ X-linked lysosomal storage disorder
 - ❖ causes a painful peripheral neuropathy, due to deposition of glycosphingolipids within small sensory fibres.
 - ❖ Nerve conduction studies are typically normal as large fibres are unaffected.
 - **Tangier's disease**
 - **Hereditary sensory and autonomic neuropathy**
 - **Sjogren's syndrome:** **pure sensory** neuropathy (ganglionopathy).
 - **Chronic idiopathic small fiber sensory neuropathy**

Small-fibre neuropathy	Large-fibre neuropathy
Loss of pain and temperature	Loss of touch, vibration and position sense Sensory ataxia
Preservation of reflexes and motor function	Reflexes lost early and motor functions impaired
Electrophysiological test is silent	Impaired nerve conduction velocity
Skin biopsy are used	

Biopsy in diagnosis of neuropathy

- ⌚ **Skin punch biopsy** can be done if a **small-fiber neuropathy** is suspected; loss of nerve endings supports that diagnosis.
- ⌚ **Nerve biopsy** is occasionally done to help differentiate demyelinating from vasculitic **large-fibre neuropathies**.
- ⌚ If vasculitis is a consideration, the **biopsy specimen should include skin and muscle** to increase the likelihood of a definitive diagnosis.
- ⌚ If all limbs are affected, **MRI** can be done to rule out cervical **spinal cord compression**.

Lead neuropathy

- **purely motor neuropathy affecting mainly the upper limbs.**

Thalamic infarcts neuropathy

- commonly cause late-onset of severe neuropathic pain weeks to months after the stroke.
- The pain is intractable to analgesics.
- **The treatment of choice for neuropathic pain is amitriptyline/gabapentin.**

Alcoholic neuropathy

Epidemiology

- Alcohol abuse and diabetes are the commonest causes of peripheral neuropathy in the United Kingdom.

Pathophysiology

- Typically, **all fibre types are affected** and it is seen with a higher alcohol consumption more than 30 units.
- affects mainly the spinothalamic pathway.
- secondary to both direct toxic effects and reduced absorption of B vitamins (**thiamine deficiency**)

Features

- slowly progressive
- sensory symptoms typically present prior to motor symptoms
- Pain is usually a more dominant feature

Treatment

- **thiamine and cessation of alcohol use**

Peripheral neuropathy: axonal vs. demyelinating

Peripheral neuropathy	Causes	Nerve conduction studies (NCS)
Axonal	<ul style="list-style-type: none"> • alcohol • isoniazid • Simvastatin • Diabetes mellitus* • vasculitis • vitamin B12 deficiency* • Renal failure • hereditary sensorimotor neuropathies (HSMN) type II (*may also cause a demyelinating picture) 	<ul style="list-style-type: none"> • normal conduction velocity • reduced amplitude
Demyelinating	<ul style="list-style-type: none"> • Guillain-Barre syndrome • chronic inflammatory demyelinating polyneuropathy (CIDP) • Paraproteinæmia • Amiodarone (Amiodarone can cause a mixed demyelinating and axonal picture) • Refsum's disease • hereditary sensorimotor neuropathies (HSMN) type I (Charcot-Marie-Tooth disease) • Leukodystrophies. 	<ul style="list-style-type: none"> • reduced conduction velocity • normal amplitude

- Nerve conduction studies (NCS) are useful in determining between axonal and demyelinating pathology
- Segmental demyelination is a feature seen in axons in the central nervous system with **multiple sclerosis**.

Wallerian degeneration

- Wallerian degeneration is degeneration of the portion of the nerve distal to the injury.
- It occurs following axonal injury in both the peripheral and central nervous systems
- usually begins within 24-36 hours of injury.

Electromyogram (EMG)

- A pattern of rapidly recruited low amplitude short duration motor units on the electromyogram (EMG) would be considered to represent myopathic changes rather than de-innervation.

Drugs causing peripheral neuropathy

- Antibiotics: nitrofurantoin, metronidazole
- Amiodarone
- **Isoniazid**
- Vincristine
- Tricyclic antidepressants

Critical illness polyneuropathy

- Prolonged periods in the Intensive Therapy Unit, irrespective of the underlying pathology, are associated with a risk of developing critical illness polyneuropathy
- It is an axonal neuropathy and thus muscle wasting may occur
- May be predominantly sensory, predominantly motor or mixed

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barré syndrome (hyporeflexia or areflexia, paraesthesia and mild sensory deficits in the upper and lower extremities, weakness) except that it follows a chronic progressive course.

Overview

- CIDP is characterised by progressive weakness and impaired sensory function in the upper and lower limbs.
- **subacute** sensory and motor peripheral neuropathy
- The cause of the demyelination is not understood,
- More common in young adults and in men.
- mainly causes motor impairment (distal and proximal).
- **CIDP causes a large fibre peripheral neuropathy (Joint position sense and vibration are carried through large fibres)**

Features

- weakness of the limbs
- **areflexia**
- abnormal sensation (which typically begins distally)
- fatigue.
- **Autoantibodies against GM1 gangliosides**

Differential diagnosis

1. CIDP is closely linked to **Guillain-Barré syndrome (GBS)**, and is thought by some to be its chronic counterpart.
 - ⇒ Both CIDP and GBS can affect motor and sensory nerves
 - ⇒ (GBS) is an **acute** (which reaches its peak in severity **within six weeks**), post-infectious neuropathy
 - ⇒ Whereas CIDP is **subacute (several months history)**
2. **Hereditary motor and sensory neuropathy (HMSN)** is normally a **very chronic** neuropathy developing **over many years** and usually with a family history of the condition.

Treatment

- Corticosteroids
- plasmapheresis
- Intravenous immunoglobulin
- Physiotherapy

Diabetic neuropathy(see endocrinology system)

Neuropathic pain

Definition

- neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system.
- It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- diabetic neuropathy
- post-herpetic neuralgia
- trigeminal neuralgia
- prolapsed intervertebral disc

Management of neuropathic pain

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
 - ⇒ please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

January 2019 exam: severe 'shooting' pains after blistering rash. What is the most appropriate next step in management? Amitriptyline

Autonomic neuropathy

Features

- impotence, inability to sweat, postural hypotension
- postural hypotension e.g. drop of 30/15 mmHg
- loss of decrease in heart rate following deep breathing
- pupils: dilates following adrenaline instillation

Causes

- diabetes
- Guillain-Barre syndrome
- multisystem atrophy (MSA), Shy-Drager syndrome
- Parkinson's
- infections: HIV, Chagas' disease, neurosyphilis
- drugs: antihypertensives, tricyclics
- craniopharyngioma

Hereditary sensorimotor neuropathy (HSMN) (Charcot-Marie-Tooth disease)

Mixed motor and sensory symptoms, slowly progressing initially in the lower limbs and then to the upper limbs, together with a family history suggests a diagnosis of Hereditary sensorimotor neuropathy (HSMN)

Definition

- hereditary nerve disorders with defective production of peripheral myelin protein-22 which is involved in the structure and function of the myelin sheath.
- Charcot-Marie-Tooth disease** is the most commonly inherited neurological disorder,

Genetics

- autosomal dominant**
- caused by deletion in the PMP22 gene, the same gene mutation responsible for hereditary neuropathy with liability to pressure palsies.
- Common peroneal nerve is the most commonly affected nerve (36%) followed by the ulnar nerve (28%).

Types

- HSMN type 1**
 - the most common form
 - primarily due to demyelinating pathology
 - hence C fibres are not affected, as they are unmyelinated.
 - Which nerve fibers are relatively preserved in this patient?
 - ◆ C fibers
 - due to defect in PMP-22 gene (which codes for myelin)
 - loss of myelin in peripheral neurons
 - features often start at puberty
 - motor symptoms predominate
 - distal muscle wasting, pes cavus, clawed toes
 - foot drop, leg weakness often first features
- HSMN type 2**
 - primarily due to axonal pathology
 - loss of peripheral neurone themselves

Features

- motor and sensory deficits.
- early weakness of the distal muscles of the limbs.
- scoliosis
- pes cavus**
 - a deformity of the foot involving high arches, muscle wasting and clawed toes.

