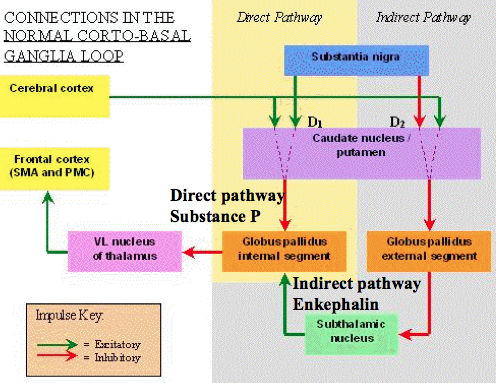
**Basal Ganglia Anatomy and Function**



* **Direct pathway:** 
  + Damage to this pathway = **poverty of movement**
  + E.g.in **Parkinson’s Disease:** loss of substantia nigra cells results in **decrease direct pathway and increased indirect pathway** thus reducing movement
* **Indirect pathway:** 
  + **Excessive movements** e.g. chorea
  + **i.e. Huntington’s disease** where there is a destruction of indirect pathway neurons leading to excessive activation of the direct pathway

**Clinical Features**

* Usually asymmetrical in onset with persistent asymmetry affecting the side of onset worse
* Syndrome of **bradykinesia** + at least one of the following
  + Resting tremor, postural instability and muscular rigidity
* **Bradykinesia/akinesia** 
  + Typically complain of slowing down, difficulty with complex motor tasks (e.g. shaving, dressing)
  + **Mask like facies, Micrographia, Monotonous Speech, Abnormal gait/posture**
* **Gait**
  + Flexed, stooped posture (**simian**)
  + Can not maintain normal posture when pressure is applied from behind
  + Difficulty in initiating movement and turning
  + Small shuffling steps
  + Increasing speed as patient walks
  + Loss of armswing
* **Rigidity** 
  + Increased muscle tone may either be **leadpipe/cogwheeling** 
    - May be increased by asking the patient to lift something with the other arm
* **Tremor** 
  + Pill rolling – present at rest and may be exacerbated by anxiety. **Improves or disappear upon action**
* **Non Motor Features** 
  + Anosmia
  + Autonomic 🡪 postural hypertension, constipation, urinary frequency and urgency
  + Psychiatric 🡪 dementia, depression, insomnia, sleep disorder, visual hallucinations
  + Dribbling saliva
  + Cranial nerves 🡪 impaired upgaze, tremulous eyelids and **glabella tap sign(**tapping on glabella produces reflex blinking each time – in normal individuals this reflex saturates

**Causes**

* **Idiopathic Parkinson’s disease**
* **Vascular parkinsonism** 🡪 multiple infarcts may cause pseudoparkinsons
  + Legs >arms
  + Usually associated with cognitive dysfunction and pyramidal signs (UMN signs – spasticity, hyperreflexia and babinski’s sign)
* **Parkinson’s Plus Syndrome** 🡪 features below may indicate a rare alternate cause of idiopathic PD
  + **Progressive supranuclear palsy** 🡪 early postural instability and falls, vertical gaze palsy, rigidity of trunk > limbs, symmetrical onset, speech and swallowing problems, tremor = unusual
  + **Multiple system atrophy 🡪** early autonomic features (postural hypotension, bladder dysfunction), cerebellar and pyramidal signs, rigidity>tremor
  + **Cortico-basal degeneration 🡪** rigidity in one limb, cortical sensory loss, apraxia (inability to repeat or mimic particular movements)
  + **Lewy body dementia 🡪** early dementia with fluctuating cognition and visual hallucination
* **Inflammatory 🡪** post-encephalopathy
* **Drug induced:** neuroleptics, anti-emetics, amiodarone
* **Toxin induced** 🡪 MPTP (by-product of heroin synthesis), copper (Wilsons disease)
* **Trauma 🡪** Punch Drunk system in boxers: parkinsonism, cerebellar damage and cognitive impairment (dementia pugilistica)

**Natural History of PD**

* **Progressive** 
  + **2 – 3 years** where dopamine treatment resolves symptoms
  + **5 years 🡪** dopamine becomes less effective and motor complications develop
  + Eventually symptoms become unresponsive to LevoDOPA e.g. freezing, falling and dementia
* **Untreated** 
  + Severe disability after 7 to 10 years
    - Bronchopneumonia, septicaemia, PE
    - Better with treatment

