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Chapter 4

Chapter 4

Neurology

• 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 Upper 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

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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 Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 Bilateral damage or injury of the nerve nuclei of cranial nerves IX, X, XI, and XII Lower motor neuron palsy of the respective muscles

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 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

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Neurology • 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) • 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 (↑ 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 ↑ 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 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).

 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 is 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

Neurology

 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 Bcells. 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

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• 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. 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. Multiple sclerosis in pregnancy Only glatiramer acetate is thought to be safe in pregnancy.

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Internuclear ophthalmoplegia (INO) 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 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.

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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

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Ptosis, Miosis and Mydriasis 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. Ptosis + dilated pupil Third nerve palsy Ptosis + constricted pupil Horner's

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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 Stroke Syringomyelia Multiple sclerosis Tumour Encephalitis Pancoast's tumour Thyroidectomy Trauma Cervical rib Carotid artery dissection Carotid aneurysm Cavernous sinus thrombosis Cluster headache

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Neurology

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

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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

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• 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 myaesthenic 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, ciclosporin 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

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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 ⅔ of LEMS cases) • May also occur independently as an autoimmune disorder. Pathophysiology • Autoantibodies directed against presynaptic voltage-gated calcium channels (antiVGCC 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, difficultly 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 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 Notes & Notes for MRCP
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Affects lower limbs first Small cell lung cancer

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Neurology 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

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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 More common (affects1 in 4,000) Less common (Affects around 1 in 100,000) Cafê-au-lait spots (≥ 6 spots, 15 mm in diameter) Axillary/groin freckles Peripheral neurofibromas Iris harmatomas (Lisch nodules) in ˃ 90% Seizures and/or focal neurologic signs due to brain lesions (especially meningiomas) Scoliosis Pheochromocytomas Notes & Notes for MRCP
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 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)

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café-au-lait spots Multiple light brown macules with irregular borders (café-aulait 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

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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

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Neurology 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 orangepeel 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 hypertonia 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 pastpointing. 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 • The most common primary brain tumour in adults, accounts for about 20% of all cerebral tumours. • Histology: Pleomorphic tumour cells border necrotic areas • Pseudopalisading tumor cells on brain biopsy are a characteristic Meningioma • The second most common primary brain tumour in adults • Histology: Spindle cells in concentric whorls and calcified psammoma bodies Schwannoma • Often seen in the cerebellopontine angle: acoustic neuroma • Bilateral schwannoms are seen in neurofibromatosis • Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades) Pilocytic astrocytoma • The most common primary brain tumour in children • Histology: Rosenthal fibres (corkscrew eosinophilic bundle) Medulloblastoma • 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 • Commonly seen in the 4th ventricle • May cause hydrocephalus • Histology: perivascular pseudo rosettes Oligodendroma • Benign, slow-growing tumour common in the frontal lobes • Histology: Calcifications with 'fried-egg' appearance Haemangioblastoma • Vascular tumour of the cerebellum • Associated with von Hippel-Lindau syndrome • Histology: foam cells and high vascularity Pituitary adenoma • Most common type is a prolactinoma • May present with bitemporal hemianopia Craniopharyngioma • 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 • 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

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Meningioma - MRI showing the typical wellcircumscribed appearance. A dural tail can be 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 falx 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.

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Neurology

Von Hippel-Lindau syndrome (VHL) 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. 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/mm^3 Conditions associated with raised lymphocytes • Viral meningitis/encephalitis • TB meningitis • Partially treated bacterial meningitis • Lyme disease • Behcet's, SLE • Lymphoma, leukaemia Early age SAH occur in Von Hippel Lindau What type of cells produce cerebrospinal fluid? Ependymal cells

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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

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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 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

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Neurology 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 Increased needle size Direction of bevel Not replacing the stylet Increased number of LP attempts Use of a Quincke (sharp) needle 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-Sequard syndrome (spinal cord hemisection)

1. Lateral corticospinal tract
2. Dorsal columns
3. Lateral spinothalamic tract Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency)
4. Lateral corticospinal tracts
5. Dorsal columns
6. Spinocerebellar tracts Friedrich's ataxia Same as subacute combined degeneration of the spinal cord (see above) Anterior spinal artery occlusion
7. Lateral corticospinal tracts
8. Lateral spinothalamic tracts Syringomyelia
9. Ventral horns

10. Lateral spinothalamic tract Multiple sclerosis Asymmetrical, varying spinal tracts involved Neurosyphilis (tabes dorsalis) Dorsal columns Loss of proprioception and vibration sensation

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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. Notes & Notes for MRCP
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1. Ipsilateral spastic paresis below lesion
2. Ipsilateral loss of proprioception and vibration sensation
3. Contralateral loss of pain and temperature sensation
4. Bilateral spastic paresis
5. Bilateral loss of proprioception and vibration sensation
6. Bilateral limb ataxia Same as subacute combined degeneration of the spinal cord (see above)
7. Bilateral spastic paresis
8. Bilateral loss of pain and temperature sensation
9. Flaccid paresis (typically affecting the intrinsic hand muscles)
10. Loss of pain and temperature sensation Combination of motor, sensory and ataxia symptoms

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Neurology • 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.