Diagnosis

- neurophysiology**: Electromyography (EMG) and nerve conduction studies (NCS) may distinguish between the demyelinating (type 1) and axonal (type 2) forms.
- Diagnosis confirmed by genetic testing.
- Nerve biopsy, usually the sural nerve, will demonstrate "**onion-bulb**" formations due to continual remyelination and demyelination of peripheral nerves.

Management

- The mainstay of the management is physical therapy.

Prognosis

- Life expectancy is normal.

MRCPUK-part-1-September 2017 exam: A woman with Charcot-Marie-Tooth disease (type 1), how likely her children will get the disease?

→ 50% (autosomal dominant)

Mononeuritis multiplex

Definition : ≥ 2 isolated mononeuropathies

Causes

- Axonal injury caused by damage to vasa nervorum
- Occurs in conditions characterized by the development of granulomas and/or microangiopathy (e.g., diabetes mellitus, rheumatoid arthritis, vasculitides, SLE, Lyme disease, amyloidosis, HIV, polyarteritis nodosa)

Features: painful, asymmetrical sensory and motor symptoms

Diagnosis: Nerve biopsy should be performed to confirm the diagnosis

Treatment: includes prednisolone and cyclophosphamide

Refsum's disease**Overview**

- autosomal recessive disorder
- caused by defective alpha oxidation of phytanic acid leading to its accumulation in tissues.
- Phytanic acid is present in a wide variety of foods including dairy products, fish, beef and lamb.
- The onset of the disease is normally in the late teens or 20s.

Features

- sensorimotor peripheral neuropathy**
- sensorineural deafness,
- anosmia,
- cerebellar ataxia
- pes cavus.
- Night blindness and visual problems occur secondary to **retinitis pigmentosa**.
- Cardiac conduction abnormalities and cardiomyopathies may also occur.
- Epiphyseal dysplasia causes a characteristic shortening of the fourth toe.
- Serum phytanic acid levels are elevated.**

Treatment

- dietary restriction of foods containing phytanic acid.

Vasculitic neuropathy**Overview**

- The presence of nail fold infarcts and the multifocal nature of the neuropathy indicate that a vasculitic cause is most likely**
- Hepatitis C infection may be associated with cryoglobulinaemia, which causes a vasculitic syndrome including neuropathy

Other conditions associated with vasculitic neuropathy include

- Polyarteritis nodosa
- Churg-Strauss syndrome
- rheumatoid arthritis
- systemic lupus erythematosus
- systemic sclerosis
- Wegener's granulomatosis

Treatment include one or several of the following

- high-dose intravenous steroids
- plasma exchange
- intravenous immunoglobulins

Guillain-Barre syndrome

FVC is used to monitor respiratory function in Guillain-Barre syndrome

- also known as **Post-infectious polyradiculopathy**

Definition

- Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection :
 - ⇒ classically *Campylobacter jejuni*
 - ⇒ **cytomegalovirus**

Pathogenesis

- cross reaction of antibodies with gangliosides in the peripheral nervous system
- correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated
- **anti-GM1 antibodies in 25% of patients**

Features

- **characteristic features**
 - ⇒ progressive weakness of all four limbs. The weakness is classically ascending i.e. the lower extremities are affected first, however it tends to affect proximal muscles earlier than the distal ones.
 - ⇒ Sensory symptoms tend to be mild (e.g. distal paraesthesia) with very few sensory signs. However, a sensory level is NOT a feature and would suggest cervical myelopathy
 - ⇒ symmetrical involvement is typical, asymmetry present in only 9% of patients.
 - ⇒ Some patients experience back pain in the initial stages of the illness.
- **Other features**
 - ⇒ areflexia
 - ⇒ cranial nerve involvement e.g. diplopia
 - ⇒ autonomic involvement: e.g. urinary retention
 - ⇒ Muscle wasting is typical with prolonged illness.
 - ⇒ **Bulbar involvement occurs in 50%,** with a risk of aspiration and respiratory insufficiency
 - ⇒ urinary incontinence or retention (in 20% of cases).
- **Less common findings**
 - ⇒ papilloedema: thought to be secondary to reduced CSF resorption

Investigations

- **CSF analysis**
 - ⇒ elevated protein, with normal glucose and no pleocytosis.
 - ⇒ a rise in CSF protein doesn't peak until the second or third week of the illness.
 - ⇒ CSF cell counts are usually within normal limits,
- Nerve conduction studies (including F waves for the proximal spinal root, looking for widespread demyelination)
- MRI may be indicated to rule out spinal cord lesions, peripheral neuropathies and neuromuscular junction disorders.

Management

- **IV immunoglobulins (IVIG):**
 - ⇒ **First line therapy.**
 - ⇒ as effective as plasma exchange. No benefit in combining both treatments.
 - ⇒ IVIG may be easier to administer and tends to have fewer side-effects
- plasma exchange
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function .
 - ⇒ **FVC of less than 1 litre would be an indication for immediate ventilation**
 - ⇒ **Forced vital capacity of 1.4 L is most likely to predict the need for invasive ventilation**
 - ⇒ FVC of less than 15ml/kg (or less than 30% of FVC predicted) or a rising PaCO₂ are indications for mechanical ventilation.

Prognosis

- 20% suffer permanent disability, 5% die
- **Poor prognostic features**
 - ⇒ age > 40 years
 - ⇒ poor upper extremity muscle strength
 - ⇒ **previous history of a diarrhoeal illness (specifically *Campylobacter jejuni*)**
 - ⇒ high anti-GM1 antibody titre
 - ⇒ need for ventilatory support
 - ⇒ There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome

MRCPUK-part-1-January 2008 exam: Regarding nerve conduction studies for suspected Guillain-Barre syndrome. Which finding would be most consistent with this diagnosis?
Reduced conduction velocity

MRCPUK-part-1-May 2019 exam: a patient developed weakness in his legs extended to his arms after viral illness. ↓ power, reflexes and sensation in his lower limbs. Developed SOB & ↓ (FVC). Given the likely diagnosis, what is the treatment of choice? **Intravenous immunoglobulin**

(Guillain-Barre syndrome (GBS) secondary to a viral illness, possibly the **Epstein-Barr virus**)

MRCPUK-part-1-May 2020 exam: H/O double vision & ↓ eye movement + unsteadiness + ↓ reflexes + past-pointing. What is the most likely diagnosis? **Miller Fisher syndrome**

Miller Fisher syndrome

- areflexia, ataxia, ophthalmoplegia
- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. **The eye muscles are typically affected first**
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- **anti-GQ1b antibodies are present in 90% of cases**

DVLA: neurological disorders

DVLA advice post CVA: cannot drive for 1 month

DVLA advice post multipler TIAs: cannot drive for 3 months

- The guidelines below relate to car/motorcycle use unless specifically stated.
- For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- **First seizure: 6 months** off driving*.
 - ⇒ *previously rule was 12 months. It is now 6 months off driving if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicated
- For patients with **established epilepsy** they must be fit free for **12 months** before being able to drive
- **Stroke or TIA: 1 month** off driving
- **Multiple TIAs** over short period of times: **3 months** off driving
- **Craniotomy** e.g. For meningioma: **1 year** off driving
 - ⇒ if the tumour is a **benign meningioma** and there is **no seizure** history, licence can be reconsidered **6 months** after surgery if remains seizure free.
- **Pituitary tumour:**
 - ⇒ craniotomy: 6 months;
 - ⇒ trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- **Glioblastoma**
 - ⇒ A patient with a high-grade glioma (that is, WHO grade 3 or 4) such as a **glioblastoma will be unable to drive for at least two years following completion of treatment.**
 - ⇒ After the two years have elapsed the DVLA will consult with the physicians involved in the patient's care and a decision is made regarding return of the licence.
- **Brain metastases**
 - ⇒ **solitary metastatic** deposit that is fully excised would be considered for a licence **one year** after primary treatment if free from recurrence and no evidence of secondary spread elsewhere.

