Parkinson's Disease

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AN
ESSAY
ON THE
SHAKING PALSY.

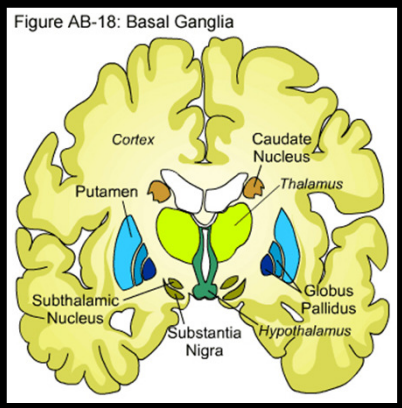
CHAPTER I.
DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

What is Parkinson's disease?

- A common, **progressive neurodegenerative disorder,**
- Caused by free radical damage to the nigrostriatal pathway (dopaminergic and inhibitory)
- Which connects the substantia nigra to the corpus striatum
- Resulting in loss of > 80% of nerve cells in the substantia nigra
- With deficient neural transmission at post synaptic D2 receptors
- resulting in significant disability 10-15 years after onset



Neurological Issues
Cardinal Motor Features

1. Rigidity
2. Bradykinesia
3. Tremor

Treatment options: increase dopamine

1. **Dopamine precursor:**
   Levodopa + carbidopa / benserazide
2. **Dopamine agonists**
   - Pramipexole
   - Ropinirole
   - (Cabergoline)
   - (Apomorphine)
   - (Bromocriptine)
   - (Pergolide)
3. **Increase release endogenous dopamine**
   - Amantadine
4. **Inhibition of COMT**
   - Tolcapone
   - Entacapone
5. **Inhibition of MAO-B**
   - Selegiline
   - Rasagiline
6. **Drugs affecting the cholinergic system**
   - Benzhexol
   - Benztropine

Treatment issues
for <u>motor</u> improvement

- Functional disability requires dopaminergic Rx in the CNS either by

1. Providing a precursor to dopamine:
   – Levodopa
2. Or by providing a Dopamine agonist:
   – Pramipexole
   – Ropinirole
   – (Carbergoline)

However....

These dopaminergic agents have long term side effects, particularly after 5-7 years of therapy:

MOTOR COMPLICATIONS (45-80%)

1. Motor fluctuations (↓ levels)
   - Wearing off phenomena (off time): periods of return of PD symptoms when medication effect wears off
   - Freezing
2. Drug induced Dyskinesias (↑ levels) (30-80%)
   - Dystonias
   - Akathisia
   - Chorea
   - Myoclonus

Rumours?

- Early use of levodopa might predispose patients to develop long-term motor complications
- dopamine agonist monotherapy may be poorly tolerated, with decreased efficacy and a delay of symptomatic benefit cf levodopa
- Dopamine agonists may reduce the risk of dyskinesias and motor fluctuations as they have a longer, less pulsatile half life
- Sustained release levodopa might prevent the wearing off phenomena (end of dose bradykinesia) cf immediate release levodopa
- Other drugs like selegiline might be neuroprotective and reduce the need for dopaminergic agents
- Selegiline might cause increase in mortality

Q: What is the role of Selegiline in the early treatment of PD?

- Selegiline: selective, irreversible inhibitor of intraneuronal MAO-B.
- Prevents the breakdown of dopamine
- Given as a single oral dose
- Well absorbed
- Extensively metabolised by the liver
- Active metabolite + amphetamine + metamphetamine
- Long half life: 39hrs

Selegiline

Adverse effects:

- Agitation and involuntary movements
- Confusion, insomnia, hallucinations
- Nausea

DDI:

- Hypertension at v. High doses when MAO-B selectivity is lost and pressor effects to tyramine are potentiated
- Amantadine and centrally active antimuscarinic agents potentiate anti-PD effects

Selegiline

- Recommendations for patients with PD who require symptomatic treatment:

Selegiline

- Confers mild symptomatic relief prior to initiating Dopaminergic treatment
- Accounts for a delay in the need for dopaminergic agents
- Does NOT confer neuro-protective benefits
- No evidence of increased mortality with selegiline, either in combo or as monotherapy

Q2: Which drugs offer best control of functional motor disability: Levodopa vs Dopamine Agonist

- Levodopa :
- Dopaminergic agonists:

Q3: Most favourable long term motor complication profile: levodopa vs dopamine agonists

Levodopa

- Dopamine can not cross the BBB
- Levodopa is a precursor to Dopamine and can cross the BBB. It can enter nerve terminals in the basal ganglia, where it is decarboxylated to form dopamine.
- 95% of levodopa is metabolised outside the brain
- Therefore given with a **peripheral** decarboxylase inhibitors to prevent metabolism before it crosses the BBB:
- Carbidopa
- Benserazide

Levodopa + carbidopa

- Allows for a 10x reduction in dose of levodopa
  - Decreased arrhythmias
  - Decreased nausea and vomiting
  - But same incidence of hallucinations!
- Availability of levodopa in brain increases

Levodopa + carbidopa

- Given t.i.d
- Start low dose
- Increase after 2 weeks
- Review every 6-8 weeks
- PK:
  - Absorbed proximal small intestine
  - Metabolised by
    - MAO and Decarboxylases GIT wall
    - Gut flora

    Short half life:2hrs
- DDI:
  - MAOI: hypertension

Levodopa adverse effects

- Nausea, vomiting (CETZ)
- Postural hypotension (usually resolves)
- End of dose motor fluctuations
- Peak dose worsening Involuntary writhing movements (dyskinesia):
  - Akathisia
  - Chorea
  - Myoclonus

- Cardiac arrhythmias
- Endocrine:
  - Stimulation GH
  - Suppression prolactin
- Psychiatric
  - Vivid dreams
  - Agitation
  - Paranoia
  - Confusion
  - Hallucinations

Sustained release vs immediate release levodopa?

- When initiating treatment with levodopa, there is no difference in the rate of motor complications between immediate release and sustained release levodopa

Dopamine agonist Ropinirole

- Agonist at D2 receptor
- Also stimulates D3 and D4
- Pk:
  - Well absorbed after oral ingestion
  - Metabolised in liver to inactive metabolites
  - Elimination half life=6hrs
- DDI:
  - Ciprofloxacin inhibits CYP1A2 , reducing ropinirole's clearance

Dopamine agonist Ropinirole adverse effects

- Somnolence; sleep "episodes"
- Nausea
- Orthostatic hypotension, syncope
- Nightmares, hallucinations

Dopamine agonists: Pramipexole

- Longer acting than levodopa
- Less tendency to cause
  - On-off effects (motor fluctuations)
  - Dyskinesias
- May have anti-oxidant effects
- AEs:

Confusion, delusions, sleep disturbances

Nausea, orthostatic hypotension

Treatment Recommendations

- Levodopa, ropinirole and pramipexole are all effective in ameliorating motor and activities of daily living (ADL) disability in patients with PD who require dopaminergic therapy
- Levodopa is more effective than ropinirole and pramipexole in treating the motor and ADL features of PD

Q3: Long term motor complications

- Dopamine agonists (ropinirole, pramipexole) result in fewer motor complications than levodopa after 2.5 years follow up
- Dopamine agonists associated with more frequent "other" adverse effects than levodopa:
  - Hallucinations
  - Somnolence
  - Oedema

Overall recommendations levodopa vs dopamine agonists

- In patients with PD who require the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used.
- The choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each individual patient with PD.

