CHRONIC NEUROLOGIC DISORDERS

AMYOTROPHIC LATERAL SCLEROSIS:

- Causes rapidly progressive muscle atrophy and weakness resulting form the degeneration of both upper and lower motor neurons
- There is no cure and muscle paralysis ultimately leads to pulmonary complications with the need for ventilatory support
- PATHOPHYSIOLOGY:
    - Most likely cause is a genetic mutation of SUPEROXIDE DISMUTASE
    - Gross NS pathology → frontal cortical atrophy, degeneration of both corticospinal and spinocerebellar tracts and a reduction in large cervical and lumbar motor neurons
- CLINICAL FEATURES:
    - UMN demyleination and dysfunction → limb spasticity, hyperreflexia (including Babinski) and emotional lability
    - Associated LMN dysfunction → limb muscle weakness, atrophy, cramps, fasciculations, dysarthria, dysphagia
    - Despite profound motor findings, sensoary and cognitive function is usually spared
    - Regardless of initial symptoms, widespread motor and respiratory dysfunction progresses within weeks to months
    - Progressive respiratory muscle weakness causes exertional SOB → eventually SOB at rest
- CLINICAL DIAGNOSIS:
    - Suggested when there are signs of both UMN and LMN dysfunction → weakness and atrophy, fasciculations, hyporeflexia without other CNS dysfunction
    - Should be referred to a neurologist for definitive diagnosis
- TREATMENT:
    - Designed to enhance muscle function → especially those that support breathing, swallowing and speech
    - RILUZOLE 50MG BD shows modest slowing of disease
- ED MANAGEMENT:
    - Most often come with diagnosed disease
    - Emergency management usually is required for acute respiratory failure, aspiration pneumonia, choking episodes or trauma related to weakness and falls
    - ABG does NOT predict impending respiratory failure → FVC <25ml/kg carries with it an increased risk of aspiration and respiratory failure
    - Ask about advanced care directives, as these patients will likely never get off a ventilator

MYASTHENIA GRAVIS:

- An autoimmune disease characterised by muscle weakness and fatigue → seen especially with repetitive use of voluntary muscles

- Acetylcholine receptors (ACHR) antibodies impair receptor function at the NMJ → weakness that is generally relieved by rest
- Requires long-term immunomodulation
- Much of the morbidity and mortality can be minimised
- DIAGNOSIS OF CHOLINERGIC AND MYASTHENIC CRISES are crucial to ED management
    - Aggressive management of respiratory complications also very important in ED setting
- PATHOPHYSIOLOGY:
    - There is a marked decreases in the number and ufnciton of muscle fibre ACHRs, despite normal nerve anatomy and function → failure to respond to ACH stimulation → weakness
    - ACHR present in nearly all patients
    - Thought to be related to THYMUS DYSFUNCTION → abnormal in 75% of patients (hyperplasia or thymoma) → thymectomy leads to resolution/improvement in most patients
- CLINICAL FEATURES:
    - Most MG patients have general weakness, especially of proximal extremities, neck extensors, facial or bulbar muscles
    - Ptosis and diplopia are most common presenting problems
    - Symptoms fluctuate through the day, usually worsening with fatigue (eg prolonged reading)
    - Usually no deficit in sensation, reflexes or cerebellar function
    - Although weakness is usually mild → LIFE-THREATENING EXTREME WEAKNES IN THE MUSCLES OF RESPIRATION CALLED **MYASTHENIC CRISIS** → RESPIRATORY FAILURE, LEADING CAUSE OF DEATH
- CLINICAL DIAGNOSIS:
    - Should be considered in any patient who complains specifically of ocular disturbances or proximal limb muscle weakness not associated with systemic causes of generalised fatigue, especially those that fluctuate and are relieved with rest
    - DIAGNOSIS ESTABLISHED WITH **EDROPHONIUM ADMINISTRATION (**an acetylcholinesterase inhibitor), EMG as well as ACHR antibodies
    - In the presence of abnormal neuromuscular transmission, edrophonium (OR NEOSTIGMINE) is expected to improve muscle strength in the weak region
    - Up to 15% of patients will have undetectable ACHR
    - MEDIASTINAL IMAGING INDICATED to look for a thymoma
- TREATMENT:
    - Treatment options include:
        - Administration of acetylcholinesterase inhibitors (PYRIDOSTIGMINE/NEOSTIGMINE)

For patients with mild disability, while therapeutic options are being considered, use:

pyridostigmine 60 mg orally, daily in the morning, then adjust the dose according to the duration of action of the medication and symptoms in each patient. Usual dose range 60 mg orally, 2 to 6 times daily.