- ⇒ **multiple metastases** would require at least **two years** off driving from time of completion of treatment. After the two years have elapsed the DVLA will consult with the physicians involved in the patient's care and a decision is made regarding return of the licence.
- **Narcolepsy/cataplexy:**
 - ⇒ cease driving on diagnosis,
 - ⇒ can restart once 'satisfactory control of symptoms'
- **Chronic neurological disorders** e.g. multiple sclerosis, motor neuron disease:
 - ⇒ DVLA should be informed,
 - ⇒ complete PK1 form (application for driving licence holders state of health)
- **Syncope**
 - ⇒ simple faint: no restriction
 - ⇒ single episode explained and treated: 4 weeks off
 - ⇒ single episode, unexplained: 6 months off
 - ⇒ two or more episodes: 12 months off

DVLA regulations : for seizure and stroke

Case	Group 1 Car & motorcycle	Group 2 Bus and lorry
First epileptic seizure/isolated seizure	no driving for 6 months.	no driving for 5 years.
Epilepsy or multiple seizures	no driving for 12 months.	must remain seizure-free for 10 years (without epilepsy medication)
Dissociative seizures	no driving for 3 months after event free.	no driving for 3 months after event free.
Withdrawal of epilepsy medication	no driving for 6 months after the last dose.	must remain seizure-free for 10 years (without epilepsy medication). (no special considerations for withdrawal)
Single TIA, Stroke	no driving for 1 month.	no driving for 1 year.
Multiple TIA	no driving for 3 months.	no driving for 1 year.

Susac syndrome

- Susac syndrome presents with the triad of:
 - ⇒ **Encephalopathy**
 - ⇒ **branch retinal artery occlusion**
 - ⇒ **and hearing loss**
- Due to involvement of the pre-capillary arterioles of the brain, retina and cochlea.

Altitude related disorders

Types

- There are three main types of altitude related disorders:
- All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes
 1. **acute mountain sickness (AMS),**
 - **Features** of AMS start to occur above 2,500 - 3,000m,
 - developing gradually over 6-12 hours and potentially last a number of days
 - ❖ headache
 - ❖ nausea
 - ❖ fatigue
 - Prevention and treatment of AMS
 - ❖ the risk of AMS may actually be positively correlated to physical fitness
 - ❖ gain altitude at no more than 500 m per day
 - ❖ acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
 - Treatment:
 - ❖ Descent
 - ❖ generally a self-limiting condition.
 2. **high altitude pulmonary edema (HAPE)**
 - A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE)
 - potentially fatal conditions
 - HAPE presents with classical pulmonary oedema features
 - Management of HAPE
 - ❖ descent
 - ❖ nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors
 - ⇒ All seem to work by reducing systolic pulmonary artery pressure
 - ❖ oxygen if available
 3. **high altitude cerebral edema (HACE).**
 - A minority of people above 4,000m go onto develop high altitude cerebral oedema (HACE),
 - potentially fatal conditions
 - HACE presents with headache, ataxia, papilloedema
 - Management of HACE
 - ❖ descent
 - ❖ dexamethasone

Complex regional pain syndrome (CRPS)

- (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia.
- (CRPS) is a chronic pain condition that can affect any area of the body, but often affects an arm or a leg, and occurs after an injury or rarely after a sudden illness such as a heart attack or stroke.
 - ⇒ typically occur following surgery or a minor injury.
- The condition can sometimes appear without obvious injury to the affected limb.
- 3 times more common in women.

- CRPS may have three stages (acute, dystrophic, and atrophic), with variable progression from one stage to another.

There are two types of CRPS:

- **type I (most common): there is no demonstrable lesion to a major nerve**
- type II: there is a lesion to a major nerve

Character of the pain

- intense and burning
- disproportionate to the original injury
- worse over time
- Spreads beyond the site of injury and
- associated with hyperalgesia, hyperpathia or allodynia on examination. These features do not occur in DVT, osteomyelitis, or cellulitis.

Features

- progressive, disproportionate symptoms to the original injury/surgery
- allodynia
- temperature and skin colour changes
- oedema and sweating
- motor dysfunction
- the Budapest Diagnostic Criteria are commonly used in the UK

Diagnosis

- clinical diagnosis
- **Plain radiographs** may show soft tissue swelling, peri-articular osteoporosis, and rarely erosions
- **MRI** may also show bone marrow oedema apart from these changes
 - ⇒ In the atrophic phase, imaging may show contractures.
- **99mTc bone scan** shows hypervascularity in the acute phase, and hypovascularity in the

Management

- early physiotherapy is important
- neuropathic analgesia in-line with NICE guidelines
- specialist management (e.g. Pain team) is required

Dystonia

Definition:

- involuntary sustained or spasmodic muscle contractions

Types

- **Focal dystonias**
 - ⇒ Involves a single body part
 - ⇒ Cervical dystonia, or torticollis, is the most common focal dystonia.
 - ⇒ In 20-30% of patients, focal dystonias become segmental or multifocal.
 - ⇒ Blepharospasm is a type of dystonia described as a sustained eyelid twitch.
 - If it is associated with stress, lack of sleep, nutrition, and strain.
 - ⇒ **writer's cramp dystonia** or musician's dystonia
 - A common upper limb dystonia
 - This task-specific dystonia, manifesting as hyperextension or hyperflexion of the wrist and fingers, → **unable to write**
 - may be triggered by repetitive activities such as writing and attempting to play the piano or other musical instruments.

- ⇒ often relieved by a geste antagoniste, in which palpation of another unaffected part of the body leads to relief of symptoms, thought to be a result of alternative sensory input to cortical networks with altered plasticity.
- Segmental dystonia
 - ⇒ Affects 2 or more contiguous regions of the body
- Multifocal dystonia
 - ⇒ Consists of abnormalities in noncontiguous body parts
- Generalised dystonias,
 - ⇒ involve a greater number of muscle groups.
 - ⇒ involves the trunk and limbs.

Treatment

- Benztropine is an anti-cholinergic drug that is used in the treatment of Parkinson's disease, Parkinsonism, and acute dystonia.

Cervical dystonia (torticollis)

- The term *torticollis* is derived from the Latin words *tortus* for twisted neck
- Torticollis is a fixed or dynamic tilt, rotation, or flexion of the head and/or neck.
- involuntary neck movements
- commonly affects women
- Secondary causes need to be excluded such as drugs (eg neuroleptics) and cervical spine abnormalities
- **Botulinum toxin injection is the first-line treatment for cervical dystonia (torticollis)**

Botulism

Descending weakness with autonomic dysfunction (fixed dilated pupils) is typical of botulism.

Definition

- Botulism is a neurological disorder caused by *Clostridium botulinum* and is characterized by flaccid paralysis due to inhibition of acetylcholine release at the neuromuscular junction.

Features

- **The clinical presentation of descending weakness with autonomic dysfunction (fixed dilated pupils) is typical of botulism.**
- Typical initial features include:
 - ⇒ Diplopia
 - ⇒ Ptosis
 - ⇒ Facial weakness
 - ⇒ Dysarthria, and
 - ⇒ Dysphagia.
- Later, respiratory difficulty and limb weakness occur.
- impaired cholinergic transmission also involves **autonomic** synapses, causing poorly reactive dilated pupils, dry mouth, paralytic ileus and occasionally bradycardia.
- Reflexes are depressed or absent,

Investigations

- It is a neuromuscular junction disorder and therefore nerve conduction studies and EMG are normal.
- Cerebrospinal fluid analysis is usually normal.
- Repetitive nerve stimulation shows incremental responses, which is diagnostic of botulism.
- sensation is normal

Treatment

- **Heptavalent antitoxin is the most appropriate therapy**

Botulinum toxin

- **Botulinum toxin is produced by Clostridium botulinum, a Gram-positive, spore-forming, obligate anaerobe**
- Botulinum toxin type A (or trade name Botox®)

Action

- block acetylcholine release at the neuromuscular junction and so to produce muscle weakness.
- myasthenia gravis would be expected to **worsen** with this treatment

Indications

- **Botulinum toxin is the treatment of choice for focal dystonia (such as torticollis, and hemi-facial spasm) and focal dystonia.**
- Botulinum toxin injections are also used in patients with:
 - ⇒ hemifacial spasm
 - ⇒ blepharospasm
 - ⇒ spasticity
 - spasticity associated with stroke
 - spasticity associated with cerebral palsy
 - ⇒ Primary axillary hyperhidrosis
 - ⇒ Strabismus
 - ⇒ Cervical dystonia.