Report of the Quality Standards Subcommittee of the American Academy of Neurology (Oct 20, 2001)

More questions

- Which medications reduce the **off time** of levodopa therapy?
  - Entacapone (COMT-I)
  - Rasagiline (MAOB-I)
- Which medications reduce **dyskinesia**?
  - Possibly Amantadine
- Which factors predict improvement after DBS (Deep Brain Stimulation) of the subthalmic nucleus?
  - Pre-operative response to levodopa
  - Younger patients with shorter disease durations

Entacapone

- Reversible competitive COMT inhibitor
- Relatively specific for CNS COMT
- Prevents l-dopa breakdown
- Increases its bioavailability at nigrostriatal nerve fibres
- Adverse effects:
  - Nausea
  - Orthostatic hypotension
  - Hepatitis
  - Hallucinations
  - Dyskinesias
- DDI
  - MAOI

Amantadine

- Stimulates release of endogenous dopamine++
- ?Inhibits reuptake of Dopamine presynaptically
- ?Direct action on dopamine receptors
- Less effective than levodopa
- Action declines with time
- PK
  - Half life 10-30hrs
  - Steady state 4-7 days
  - 95% eliminated by kidney
  - Contraindicated in renal failure

Amantadine

Adverse effects:

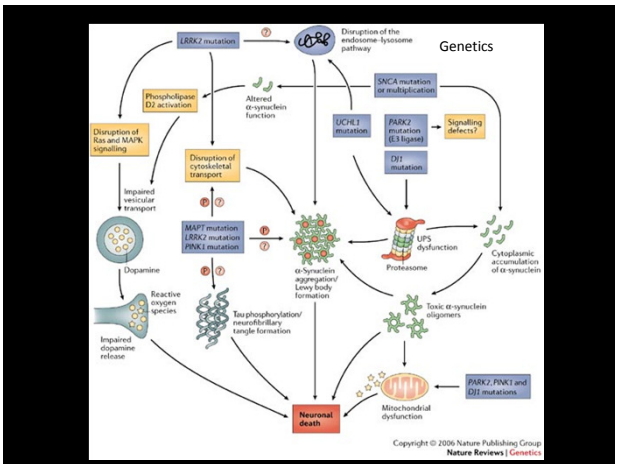
- Peripheral oedema
- GIT upsets
- Dry mouth
- CNS toxicity
  - Nightmares
  - Insomnia
  - Dizziness
  - Hallucinations
  - Convulsions
- Leukopaenia

Anticholinergics

- Restore balance between dopaminergic / cholinergic pathways
- (Ach inhibits dopaminergic response)
- Reduce tremor
- Dose limiting CNS side effects are common (elderly)
  - Dry mouth, blurred vision, constipation
  - Precipitate glaucoma, urinary retention
  - Confusion, excitement, psychosis
- First line for parkinsonism caused by essential antipsychotic drugs

Summary

Issue	Class	Drug
Mild symptomatic relief prior to initiating dopaminergic treatment?	MAOI –B (irreversible)	Selegiline
Motor improvement?	Dopamine precursor (best) Dopamine agonist	Levodopa Pramipexole Ropinirole
Fewer motor complications ?	Dopamine agonist	Pramipexole Ropinirole
Which medications reduce the off time of levodopa therapy?	COMT-I MAOB-I	Entacapone Rasagiline
Which medications reduce dyskinesia?		Amantadine
First line for parkinsonism caused by essential antipsychotic drugs?	Anticholinergic	Benzhexol Benztropine


LRRK2 mutation
Disruption of the endosome–lysosome pathway
Genetics
SNCA mutation or multiplication
Phospholipase D2 activation
Altered α-synuclein function
UCHL1 mutation
PARK2 mutation (E3 ligase)
Signalling defects?
Disruption of Ras and MAPK signalling
DJ1 mutation
Disruption of cytoskeletal transport
Impaired vesicular transport
MAPT mutation
LRRK2 mutation
PINK1 mutation
UPS dysfunction
Cytoplasmic accumulation of α-synuclein
Dopamine
α-Synuclein aggregation/ Lewy body formation
Proteasome
Reactive oxygen species
Tau phosphorylation/ neurofibrillary tangle formation
Toxic α-synuclein oligomers
Impaired dopamine release
PARK2, PINK1 and DJ1 mutations
Mitochondrial dysfunction
Neuronal death
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