- THYMECTOMY
- CHRONIC IMMUNE SUPPRESSION → STEROIDS, AZATHIOPRINE, CYCLOSPORIN, MYCOPHENOLATE → LATTER AGENTS ARE STEROID SPARING
- ACUTE IMMUNE MODULATION → IVIG, PLASMA EXCHANGE (reserved for those with severe disability

- Variability in amount of weakness can be seen in response to asthma exacerbations, infection, menstruation, pregnancy, emotional stress, hot weather

- EMERGENCY DIAGNOSIS AND MANAGEMENT:
  - Many drugs are known to affect neuromuscular function and should be used with caution

Table 167-1 Drugs that Should Be Avoided in Myasthenia Gravis

Steroids	Adrenocorticotropic hormone,* methylprednisolone,* prednisone*
Anticonvulsants	Phenytoin, ethosuximide, trimethadione, paraldehyde, magnesium sulfate, barbiturates; lithium
Antimalarials	Chloroquine,* quinine*
IV fluids	Na lactate solution
Antibiotics	Aminoglycosides, fluoroquinolones,* neomycin,* streptomycin,* kanamycin,* gentamicin, tobramycin, dihydrostreptomycin,* amikacin, polymyxin A, polymyxin B, sulfonamides, viomycin, colistimethate,* lincomycin, clindamycin, tetracycline, oxytetracycline, rolitetracycline, macrolides, metronidazole
Psychotropics	Chlorpromazine,* lithium carbonate,* amitriptyline, droperidol, haloperidol, imipramine
Antirheumatics	D-Penicillamine, colchicine, chloroquine
Cardiovascular	Quinidine,* procainamide,* β-blockers (propranolol, oxprenolol, practolol, pindolol, sotalol), lidocaine, trimethaphan; magnesium; calcium channel blockers (verapamil)
Local anesthetics	Lidocaine,* procaine,*
Analgesics	Narcotics (morphine, hydromorphone, codeine, Pantopon, meperidine)
Endocrine	Thyroid replacement*
Eyedrops	Timolol,* echothiophate
Others	Amantadine, diphenhydramine, emetine, diuretics, muscle relaxants, central nervous system depressants, respiratory depressants, sedatives, procaine,* phenothiazines
Neuromuscular blocking agents	Tubocurarine, pancuronium, gallamine, dimethyl tubocurarine, succinylcholine, decamethonium

- In patients seen in ED, ensure usual dose of cholinergic inhibitors → if dose has been missed, the next dose is usually doubled. If unable to take PO → consult neurology for optimal IV dose (neostigmine 0.5mg often given(
- MOST SIGNIFICANT COMPLICATION IN ED IS RESPIRATORY FAILURE → usually precipitated by infection, surgery, rapid tapering of immunsuppressives
- BECAUSE OF SENSITIVITY OF M.G. PATIENTS → AVOID NMJ BLOCKERS → ESPECIALLY SUCCINYLCHOLINE (PERSISTS FOR MUCH

LONGER THAN EXPECTED) → short-acting agents such as propofol, fentanyl used as "paralysing agents" → if paralysing agents required → half the usual dose

- Up to 15-20% of MG patients will undergo a crisis AT SOME POINT
  - MUST BE DISTINGUISHED FROM A CHOLINERGIC CRISIS (due to excessive cholinergic effects of therapeutic agents)
  - Differentiation can be done by using EDROPHONIUM → if myasthenic crisis, symptoms will improve after test dose of edrophonium (1-2mg slow IV push) → if due to cholinergic crisis then patient will develop fasciculations, respiratory depression or cholinergic symptoms (further edrophonium is contraindicated) → if no adverse effects → 10mg can be given (DOSE IN KIDS 0.15MG/KG UP TO 10MG)
  - CARE MUST BE TAKEN IN THOSE WITH CARDIAC DISEASE →CAN CAUSE BRADYCARDIA AND CARDIAC ARREST