Side effects

- Occasionally **systemic absorption of the toxin can affect distal muscles causing symptoms such as diplopia and dysphagia.**
- The main side-effect is excessive weakness in the treated muscle

Contra-indications

- myasthenia gravis
- other generalised muscle conditions

Paraneoplastic cerebellum syndrome

The patient with progressive ataxia and dysarthria following malignancy

Causes

- Associated malignancies are lung cancer (usually with small cell lung carcinoma), breast cancer, ovarian cancer and lymphoma

Features

- include ataxia, dysarthria, vertigo, oscillopsia, nystagmus and dysmetria

Investigations

- Brain imaging and CSF analysis are either normal or show non-specific changes

- antibodies
 - ⇒ **anti-Hu antibody** (a type of antineuronal antibody)
 - ⇒ anti-Purkinje-cell antibodies
- CT chest, abdomen and pelvis and mammogram are required to look for a primary neoplasm.
- A whole body positron emission tomography (PET) scan is preferable but not widely available.

Treatment

- Occasionally patients respond to steroids, immunoglobulins or plasmapheresis.

Lumbosacral plexopathy

The patient presents with generalised weakness of the right leg associated with pelvic pain, leg oedema and autonomic dysfunction. The most likely diagnosis is a lumbosacral plexopathy.

Overview

- Anatomically, the lumbosacral plexus consists of lumbar (L1-L4) and sacral (S1-S5) portions.
- **Upper: lumbar plexus** lesion will cause weakness of hip flexion and adduction of the thigh and extension of the leg with anaesthesia over the anterior thigh and leg.
- **Lower: sacral plexus lesions** will weaken the posterior thigh and foot muscles.
- **Lesions affecting the entire plexus** will affect all muscle groups causing weakness or paralysis of the leg, areflexia and anaesthesia from the toes, to involve the perianal area.

Causes

- **Trauma:** Posterior hip dislocation, Sacral fracture
- **Metabolic**, inflammatory, and autoimmune causes: DM (diabetic amyotrophy), Amyloidosis, Sarcoidosis
- **Infections and local abscess** (e.g. vertebral osteomyelitis, tuberculosis, fungal infections, psoriasis abscess)
- **Radiation** therapy of the abdominal and pelvic malignancies.
- **Pregnancy-related:** Mostly occur in the third trimester and after delivery due to birth trauma.
- **Damage to the vasculature innervating the LS plexus:** femoral vessel catheterization

Epidemiology

- More common in women due to the predisposing risk factors of pregnancy and gynecological cancers.

Pathophysiology

- Direct injury, compression or traction on the plexus (Trauma, tumor, hematoma)
- Microvascular injury and ischemic damage (Radiation)
- Inflammatory or microvascular changes (Diabetic and non-diabetic)

Features

- **Low back pain** radiating to **one side**.
 - ⇒ Pain may be positional, worse in a supine position.
 - ⇒ Patients with diabetic LS plexopathy (**diabetic amyotrophy**) typically complain of unilateral pain in the **proximal thigh**.
 - ⇒ **lumbosacral plexopathy secondary to radiotherapy is usually painless.**

- **Muscle weakness** and atrophy may occur in severe cases.
- A straight leg raise test is positive in more than half of the patients.
- Knee jerk reflex is affected in **lumbar plexopathy** and ankle jerk is affected in **sacral plexopathy**.
- **Muscle weakness** in **hip flexion, knee extension, or adduction** suggests a possible injury to the **lumbar plexus**.
- **Sensory changes** ((numbness, paresthesias, dysesthesias (painful sensations elicited by nonpainful cutaneous stimuli, e.g., light touch)).
 - ⇒ Medial thigh, anterior thigh, and medial suggest lumbar plexus involvement
 - ⇒ Posterior thigh, dorsum of the foot, and perineum suggest sacral plexus involvement.

A history of a road traffic accident, abdominopelvic neoplasm, radiotherapy, abdominal surgery, diabetes mellitus, bleeding disorders, or recent pregnancy hints towards lumbosacral plexopathy and narrows down the etiology.

Radiation plexopathy can often present without pain, only weakness and sensory changes. Unlike other types of plexopathy, it is usually bilateral and can occur even years after radiation.

Diagnosis

- MRI with gadolinium contrast is the best test for the evaluation of the LS plexus.
- When there are contraindications to MRI (e.g., a noncompatible pacemaker), a computed tomography (CT) scan with contrast can be utilized.
- Electromyography (EMG) differentiate lumbosacral plexopathy from other types of neuropathy or radiculopathies.
 - ⇒ Denervation of the paraspinal muscles is commonly seen in radiculopathy and helps to differentiate from lumbosacral plexopathy.

Treatment

- Treatment of underline cause: e.g. relieve of compression
- Symptomatic treatment with analgesics and muscle relaxants:
 - ⇒ Compression: NSAIDs, opioids
 - ⇒ Neuropathic pain: pregabalin, gabapentin, duloxetine, amitriptyline
 - ⇒ Diabetic amyotrophy is a transient condition that usually resolves with good glycemic control.
- For radiation-induced plexopathy: there are no known treatments , physiotherapy and rehabilitation are the mainstays of treatment. Further radiotherapy sessions should be discontinued.

Cervical roots

Root	Dermatome distribution	Myotome distribution	Tendon reflex
C2	Posterior half of the skull (cap)	-	-
C3	High turtleneck shirt	-	-
C4	Upper outer shoulder, Low-collar shirt	Shoulder abduction	Nil
C5	Outer arm, forearm	Shoulder abduction, elbow flexion	Bicep
C6	Index and thumb	Wrist extension	Supinator
C7	Middle finger centre of palm	Finger and elbow extension	Triceps
C8	Little and ring finger, ulnar border of hand	Wrist/finger flexion	Finger jerk

C6: Make a 6 with your left hand by touching the tip of the thumb & index finger together

Symptoms and signs of a C6 root lesion include

- Paraesthesia in the thumb or lateral distal forearm
- Weakness of brachioradialis, biceps, or triceps and
- Diminished biceps and brachioradialis reflexes in conjunction with an increased triceps reflex.

Winging of the scapula is caused by paralysis of the long thoracic nerve to serratus anterior (C5, 6, 7).

Spinal lesion at the level of C8:

- Weakness of finger flexion + Loss of sensation over the medial aspect of the arm; forearm and hand (Lateral aspect of arm is C5)

Erb-Duchenne palsy ('walter's tip')

- due to damage of the upper trunk of the brachial plexus (C5,C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

Weakness of shoulder abduction

- May be due to C5 or an axillary nerve lesion:
 - ⇒ **C5 lesion**
 - weakness of biceps (C5, C6)
 - loss of the sensation of the **lateral aspect of the upper arm**
 - ⇒ **Axillary nerve lesion**
 - spinal root : C5/C6

- motor function: innervate teres minor and deltoid muscles
- sensory function: give rise to superior lateral cutaneous nerve of arm which innervate the skin over the lower deltoid (regimental badge area)
- loss of sensation of the **regimental badge area**
- Absence of sensory loss indicates a lesion at the anterior horn cell.

Thoracic roots

Root	Dermatome	Myotome	Reflex
T 4	Nipples		
T 5	Inframammary fold		
T 7	Xiphoid process		
T 10	Umbilicus		

T1 nerve root injury:

damage to both the median and ulnar nerves → Global muscle wasting of the hand

Lumber roots

Root	Dermatome	Myotome	Reflex
L1	Inguinal ligament	-	-
L2	Upper anterior and medial thigh	Psoas hip abductor	-
L3	Mid anterior and medial thigh	Psoas quadriceps	Patella (L3,L4)
L4	Knee caps, medial aspect of leg, lower lateral thigh	Tibialis anterior, extensor hallucis	Patella (L3,L4)
L5	Big toe, dorsum of foot (except lateral aspect), lateral aspect of leg	Extensor hallucis, peroneal, gluteus medius, dorsiflexors, hamstrings	L5 has no reflex. Therefore, an acute lumbar disc prolapse resulting in L5 radiculopathy is commonly misdiagnosed as malingering.

