Version 2.0

Parkinsonism and Parkinson's Disease

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Movement disorder characterised by degeneration of the dopaminergic nigrostriatal pathway in the brain. Leads to dopamine reduction, ACh excess.

Causes

- Idiopathic (Parkinson's disease)
- Drugs – neuroleptics, dopamine antagonists
- Encephalitis
- Toxins, e.g. Cu, Mn, carbon disulfide, severe CO poisoning.

Epidemiology

- Incidence & prevalence: widely variable reports ~5-350 per 100,000 per year.
- Prevalence: 65-12,500 per 100,000
- Risk factors
    - Increasing prevalence with age and slightly commoner in men.
    - Smoking and pesticide exposure.
    - Spring birth for Parkinson's Disease.

Presentation

Insidious onset with peak age of onset at 55-65 years.

Main features are:

Resting **T**remor (incl pill rolling)	Increase in tone	Micrographia
Cog wheel **R**igidity	Shuffling, festinating gait	Drooling
Brady/**A**kinesia	Expressionless face	Quiet voice
Impaired **P**ostural reflexes	Positive glabella tap	

Differential diagnosis

- Multiple system atrophies - initially appears as parkinsonism but has more rapid pulse and is characterised by an inability to look down voluntarily.
- Benign essential tremor - far more common, tremor is worse on movement
- Huntington's disease - can present earlier with rigidity instead of chorea
- Wilson's disease - earlier onset with Kayser-Fleischer rings and hepatitis.
- Progressive supranuclear palsy -characterised by paresis of conjugate vertical gaze
- Corticobasal degeneration - cortical dysfunction, e.g. apraxia, dementia and aphasia.
- CJD - dementia usually apparent with myoclonic jerking, ataxia and pyramidal signs.
- Multi-infarct dementia - cognitive impairment, spasticity, and extra-pyramidal signs.
- Pick Disease - affects the frontal and/or temporal lobes. Parkinsonism is usually mild.
- Drug or toxin induced tremor, notably SSRIs, caffeine, amphetamines, BB, TCA, Li.
- Cerebellar tremor - unilateral or bilateral, low-frequency intention tremor.
- Pyschogenic tremor - the tremor is variable, increases under direct observation

Investigations

Diagnosis is clinical and can be confirmed by a dopamine challenge. Investigations for DDx:

- CT or MRI brain scan: not usually needed unless ? SOL, hydrocephalus or vascular
- PET scanning with fluorodopa can localise dopamine deficiency in the basal ganglia
- Autonomic tests and sphincter electromyography may Dx multiple-system atrophy.
- Further investigations for young-onset or atypical disease may include : ceruloplasmin levels (Wilson's disease), tests for the Huntington gene and syphilis serology.

Associated diseases

- Dementia (in over 20% of patients with Parkinson's disease).
- Depression (50% of patients with Parkinson's disease).
- Shy Drager syndrome - Autonomic neuropathy, hypopituitarism, anhydrosis, hair loss
- Steele Richardson syndrome – Midbrain & subthalamic nuclei degeneration. Supranuclear ophthalmoplegia, neck dystonia, pseudobulbar palsy, behavioural & cognitive impairment imbalance and difficulties walking, frequent falls

Management

Multidisciplinary team – Speech/Occupational/Physio therapists, nursing & medical.

Initial drug treatments

- Levodopa ± carbidopa Virtually all respond initially. Use the lowest effective dose.
    - SE: N&V, postural ↓BP, therapeutic index narrows in time, on-off phenomena
- Dopamine agonists (pramipexole and ropinirole, bromocriptine, cabergoline, lisuride, pergolide).
    - Can be used first line (esp younger patients) or as adjuvant. They reduce dyskinesia and motor fluctuations compared with levodopa, but are associated with ↑Rx withdrawal and poorer motor scores.
    - Non-ergot-derived agonists are preferred (pramipexole and ropinirole); others (all ergot derivatives) need renal function, ESR and CXR before use.
- Selegiline - (a monoamine-oxidase-B inhibitor).
    - RCTconfirmed improvement of symptoms and a delay in the need for levodopa.
    - But early research suggesting Selegiline was neuroprotective was disproved.