**Pathophysiology**

* Loss of substantia nigra pars compacta neurones
  + Presence of **Lewy bodies** (intracellular inclusions) in the remaining neurones
* Reduced striatal dopamine levels
* Reduced direct pathway
* Increased indirect pathway
* Overall = suppression of movement

**Definitions and Risk Factors for PD**

* **Parkinson’s Disease** (idiopathic) is a neurodegenerative disorder characterised by features of parkinsonism plus a variety of non-motor symptoms **–** mean age of onset 65%, 1% prevalence
  + **Classical Triad: TRAP**
    - **Tremor, Rigidity, Akinesia/Bradykinesia, Postural Instability**

**Risk Factors**

* Male, Family history, History of Traumatic brain injury

**Making the diagnosis**

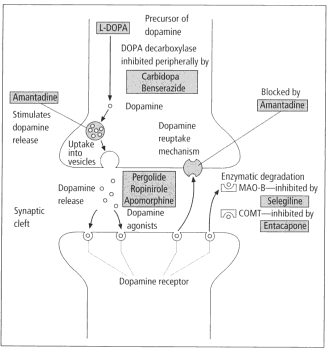
* **TRAP**
* **Asymmetrical findings @ onset of the disease**
* If history and examination not helping with diagnosis – investigations:
  + CT/MRI not usually helpful
  + PET scanning 🡪 not routinely used but may distinguish neurodegenerative PD from vascular or drug induced parkinsonism
  + **Caeruloplasmin** low in wilson’s disease
  + Genetic testing if there is a family history
* Urine
  + 24h urine copper increased in Wilsons

**Differential Diagnosis of tremor**

|  |  |  |
| --- | --- | --- |
| **Rest tremor** | **Postural tremor** | **Kinetic tremor** |
| Present at rest. Better on movement | Maximal with maintained posture against gravity | During movement, often worse as target is approached (intention tremor |
| * Idiopathic PD * Any cause of parkinsonism | * Essential * Physiological (present in everyone) but may be enhanced by:   + Anxiety   + Thyrotoxicosis   + Alcohol   + Drugs → amphetamines, beta-agonists, caffeine, fluoxetine | * Cerebellar disease   + MS   + Hereditary   + Tumour   + Infarct   + Haemorrhage |

**Differential Diagnosis**

* **Normal pressure hydrocephalus (DIG) 🡪 d**ementia, **i**ncontinence, **g**ait abnormalities
* **Structural 🡪** Tumour, hydrocephalus, subdural haematoma
* **Hereditary disease 🡪** Huntington’s, Wilson’s
* **Infection 🡪**  HIV



**Management**

* Progressive and incurable 🡪 MDT approach to improve QoL
* **Medical Therapy** 
  + **Efficacy reduces with time, requiring larger and more frequent doses, with worsening side effects**
  + **SOOOOO BASICALLY TYPICAL TREATMENT:** 
    - **LDOPA + Carbidopa + Domperidone (if vomiting) ( + ) Risperidone/Quetiapine if hallucinating ( + ) Anticholinergics like Procyclidine if tremors**
  + **Second Line + Selegiline (MAO-B inhibitor)/ COMT inhibitor (entacapne)** or / **Dopamine agonist** (**Bromocriptine, cabergoline, apomorphine, ropinerole\_** if still struggling
  + **Levodopa 🡪** mainstay of treatment if motor symptoms affecting patient. DO NOT STOP SUDDENLY
    - often combined with **DOPA decarboxylase inhibitors (Carbidopa, Benserazide)**
      * Reduces peripheral side effect i.e. N&V
    - Central side effects of LDOPA includes postural hypotension, confusion, hallucinations, delusions
      * Treat Nausea with **Domperidone (dopamine antagonist)**
      * Hallucinations 🡪 atypical antipsychotics i.e. **Risperidone, Quetiapine**
  + **Ropinerole/Bromocriptine/cabergoline (Dopamine Agonist)** 🡪 helps in **early PD** and delay start of LDOPA
    - Bromocriptine and Cabergoline associated with pulmonary, retroperitoneal and cardiac fibrosis. Can also cause impulse control disorders and excessive daytime drowsiness
    - Echo, CXR, ESR and creatinine prior to starting treatment
  + **Apomorphine 🡪** potent DA agonist used for sudden freezing or to even out end of dose effects
  + **MAO-B** inhibitors 🡪 e.g. **selegiline** may be used. Inhibits breakdown of dopamine
  + **Anticholinergics (i.e. Orphenadrine, Procyclidine, Trihexyphenidyl)** often used to help with **tremors**
  + **Amatadine 🡪** used in late PD and may help with LDOPA induced dyskinesia. Cerebella side effects + livedo reticularis (**side note, also used for excessive tiredness in MS**)
  + **COMT inhibitors e.g. Entacapone, Tolcapone.** COMT normally breaks down dopamine.
    - Lessen off time in those with severe end-of-dose wearing off
  + **Antimuscarinics i.e. Procyclidine / Benzotropine / Benzhexol** used to treat **drug-induced Parkinsonism**
  + **Long term side effects** 
    - **MOTOR FLUCTUATIONS**
    - **DYSKINESIAS** 🡪 Involuntary movements occurring with treatment
      * Twisting and turning movements when dopamine levels are high (peak dose dyskinesias)
      * Painful, sustained contractions (usually of the feet) when dopamine levels are low (wearing off dystonias)
      * May be reduced by having more frequency, smaller doses, or adding MAO-B inhibitors e.g. Selegline, COMT inhibitors (entacapone) or dopamine agonists (bromocriptine, cabergoline, apomorphine)