L1: Inguinal ligament (L for ligament, 1 for 1inguinal)

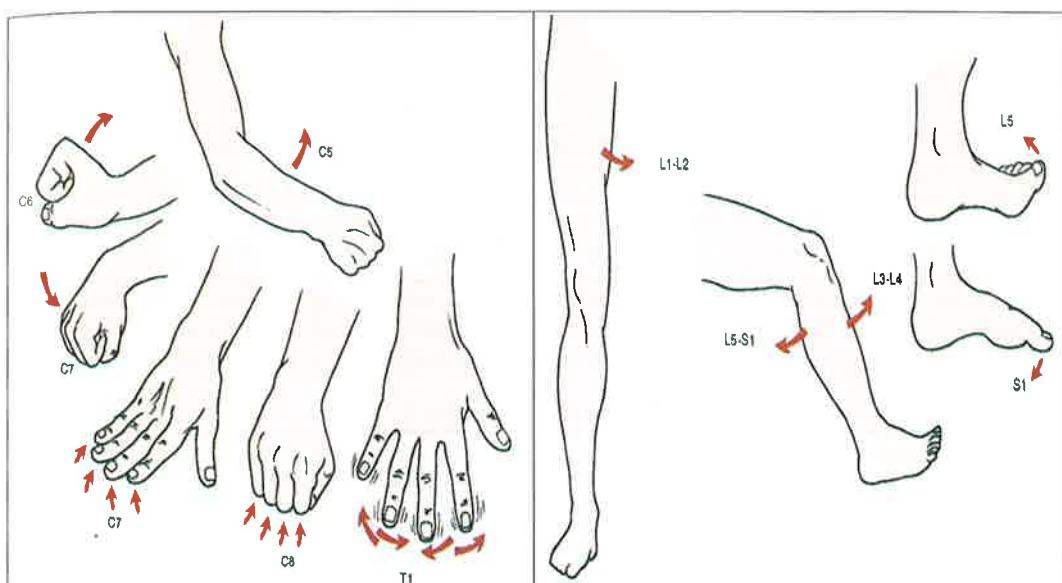
The L4 dermatome is located at the knee caps

L5 = Largest of the 5 toes

L5 lesion features: loss of foot/big toe dorsiflexion + sensory loss dorsum of foot

Sacral roots

Root	Dermatome	Myotome	Reflex
S1	Lateral foot, small toe , sole of the foot, Posterior, lateral thigh and calf	Peroneal planter flexor	Ankle (S1, S2)
S2	Popliteal fossa	-	Ankle (S1, S2)
S3-5	Medial buttock and perianal skin in a concentric manner with S3 most lateral and S5 closest to the anus	Bladder, rectum	S2-4 reflex is part of the anocutaneous reflex or anal wink.



Deep tendon reflexes: which test for which nerve root?

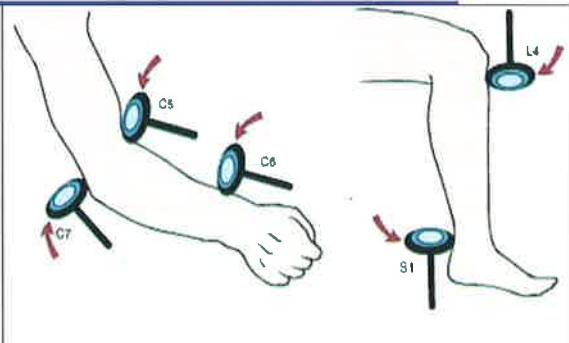
C5 – Biceps

C6 – Biceps, Brachioradialis

C7 – Triceps

L4 – Patellar (knee jerk) (femoral nerve mediated)

S1 – Achilles (ankle jerk) (tibial nerve mediated)



Inverted brachioradialis reflex (inverted supinator jerk):

- An inverted supinator jerk, where the **biceps jerk is absent** but generates a supinator jerk with **reflex flexion of the fingers**, is indicative of **cervical myelopathy with C5/6 nerve root damage.**

MRCPUK-part-1-September 2019 exam: H/O neck & arm pain like 'electric shocks', worse on turning head + decreased sensation on the dorsal aspect of the thumb and index finger. What is the most likely underlying diagnosis?

→ **C6 radiculopathy**

MRCPUK-part-1-septemer-2017: Which nerve (and its nerve root) are you tested in triceps reflex?

→ **Radial nerve C7**

Which spinal dermatome is responsible for the initial vague perumbilical discomfort in appendicitis?

⇒ **T10**

mrcpuk.org SCE sample question: H/O pain affecting buttock region and the lateral border and sole of his foot, in association with paraesthesiae of the sole on walking. What is the correct nomenclature for the nerve root from which these symptoms have arisen?

→ **S1** (The S1 nerve root is mapped to the sole of the foot)

Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury
Axillary nerve (C5, C6)	Shoulder abduction (deltoid muscle)	Inferior region of the deltoid muscle	Humeral neck fracture/dislocation Results in flattened deltoid
Radial nerve (C5-C8)	Extension (forearm, wrist, fingers, thumb)	Small area between the dorsal aspect of the 1st and 2nd metacarpals	Humeral midshaft fracture Palsy results in wrist drop
Median nerve (C6, C8, T1)	LOAF* muscles Features depend on the site of the lesion: <ul style="list-style-type: none">• wrist: paralysis of thenar muscles, opponens pollicis• elbow: loss of pronation of forearm and weak wrist flexion	Palmar aspect of lateral 3 and half fingers	Wrist lesion → carpal tunnel syndrome
Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF* Wrist flexion	Medial 1 and half fingers	Medial epicondyle fracture Damage may result in a ' claw hand '
Long thoracic nerve (C5-C7)	Serratus anterior		Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy Damage results in a winged scapula

*LOAF muscles

- Lateral two lumbricals
- Opponens pollicis
- Abductor pollicis brevis
- Flexor pollicis brevis

Radial nerve

Overview

- arises from the posterior cord of the brachial plexus (**C5-8**)
- It is susceptible to compression or traumatic damage as it winds around the humerus (including 'Saturday night palsy', a pressure palsy sustained while sleeping in an awkward position under the influence of alcohol),
- may also be compressed in the axilla (eg from using a crutch).

Regions innervated

Motor (main nerve)	<ul style="list-style-type: none"> • Triceps • Anconeus • Brachioradialis • Extensor carpi radialis
Motor (posterior interosseous branch)	<ul style="list-style-type: none"> • Supinator • Extensor carpi ulnaris • Extensor digitorum • Extensor indicis • Extensor digiti minimi • Extensor pollicis longus and brevis • Abductor pollicis longus
Sensory	<ul style="list-style-type: none"> • Dorsal aspect of lateral 3 1/2 fingers • The commonest site of sensory loss is at the anatomical snuffbox (small area between the dorsal aspect of the 1st and 2nd metacarpals)

Patterns of damage

- **wrist drop** with hand pronation and thumb adduction
- sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above
- paralysis of triceps

Features according to site of damage

Site of lesion	Sensory symptoms	Motor symptoms
Axilla	<ul style="list-style-type: none"> All below 	<ul style="list-style-type: none"> All below Paralysis of triceps m
Mid-arm	<ul style="list-style-type: none"> All below Numbness, paresthesia, pain along lateral posterior arm 	<ul style="list-style-type: none"> All below Wrist drop ⇒ weakness of extensors (hand, finger and wrist joint).
Elbow (radial tunnel)	<ul style="list-style-type: none"> Pain and tenderness following extension or repetitive pronation/supination 	<ul style="list-style-type: none"> Sometimes weakness of extension and supination, secondary to pain (not to missing innervation)
Deep Forearm (posterior interosseous nerve)	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Paralysis of the finger extensors (no true wrist drop)
Superficial forearm and wrist (superficial radial nerve)	<ul style="list-style-type: none"> Deficits on the radial side of the dorsum of the hand (thumb, index finger, and the radial half of the middle finger) 	<ul style="list-style-type: none"> None