Common Management Problems and Complications

- Long-term levodopa assoc with adverse motor effects that limit its use.
    - Motor fluctuations (on-off phenomena, wearing off, dose failures, and freezing)
    - Dyskinesias (peak-dose dyskinesias, diphasic dyskinesia, and dystonia).
- They occur in 50-90% of people who have received levodopa for 5-10 years. Dopamine agonist rather than L-dopa is often initiated in younger patients.
- "Wearing off" phenomenon - several strategies are available:
    - Smaller, more frequent doses of L-dopa.
    - Adding liquid carbidopa, selegiline or a dopamine agonist may help.
    - COMT inhibitors (e.g. entacapone) can be used to prolong the action of L-dopa
- "On Off" fluctuations (switch from severe dyskinesia to immobility in a few minutes):
    - Combine levodopa with a dopamine agonist e.g. cabergoline.
    - Fewer doses of levodopa with intermittent apomorphine injections
    - Liquid forms of levodopa (enable tighter titration of dose).
    - Diet: small snacks and one large evening meal.
- Dyskinesias (may occur at the beginning or end of a dose, or sometimes at its peak):
    - At peak dose (usually choreic):
        - Make doses smaller but more frequent (same daily total).
        - Add a long-acting dopamine agonist.
        - Frequent dyskinesias may respond to slow release or liquid L-dopa.
        - Surgery may be indicated.
    - At the beginning or end of dose:
        - Try soluble levodopa before meals or add COMT inhibitor.

- Depression and anxiety:
    - Depression and anxiety are common. Either tricyclics or SSRIs can be used.
    - Psychotherapy and support groups are helpful (both for patient and carers).
- Hallucinations and psychosis:
    - Consider gradual withdrawal of PD drugs, atypical antipsychotics e.g. clozapine
- Dementia: confusion and hallucinations imply a bad prognosis with high mortality within 1-2 years. Mx is very difficult and admission to a nursing home is often required.

Adjuvant therapy for more advanced PD

- 1st choice drugs in later PD are dopamine agonists, MAOI-B, or COMT inhibitors.
- Catechol-O-methyltransferase (COMT) inhibitors
    - Reversibly inhibit the peripheral breakdown of L-dopa by the COMT enzyme,
    - Produce benefits if levodopa motor fluctuations or if stable response to L-dopa.
    - Entacapone as combo (L-dopa carbidopa entacapone) because of poor patient compliance. Tolcapone if entacapone fails (needs 2 weekly LFT's for first year).
- Antimuscarinic Drugs (benzatropine, orphenadrine, procyclidine, and benzhexol)- evidence for efficacy is poor[2]:
    - May have beneficial effects on tremor and reducing sialorrhoea.
    - Adverse effects include confusion, hallucinations, and memory impairment
    - Frequent SE limit use. May worsen tardive dyskinesia.
- Amantadine has a limited usefulness as monotherapy in early PD (for tremor or bradykinesia) and can be used as an adjuvant in later PD for reducing dyskinesia.
- Apomorphine SC is used as a rescue agent in advanced disease to provide rapid but short-lived benefit for sudden, severe 'off' episodes
- Modified release l-dopa can also help with symptom control in later stages.

Surgical

- Pallidotomy: indicated for unilateral dyskinesia, severe 'on/off' fluctuations and drug failure .One systematic review found that unilateral pallidotomy improved motor examination and ADLs compared with medical treatment, but high incidence of SE.
- Thalamic surgery: effective method of controlling tremor but has no effect on bradykinesia. No randomised trials comparing this with medical treatment.
- Subthalamic surgery: can improve tremor, bradykinesia and rigidity but may provoke dyskinesias and hemiballismus.
- Deep brain stimulation: electrodes in basal ganglia attached to internal stimulator placed subcut below the clavicle. May be used to provide uni- or bilateral stimulation. May reverse akinesia, rigidity and tremor. Cx include ICH and confusion.

Complications

- Bed sores
- Poor nutrition
- Falls
- Contractures
- Sleep disturbance
- Bowel and bladder disorders
- Infections & aspiration pneumonia
- Psychiatric: depression, dementia, and psychosis.

Prognosis

Slowly progressive with a mean duration of 15 years. Severity however varies widely.