Table 167-2 Edrophonium Testing in Myasthenia Gravis

	Myasthenic Crisis	Cholinergic Crisis
Pathology	Undermedication, decrease in acetylcholine receptor causes decreased stimulation by ACh	Overmedication, excess anticholinesterase drugs, overstimulation by ACh
Finding after edrophonium administration	Visible improvement in muscle contractibility, fusion of diplopia, or resolution of ptosis	Worsening of symptoms, muscle weakness, and possible respiratory paralysis
Implication of edrophonium test finding	Patient positive for myasthenia gravis, undermedication of anticholinesterase drugs	Overmedication has occurred, possibly due to insufficient effect from anticholinesterase drugs
Clinical treatment required based on test results	Increase in anticholinesterase drugs, such as pyridostigmine and neostigmine	Treat with atropine, if respiratory paralysis occurs, assist with ventilation

- Patients who worsen with edrophonium require immediate management of respiratory failure and excessive secretions (bronchorrhoea) as well as bronchospasm→ ATROPINE

MULTIPLE SCLEROSIS:

- A neurologic disorder that casuses variable motor, sensoary, visual and cerebellar dysfunction as a result of multifocal areas of CNS myelin destruction → most often with a relapsing and remitting course (can be relapsing/progressive or chronically progressive course)
- Mild-moderate lifetime morbidity with good immunsuppression → life expectancy only decreased by 5-10 years
- PATHOPHYSIOLOGY:
  - CAUSE IS UNKNOWN
  - Results from a dysfunction in oligodendrocytes such that axonal myelin sheaths are damaged, slowing nerve impulse conduction → scattered cerebral and spinal plaques causing gliosis primarily in the white matter with relative axon sparing
- CLINICAL FEATURES:
  - Suggested when a young person presents multiple times with neurologic symptoms that suggest different areas of pathology

    - Examination may reveal → clonus, ↑reflexes, Babinski, decreased strength, ↑d tone, decreased vibration/proprioception
    - Patients describe weakness, heaviness, stiffness or extremity numbness
    - LHERMITTE SIGN → electric shock down back resulting from neck flexion
    - RARELY → MS patients present with TRANSVERSE MYELITIS → complete loss of motor function
    - OPTIC NEURITIS → may be initial sign in up to 30% cases (central visual loss, acute or subacute) → preceded by retrobulbar pain, extraocular pain, RAPD (Marcus Gunn pupil)
    - INTRANUCLEAR OPHTHALMOPLEGIA → INABILITY OF ADDUCTION with nystagmus in contralateral eye and sparing of convergence → if bilateral → highly suggestive of MS
    - Autonomic dysfunction can occur
    - Cognitive and emotional changes in many patients
    - MS SYMPTOMS OFTEN WORSEN WITH ELEVATIONS IN BODY TEMPERATURES
- CLINICAL DIAGNOSIS:
    - Suggested when A PATIENT HAS EITHER TWO OR MORE PROLONGED OR WORSENING EPISODES OF NEUROLOGIC DYSFUNCTION THAT SUGGEST DISTINCT WHITE MATTER PATHOLOGY OR SPINAL CORD DYSFUNCTION INTWO OR MORE DISTINCT LOCATIONS
    - Nearly all patients will have some pathology on MRI → T2 weighted images demonstrate discrete lesions in white matter
    - CSF protein and gamma-globulin are increased
- TREATMENT:
    - Glucocorticoids, interferon-beta, glatiramer
    - High-dose methylprednisone shortens exacerbations
- EMERGENCY DIAGNOSIS AND MANAGEMENT:
    - Emergency therapy is directed at identifying the complications of acute exacerbations → respiratory distress, optic neuritis, pulmonary infections, severe constipation and worsening muscle weakness
    - Beware hypotension on RSI due to high prevalence of autonomic dysfunction
    - Reduce fever ASAP as ↑d temp worsens symptoms
    - Exclude UTI
    - Hospitalisation indicated for any patient whose exacerbation is associated with significant morbidity or when IV antibiotics/steroids is to be initiated

LAMBERT-EATON MYASTHENIC SYNDROME:

- RARE
- Autoimmune disorder that causes fluctuating weakness and fatigue → especially in proximal limb muscles → improves with repetition or exercise → LAMBERT SIGN, when a patient squeezes the examiners' hands and it becomes more forceful over time

- Antibody attack of P/Q type voltage-gated calcium channels
- OFTEN ASSOCIATED WITH MALIGNANCY → PARANEOPLASTIC SYNDROME → APPROXIMATELY HALF OF THESE PATIENTS HAVE SMALL CELL LUNG CANCER. Can precede detection of malignancy by years in some cases
- TREATMENT IS SUPPORTIVE AND IF NO MALIGNANCY KNOWN → GO LOOKING!