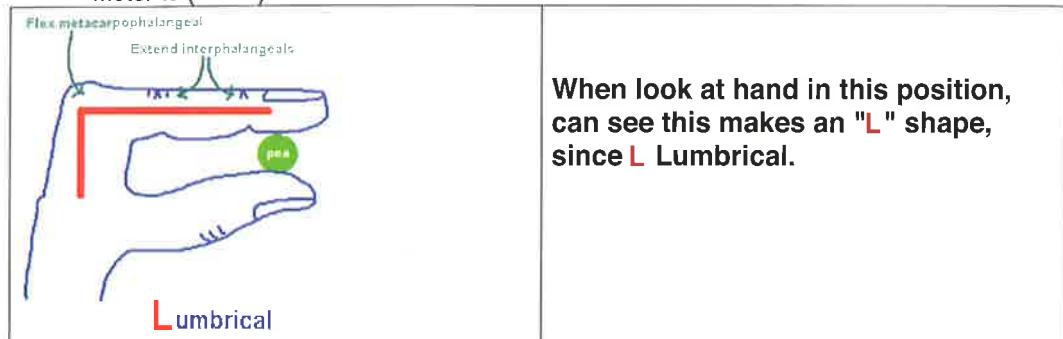
Common questions about radial nerve:

Question	Answer
Rout?	C5-8
Typical injury	<ul style="list-style-type: none"> Fractured midshaft of humerus/compression of axilla by chair-crutches. 'Saturday night palsy',
Motor loss?	extensor muscles (forearm, wrist, fingers, thumb)
Sensory loss?	<ul style="list-style-type: none"> dorsal aspect of lateral 3 1/2 fingers anatomical snuffbox
The commonest site of sensory loss	anatomical snuffbox (small area between the dorsal aspect of the 1st and 2nd metacarpals)
Sign?	wrist drop

Median nerve

Overview

- arises from lateral and medial cords of the brachial plexus (C6-8, T1)
- Motor to (LOAF)



When look at hand in this position, can see this makes an "L" shape, since **L** Lumbrical.

- ⇒ Lateral two lumbricals
- ⇒ Opponens pollicis → rotates and flexes the thumb
- ⇒ Abductor pollicis brevis → **Abduction** and opposition of the thumb
- ⇒ Flexor pollicis brevis → Flexes the thumb at the first metacarpophalangeal joint
- the above three form the **thenar eminence muscles**
- also supplies flexor muscles of the forearm
- Sensory to** → palmar aspect of lateral (radial) 3 1/2 fingers

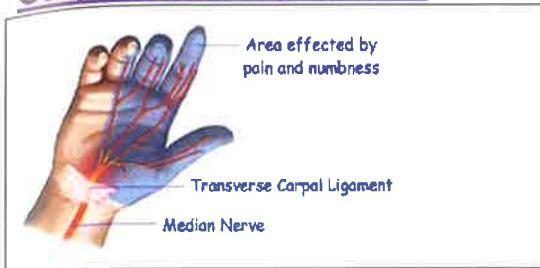
Patterns of damage

- Damage at wrist**
 - ⇒ e.g. carpal tunnel syndrome
 - ⇒ paralysis and wasting of thenar eminence muscles
 - ⇒ sensory loss to palmar aspect of lateral (radial) 3 1/2 fingers
- Damage at elbow, as above plus:**
 - ⇒ unable to pronate forearm
 - ⇒ **weak wrist flexion**
 - ⇒ **ulnar deviation of wrist**
- Anterior interosseous nerve** (branch of median nerve)
 - ⇒ leaves just below the elbow
 - ⇒ results in loss of pronation of forearm and weakness of long flexors of thumb and index finger

Common questions about median nerve:

Question	Answer
Rout	C6-8, T1
Typical injury?	Fracture of supracondylar humerus/ Carpal tunnel syndrome
Motor deficit?	Opposition of thumb/Lateral finger flexion (ulnar deviation of wrist)/ wrist flexion /(LOAF) muscles
Sensory deficit	Dorsal-palmar lateral 3.5 fingers/thenar eminence
Sign?	Ape hand (loss of Opponens pollicis)/Pope's hand (open digits 1-3 when trying to make fist)

Carpal tunnel syndrome



Overview

- Carpal tunnel syndrome is caused by **compression of median nerve in the carpal tunnel**.
- More common in females (F:M, up to 8:1).
- Commonly bilateral with dominant hand typically affected first.

Causes

- idiopathic
- pregnancy
- oedema e.g. heart failure
- lunate fracture
- **rheumatoid arthritis**

History

- pain/pins and needles in thumb, index, middle finger
- unusually the symptoms may 'ascend' proximally
- patient shakes his hand to obtain relief, classically at night

Examination

- weakness of thumb abduction (abductor pollicis brevis)
- wasting of thenar eminence (NOT hypotenar → supplied by ulnar nerve)
- **Tinel's sign:** tapping causes paraesthesia
- **Phalen's sign:** flexion of wrist for 60 seconds causes symptoms
- **Which area supplied by the median nerve will be spared if the problem is at the carpal tunnel?**

➤ **the skin over the thenar eminence**

- The palmar cutaneous branch of the median nerve lies superficial to the flexor retinaculum and does not pass through the carpal tunnel. It supplies the skin over the thenar eminence, which is therefore spared in carpal tunnel syndrome.

Electrophysiology

- **The most appropriate further investigation → Electromyogram (EMG)/nerve conduction studies**
 - ⇒ (EMG)/nerve conduction study is useful for confirming clinical diagnosis prior to actual surgery.
 - ⇒ nerve conduction studies show:
 - **decreased conduction velocity** in the median nerve.
 - **prolongation of the action potential**

Treatment

- In patients with mild carpal tunnel syndrome the management should be behavior modification.
- corticosteroid injection
- wrist splints at night
- surgical decompression (flexor retinaculum division)

Pronator teres syndrome

Definition

- entrapment of the **median nerve** between the two heads of the pronator teres muscle **at the elbow**

Features

- **The characteristic physical finding is tenderness over the proximal median nerve, which is aggravated by resisted pronation of the forearm.**

Diagnosis

- Examination involves excluding carpal tunnel syndrome and pronation of the affected forearm against resistance, which brings on the pain.
 - ⇒ Unlike carpal tunnel syndrome, the median nerve proximal to the wrist may be tender to palpation.

Treatment

- Injection of corticosteroids into the pronator teres muscle may produce relief of symptoms, but a strong response to a steroid injection would be more consistent with carpal tunnel syndrome

Anterior interosseous syndrome

Definition

- Anterior interosseous syndrome or **Kiloh-Nevin syndrome** is a damage to the anterior interosseous nerve, a **motor branch of the median nerve**, which **arises just below the elbow**.
- **innervates the long flexor muscles of the thumb** (Flexor pollicis longus), **index and middle finger** (flexor digitorum profundus).

Causes

- neuritis (inflammation of the nerve) in most cases, compression or Trauma

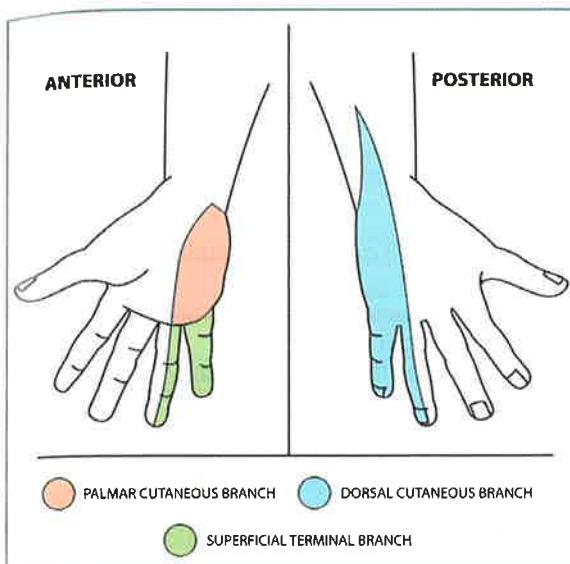
Feature

- Pain in the forearm
- **Characteristic weakness of the pincer movement of the thumb and index finger.**
- If asked to make the "OK" sign, patients will make a triangle sign instead.
 - ⇒ This 'Pinch-Test' exposes the weakness of the Flexor pollicis longus muscle and the flexor digitorum profundus leading to weakness of the flexion of the distal phalanges of the thumb and index finger.
- **Difficulty picking up a small item, such as a coin, from a flat surface**

Diagnosis

- Electromyography (EMG) is generally most useful and will reveal abnormalities in the flexor pollicis longus, flexor digitorum profundus I and II and pronator quadratus muscles.

