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• 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 • Paraesthesias 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 anemia, vitamin deficiency Drugs : H1 antihistamines, Antidepressants, Dopamine antagonists (neuroleptics, metoclopramide, MDMA), Lithium, Beta blockers Pregnancy Diagnosis criteria • Exclude iron deficiency anaemia • The international restless legs syndrome study group four basic criteria for diagnosing RLS:

1. A desire to move the limbs, often associated with paraesthesias or dysaesthesias
2. Symptoms that are worse or present only during rest and are partially or temporarily relieved by activity
3. Motor restlessness, and
4. 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) A low serum ferritin is most likely to be a cause of secondary restless legs syndrome

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

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Holmes tremor

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 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 Holmes tremor → lesion in the red nucleus Friedreich's ataxia: most common cause of death →heart failure due to hypertrophic cardiomyopathy

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Neurology 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

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Ataxic telangiectasia 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 typical 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.

Sleep Sleep Stage Description EEG Waveform • Awake and alert • Beta • Awake and eyes closed • Alpha Stage N1 • Light sleep • Theta Stage N2 • Deeper sleep • Sleep spindles and K complexes Stage N3 • Deepest non-REM sleep • Sleep walking • Night terrors • Bed wetting • Delta REM • Dreaming • Beta The 4 A's of ataxia telangiectasia: ATM gene, Ataxia, spider Angiomas, and IgA deficiency. Avoid x-ray exposure because of high sensitivity to radiation and increased risk of malignancy.

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Neurology • 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

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_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 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 orexigenic 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. Hypnagogic hallucinations occur while going to sleep.

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Neurology 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 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. Features features of raised intracranial pressure lucid interval

(apparent recovery from the initial concussion, but deterioration is usually within 15-30 minutes). Subdural haematoma 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 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 The inner most layer around the brain tissue Between the dura mater and arachnoid mater Location 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. Mechanism Pain Sudden onset, painful Possible dull headache Likely, and often severe, but not sudden onset May become impaired quickly – if so, a very bad prognostic indicator Fluctuates, often over weeks or even months Consciousness Often insidious. May involve memory impairment, epilepsy, drowsiness, dizziness. Often occur weeks / months after injury May be present; are a poor prognostic indicator Neurological signs 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 – CT / MRI – classically shows a crescent of blood around the brain tissue, and midline shift Investigations xanthochromia) 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
Management Notes & Notes for MRCP
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The outermost layer, between the skull and dura mater 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 Classically, an initial lucid period, followed by impaired consciousness Typically after a lucid period, severe headache, impaired consciousness. Vomiting, seizures, drowsiness, confusion, and later, coma. CT / MRI – described as a lens Shaped lesion – meaning it is biconvex. LP is contraindicated! X-ray may show skull fracture

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Neurology 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

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Extradural (epidural) haematoma: Subdural haematoma

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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.

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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.

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Neurology 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 • 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

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

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.

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Neurology 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) 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. HSE: behavioral changes and CT head showing temporal lobe changes

Neurology 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%

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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 • 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

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Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions 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 Notes & Notes for MRCP
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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.

Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage. Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. The table below gives some general differences. Condition CT finding Toxoplasmosis Multiple lesions Ring or nodular enhancement Thallium SPECT negative Lymphoma Single lesion Solid (homogenous) enhancement Thallium SPECT positive Tuberculosis single enhancing lesion Encephalitis oedematous brain Cryptococcus meningeal enhancement, cerebral oedema Progressive multifocal leukoencephalopathy (PML) 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 Notes & Notes for MRCP
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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. single or multiple lesions,

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• 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 papiloedema 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 lumber 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:

1. positive anti-JC viral serum antibodies,
2. prior use of immunosuppressants, and
3. increased duration of natalizumab treatment and its number of infusions (25-49 infusions).

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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 37.2ºC. 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)

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Neurology

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 un known 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 • 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