PARKINSON'S DISEASE:

- An EXTRAPYRAMIDAL MOVEMENT DISORDER CHARACTERISED BY A RESTING TREMOR, COGWHEEL RIGIDITY, BRADYKINESIS/AKINESIA, IMPAIRED POSTURAL REFLEXES
- Associated with reduction in number of functional dopaminergic receptors in the substantia nigra
- PATHOPHYSIOLOGY:
    - Characterised by inclusions called LEWY BODIES
    - Depigmentation of substantia nigra with dopaminergic neuron loss and gliosis → causes a decrease in the overall level of striatal dopamine
- CLINICAL FEATURES:
    - Think TRAP → resting Tremor, cogwheel Rigidity, bradykinesia and Akinesia, impairment of Posture and equilibrium → also note facial/postural changes, voice (quiet), depression, muscle fatigue (micrographia)
    - Tremor is a repetitive low amplitude movement usually involving fingers and thumb (PILL-ROLLING) → improves with intentional movement
    - Bradykinesia is often considered the most debilitating symptom
    - Postural problems can lead to impaired ablity to turn or change direction while walking
    - No definitive lab or neuroimaging study that is pathognomonic for diagnosis
- TREATMENT:
    - Currently available therapies CAN SIGNIFICANTLY REDUCE SYMPTOMS, but do not change underlying pathology
    - ANTICHOLINERGICS (e.g. benztropine)
    - DRUGS THAT INCREASE CENTRAL DOPAMINE:
        - Amantadine (antiviral agent)
        - Levodopa → converted to dopamine by decarboxylases peripherally (peripheral symptoms of anorexia, N+V) → hence combined with carbidopa/benserazide (peripheral dopa-decarboyxlase inhibitors)
            - Efficacy decreases over time → ON/OFF phenomena → consider drug holiday
    - DOPAMINE RECEPTOR AGONISTS → bromocriptine, pergolide
    - SURGICAL OPTIONS → pallidotomy, thalamotomy, deep brain stimulation
- EMERGENCY DIAGNOSIS AND MANAGEMENT:

- Complications related to motor, gait and truncal disabilities including DVT/PE, aspiration, trauma from falls, compressive neuropathies
- Most common cause of death is respiratory failure
- Dopaminergic therapy toxicites can include cardiac dysrhythmias, orthostatic hypotension, dyskinesias and dystonias
- Use psychotropics with caution (if at all) in patients with Parkinson's diseases

POLIOMYELITIS AND POSTPOLIO SYNDROME:

- Poliovirus is a NEURTROPIC ENTEROVIRUS that casues paralysis thorugh motor neuron destruction, muscle denervation and atrophy → largely eradicated due to IMMUNISATION → still rife in the subcontinent
- Can still see POST POLIO SYNDROME → progressive muscular atrophy
- Causes paralysis in <5% infected patients
- PATHOPHYSIOLOGY:
  - Oral-oral, faecal-oral transmission → virus reproduces in GI lymphoid tissue → spreads to large motor nuclei of the spinal cord, the brainstem and reticular formation with LOSS OF INFECTED NEURONS
- CLINICAL FEATURES:
  - Remains asymptomatic in 90% cases → only 1-2% result in major illness associated with neurologic involvement
  - Muscle pain, stiffness and weakness may premonitory of later paralysis
  - Most commonly, the anterior horn cells are affected → asymmetric proximal limb weakness
  - Flaccid and weak muscles, absent DTR and fasciculations characterise spinal polio → maximal paralysis in 5 days
  - POST POLIO SYNDORME OCCURS ON AVERAGE 30 YEARS AFTER MAXIMAL RESOLUTION
  - THE MOST IMPORTANT DIFFERENT DIAGNOSIS THAT MUST BE CONSIDERED AND EXCLUDED IS GUILLAIN-BARRE SYNBDROME → CAUSES A MORE **SYMMETRIC MUSCLE WEAKNESS**