Ulnar nerve



Overview

- **Root**
 - ⇒ arises from medial cord of brachial plexus (**C8, T1**)
- **Motor innervation**
 - ⇒ Third and fourth lumbricals (medial two lumbricals)
 - ⇒ Flex at metacarpal phalangeal (MCP) joint
 - ⇒ Extend at proximal interphalangeal (PIP) joint
 - ⇒ **Adductor pollicis: adducts the thumb**
 - ⇒ Abductor digiti minimi: abducts the little finger
 - ⇒ Flexor carpi ulnaris: helps flex the wrist
 - ⇒ Dorsal and palmar interossei: finger abduction and adduction respectively
 - ⇒ Flexor digiti minimi brevis: flexes the MCP joint
- **Sensory innervation**
 - ⇒ medial 1 1/2 fingers (palmar and dorsal aspects)

Causes

- The ulnar nerve is most commonly compressed at or near the **cubital tunnel** of the elbow and **Guyon canal** of the wrist.
 - ⇒ **Cubital tunnel syndrome (ulnar nerve compression at the elbow)**
 - Leaning on the elbow or prolonged elbow flexion during occupational activities (e.g., leaning on a desk), athletic activities, or surgical procedures (e.g., during general anesthesia)
 - Blunt trauma
 - Masses (e.g., tumors, hematomas)
 - Metabolic abnormalities (e.g., diabetes)
 - ⇒ **Guyon canal syndrome (ulnar nerve compression at the wrist in Guyon's canal)**
 - Often associated with cycling, likely caused by direct pressure from the handlebars

- Blunt trauma (e.g., hook of hamate fracture)
- Masses (especially ganglion cysts)
- The most common ulnar neuropathies are
 - ⇒ cubital tunnel syndrome
 - **the commonest site** for entrapment of ulnar nerve
 - caused by ulnar nerve compression at the elbow
 - may be due to chronic pressure, leaning on the elbows, and direct trauma.
 - ⇒ ulnar tunnel syndrome
 - caused by ulnar nerve compression at the wrist in Guyon's canal

Risk factors

- **Ulnar neuropathy is a common complication with ill patients in hospital.**

Features

- Wasting and paralysis of intrinsic hand muscles (**except lateral two lumbricals**)
- **Claw hand** (where the little and ring fingers curl into the palm).
 - ⇒ hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- **Weak pinch (Froment sign)**
 - ⇒ little finger in persistent abduction due to weak third palmar interosseous muscle
- **Radial deviation of wrist**
- **Wartenberg sign:** little finger in persistent abduction due to weak third palmar interosseous muscle
- **Froment sign:** The thumb flexes at the interphalangeal joint while pinching a piece of paper to compensate for a weak adductor pollicis muscle.
- **Sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)**

Proximal and distal lesions of the ulnar nerve lead to claw hand deformity.

Diagnosis

- **Nerve conduction studies will confirm the site of the lesion.**

Common questions about ulnar nerve

Question	Answer
Rout ?	C8-T1
Typical injury?	Fracture of epicondyle of humerus
Motor deficit?	Medial finger flexion/wrist flexion
Sensory deficit?	Medial 1.5 fingers/hypothenar eminence
Sign?	Radial deviation of wrist upon flexion/ claw hand

MRCPUK-part-1-sep 2017: H/O dropping things on a frequent basis and muscle wasting at the back of the right hand. On examination, you note wasting of the dorsal interossei. What is the nerve supply of the dorsal interossei?

→ C8/T1

Rotator cuff muscles

Muscle	Notes
Supraspinatus	aBDucts arm before deltoid Most commonly injured
Infraspinatus	Rotates arm laterally
teres minor	aDDucts & rotates arm laterally
Subscapularis	aDDuct & rotates arm medially

Klumpke's palsy

Definition

- **Injury to the lower trunk of the brachial plexus (C8-T1)**
- This root eventually supplies the **median and ulnar nerves**.
- The ulnar nerve supplies all of the intrinsic hand muscles except for those of the thenar eminence and the **first and second lumbricals which are innervated by the median nerve.**

Causes

- **Hyperabduction of the arm**
 - ⇒ Trauma (e.g., breaking a fall by grabbing a branch)
 - ⇒ Birth injury: excessive upward traction on the arm during delivery
- **Compression** of the lower trunk of brachial plexus (subacute to chronic onset)
 - ⇒ Pancoast tumor
 - ⇒ Cervical rib

Features

- **Weakness of intrinsic hand muscles** (thenar, hypothenar, lumbricals, interossei) → total **claw hand** (persistent flexion of the interphalangeal joints and extension of the metacarpophalangeal joints in the hand)
- Preganglionic **Horner syndrome** if injury occurs proximal to the white ramus communicans
- Decreased peripheral pulses if subclavian vessels are compressed by a Pancoast tumor or cervical rib.
- Sensory loss in the C8 and T1 dermatomes (little finger and medial surface of the forearm and arm)

Treatment

- Splinting the hand to correct the claw hand
- Physiotherapy
- Surgery for severe nerve damage

Stretch injury of the arm

- Sudden upward movement of the abducted arm (fall that has been stopped by grasping a fixed object with one hand) → causes features of an ulnar nerve palsy which is supplied by the **lower brachial plexus** roots C8 and T1 (Klumpke's paralysis)

Commonly tested nerves of the lower limbs

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Femoral nerve	Knee extension, thigh flexion	Anterior and medial aspect of the thigh and lower leg	<ul style="list-style-type: none"> • Hip and pelvic fractures • Stab/gunshot wounds
Obturator nerve	Thigh adduction	Medial thigh	Anterior hip dislocation
Lateral cutaneous nerve of the thigh	None	Lateral and posterior surfaces of the thigh	Compression of the nerve near the ASIS → meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve
Tibial nerve	Foot plantarflexion and inversion	Sole of foot	<ul style="list-style-type: none"> • Not commonly injured as deep and well protected. • Popliteal lacerations, posterior knee dislocation
Common peroneal nerve	Foot dorsiflexion and eversion Extensor hallucis longus	Dorsum of the foot and the lower lateral part of the leg	<ul style="list-style-type: none"> • Injury often occurs at the neck of the fibula • Tightly applied lower limb plaster cast • Injury causes foot drop
Superior gluteal nerve	Hip abduction	None	<ul style="list-style-type: none"> • Misplaced intramuscular injection • Hip surgery • Pelvic fracture • Posterior hip dislocation • Injury results in a positive Trendelenburg sign
Inferior gluteal nerve	Hip extension and lateral rotation	None	<ul style="list-style-type: none"> • Generally injured in association with the sciatic nerve • Injury results in difficulty rising from seated position. Can't jump, can't climb stairs

Sciatic nerve palsy

Nerve root

- L4–S3
- Sciatic nerve splits into **tibial nerve** and **common peroneal nerve**

Causes

- Total hip arthroplasty
 - ⇒ known complication of a total hip replacement (femoral nerve palsy can occur but is much less common).
- Herniated lumbar disc
- Posterior hip dislocation
- Iatrogenic (misplaced intragluteal injection)

Feature

- **Motor**
 - ⇒ **Impaired knee flexion and hip adduction**
 - ⇒ **Global weakness of the ankle** due to the involvement of both of its branches: tibial nerve (plantarflexion and inversion) and common peroneal nerve (dorsiflexion and eversion).
 - ⇒ **Absent ankle jerk is due to tibial nerve involvement.**
- **Sensory**
 - ⇒ Sensory loss is variable but most commonly occurs around the dorsum of the foot and lateral aspect of the leg
 - ⇒ Tibial nerve injury → Sensory loss over sole of the foot
 - ⇒ The skin over the medial malleolus and medial border of the foot is innervated by the saphenous nerve and is therefore spared.