|  |  |  |  |
| --- | --- | --- | --- |
| Category | Examples | Mechanism | SEs |
| **Dopamine agonists** | **Ropinerole** | Direct DA agonism | Drowsiness, nausea, hallucinations and compulsive behaviour |
| **MAO-B inhibitors** | **Selegiline** | May delay dopamine breakdown | Postural hypotension and AF |
| **Anticholinergics** | **Benzhexol** | Increased cholinergic transmission | Central → confusion, anxiety, hallucinations  Peripheral → dry mouth, dizziness, blurred vision, urinary retention |

* **Surgery** 
  + Deep brain stimulation, Pallidectomy

**,M**

**Essential Tremor**

* Most common form of pathological tremor
* Inherited in **AD** fashion 🡪 check FH
* Common 🡪 0.5 🡪 5%
* Present in early adulthood but it is progressive 🡪 mostly presents in older patients
* Typically an action tremor
  + **Postural tremor** 🡪 symmetrical. Difficulty holding cups or writing, but **relieved at rest** 🡪 may affect the **head and neck** (worse if hands outstretched
  + Can cause severe social impairment 🡪 25% may retire early or change career
* No other neurological findings
* Tremor **relieved by alcohol**
* Treated with **propranolol**  (primidone)

**Huntingtons Disease**

* **Autosomal dominant neurodegenerative disorder caused by a CAG repeat within the huntington gene – degeneration of cholinergic and GABAergic neurones in the striatum of the basal ganglia (defect in chromosome 4)**
* **Clinical feature:** age 35 – 40 @onset, insidious then progressive signs, chorea 🡪 irritability 🡪 dementia 🡪fits 🡪 death
* **Neuropsychiatric symptoms:** personality changes, irritability, impulsiveness, dementia
* **Motor changes:** chorea, deficits in fine motor coordination, slowed saccadic eye movement

**Chorea, athetosis and dystonia**

* **Chorea**: irregular, random and variable movements which have a flowing or dancing quality which may appear semi purposeful

|  |  |
| --- | --- |
| **Acquired** | **Hereditary** |
| * **Post infectious** (**Sydenham’s chorea post rheumatic fever** – remember **PECCS** – polyarthritis, erythema marginatum, carditis, chorea, subcutaneous nodules) * **Polycythaemia rubra vera (JAK2, pruritis, splenomegaly etc)** * **SLE** * **Thyrotoxicosis** * **Drugs** → L-DOPA, phenytoin, neuroleptics | **Huntington’s disease**  A number of rare, inherited disorders |

* **Athetosis:** slower and more writhing in quality than chorea. It represents transition from one dystonic posture to another. It is typically associated with **congenital brain damage** (cerebral palsy). The **hands and feet** are typically affected
* **Dystonia:** involuntary, sustained,painful muscle contractions resulting in **abnormal posture.** Often caused by antipsychotic medications: classified as generalised or focal
  + **Focal:**
    - **Blepharospasm:** involuntary eye closure
    - **Oculogyric crisis:** eye rolled upwards (seen in post-encephalitic parkinsonism)
    - **Spasmodic torticollis** 🡪 SCM contraction may turn the head to one side or move it forward or backward
    - **Laryngospasm**
    - **Trismus**
    - **Writers cramp**

Text, whiteboard

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