Injuries of sciatic nerve branches

	Common peroneal nerve injury	Tibial nerve injury
Nerve root	L4–S2	L4–S3
Common causes	<ul style="list-style-type: none"> Fracture of the fibular head Compression: tight casts, sitting cross-legged, lithotomy position during surgery 	<ul style="list-style-type: none"> Trauma of the knee or leg (e.g., tibial fracture) Baker cyst (causes proximal lesion) Tarsal tunnel syndrome (causes distal lesion)
Motor deficit	<ul style="list-style-type: none"> Superficial peroneal nerve: paralysis of peroneus longus and peroneus brevis → impaired eversion of the foot Deep peroneal nerve: paralysis of foot and toe extensors (dorsiflexors) (e.g., tibialis anterior), leading to: <ul style="list-style-type: none"> Foot drop Steppage gait 	<ul style="list-style-type: none"> Paralysis of biceps femoris (long head) Paralysis of foot flexors (e.g., triceps surae) → inability to stand on or curl toes and to invert foot Proximal lesions: eversion of the foot at rest
Sensory deficit	<ul style="list-style-type: none"> Superficial peroneal nerve: lateral surface of the lower leg, dorsum of the feet and toes, except for the space between the first and second toe Deep peroneal nerve: area between the first and second toes (flip-flop zone) 	<ul style="list-style-type: none"> Sensory loss over sole of the foot

Common peroneal nerve lesion

The commonest cause of acute foot drop after prolonged bed rest is entrapment common peroneal neuropathy at the neck of fibula.

Overview

- The sciatic nerve divides into the tibial and common peroneal nerves in the popliteal fossa.
- Nerve root** → L4–S2
- Common peroneal nerve divides into a superficial and a deep branch**
 - ⇒ Deep peroneal nerve supplies muscles, which **dorsiflex the foot and toes**:
 - tibialis anterior
 - extensor hallucis longus
 - extensor digitorum longus
 - ⇒ Superficial nerve supplies the muscles, which **evert the foot**
 - peroneus longus and brevis

- Injury often occurs at the neck of the fibula.

Causes

- Fracture of the fibular head
- Compression: tight casts, sitting cross-legged, lithotomy position during surgery

Features

- **Foot drop** (the most characteristic feature)
 - ⇒ **Superficial peroneal nerve**: paralysis of peroneus longus and peroneus brevis → impaired eversion of the foot
 - ⇒ **Deep peroneal nerve**: paralysis of foot and toe extensors (**dorsiflexors**) (e.g., tibialis anterior), leading to: **Foot drop** and Steppage gait
- **Sensory loss over the dorsum of the foot and the lower lateral part of the leg with sparing of the fifth toe.**
 - ⇒ Superficial peroneal nerve: lateral surface of the lower leg, dorsum of the feet and toes, except for the space between the first and second toe
 - ⇒ Deep peroneal nerve: area between the first and second toes (flip-flop zone)

Foot-drop

- Weakness of eversion + dorsiflexion + inversion → **L4 - 5 radiculopathy**
- Weakness of eversion + dorsiflexion → **common peroneal nerve palsy**
(ankle inversion is spared with common peroneal nerve palsy)

Differences between tibial nerve and peroneal nerve injuries:

- **Tibial** → impaired foot **Inversion** and **Plantarflexion**
- **Peroneal** → impaired foot **Eversion** and **Dorsiflexion**

Femoral nerve palsy

Nerve root

- L2-L4

Causes

- **Compression**: Prolonged pressure on the nerve:
 - ⇒ Psoas haematoma (due to anticoagulant therapy or haemophilia), Psoas abscess
 - ⇒ Tumours - eg: Synovial cyst, Sarcoma
 - ⇒ Aortic or iliac aneurysms
- **Trauma**: Direct injury to the nerve
 - ⇒ Hip or pelvic fractures
 - ⇒ Iatrogenic: eg: Hip arthroplasty, pelvic surgery, femoral line placement, coronary angiography).
- **Diabetic amyotrophy** (proximal neuropathy, in diabetic patients, causes burning pain in the hip and thigh and wasting of thigh muscles)

Feature

- **Motor**
 - ⇒ Paralysis of iliopsoas, pectineus, rectus femoris, and sartorius muscles → **impaired hip flexion**
 - ⇒ Paralysis of quadriceps femoris muscle →
 - **Impaired knee extension:** instability of the knee (often described as 'buckling') on climbing stairs.
 - **Decreased patellar tendon reflex (absent knee jerk)**
- **Sensory**
 - ⇒ Decreased sensation in **anterior thigh** (meralgia paraesthetica) and **medial distal leg** (saphenous nerve)

Hip weakness:

- **Weakness of hip Abduction (Gluteus medius)** → superior gluteal nerve palsy
- **Weakness of hip adduction (Adductor magnus and minimus)** → Obturator nerve palsy
- **Weakness of hip flexion (iliopsoas muscle)** → Femoral nerve palsy
- **Weakness of hip extension (Gluteus maximus)** → inferior gluteal nerve

Obturator nerve injury

- **Root:** L2–L4
- **Common causes:** Pelvic surgery, pelvic ring fractures
- **Motor deficits:** Paralysis of hip adductors (adductor longus, adductor brevis, adductor magnus, obturator externus, gracilis, pectineus)
- **Sensory deficits:** Howship-Romberg sign: pain and paresthesia over the inner aspect of the thigh.

Meralgia paraesthetica

Burning thigh pain - ? meralgia paraesthetica - lateral cutaneous nerve of thigh compression

Nerve root

- L₂–L₄

Pathology

- compression of lateral cutaneous nerve of thigh

Causes of compression

- Most likely causes → **entrapment at the lateral inguinal ligament:**
 - ⇒ Increased intra-abdominal pressure (e.g., pregnancy, obesity, ascites)
 - ⇒ External compression (e.g., tight belts, pants, or compression dressings)
 - ⇒ Local compression (e.g., tumors, hematomas)
- Less likely causes → trauma, ischaemia, or a retroperitoneal lesion.

Features

- typically burning sensation over antero-lateral aspect of thigh
- pure sensory loss
- numbness when tapping on the inguinal ligament

Treatment

- Can be improved by wearing looser clothing and/or losing weight

Healthy patient came with burning thigh pain. What is the next step in management?

→ Advice the patient to wear loose pant

MRCPUK-part-1- May 2006 exam: A patient presents with a burning sensation over antero-lateral aspect of thigh. Which nerve is most likely to be affected?

→ Lateral cutaneous nerve of thigh

Saphenous nerve injury

Overview

- Saphenous nerve is a terminal cutaneous branch of the femoral nerve.
- It supplies the skin over the anteromedial side of the knee, leg and medial malleolus.
- It is strictly a sensory nerve; it has no motor component.
- It is commonly blocked to complement anesthesia of the lower leg.

Causes

- Saphenous vein harvest for coronary artery bypass grafting (CABG) (most common).
- Femoral artery catheterization for angiography.
- Trochanter placement during knee arthroscopy.
- Long saphenous vein stripping for varicose veins.

Features

- Loss of sensation over the medial aspect of the lower leg.

Tarsal tunnel syndrome

Tarsal tunnel syndrome

entrapment of the posterior tibial nerve as it travels through the tarsal tunnel, this tunnel is found along the inner leg behind the medial malleolus → painful foot

Overview

- also, known as posterior tibial neuralgia
- It is analogous to carpal tunnel syndrome of the wrist.

Definition

- peripheral neuropathy caused by compression of the tibial nerve by the flexor retinaculum of the foot at the medial ankle

Causes

- Trauma (most common): fracture or sprain of the ankle (talus, calcaneus, medial malleolus)
- Rheumatoid arthritis

Features

- Symptoms develop in areas innervated by the tibial nerve (distal to the medial malleolus):
 - ⇒ Neuropathic pain and paresthesia in the **heel**, **sole of the foot**, and **first three toes**
 - ⇒ **Weakness and atrophy of intrinsic foot muscles** (severe cases)
- Symptoms worsen with walking, prolonged standing, and at night

Diagnosis

-
- Usually a clinical diagnosis
- Positive **Tinel sign**: radiating paresthesia triggered by tapping the flexor retinaculum posterior to the medial malleolus
- **Pain** upon foot dorsiflexion with eversion
- Diminished sensation on the plantar area of the foot
- Nerve conduction studies: slow conduction velocity in the medial and lateral plantar nerves

Treatment

- Initially conservative (Rest, NSAIDs, physiotherapy, use of orthotic shoes)
- Local injection of steroids into the tarsal canal (if no improvement)
- Surgical decompression