Secondary Parkinsonism

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EXOGENOUS TOXINS

CO
Manganese

DRUG-INDUCED PARKINSONISM

1) **dopamine receptor-blocking drugs**: neuroleptics (phenothiazines, butyrophenones), antiemetics (metoclopramide).
   most offensive neuroleptics are potent D_2 receptor antagonists + have little anticholinergic effect: piperazine phenothiazines, haloperidol, thiothixene.
2) **dopamine-depleting agents**: reserpine, tetrabenazine.
3) α-methyldopa, lithium, flunarizine, cinnarizine, amiodarone.

- **drugs** cause 8% of all parkinsonism cases!
- women and elderly have increased risk.
- signs usually develop within 3 months of starting causal agent.
- all cardinal signs of parkinsonism syndrome.
  - typically symmetric!!!
  - tremor is less common.
- upon withdrawal of offending drug, symptoms slowly disappear (in weeks or months; if persist > 6 months – it is PD).
- treatment of neuroleptic-induced parkinsonism:
  1) discontinue drug / substitute with greater anticholinergic potency or "atypical" neuroleptic
  2) add **anticholinergic** (e.g. TRIHEXYPHENIDYL, BENZTROPINE)
     Remember, anticholinergics + phenothiazines potentiate **tardive dyskinesia**!
  3) add AMANTADINE.

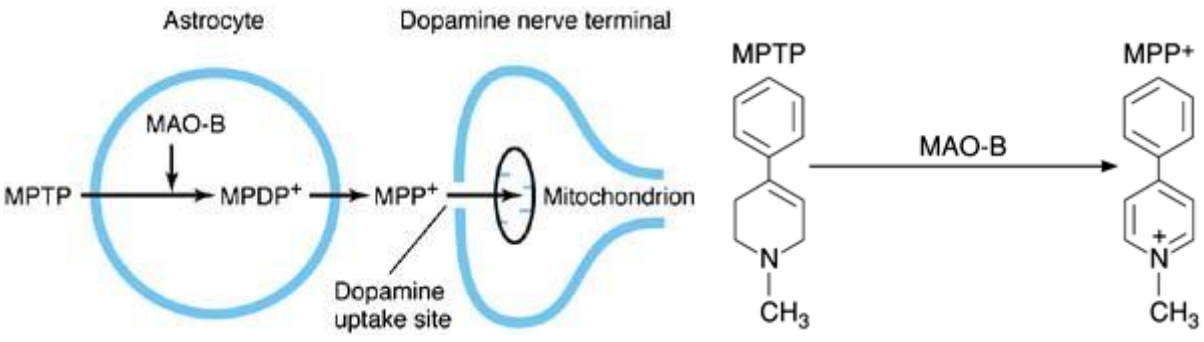
> N.B. LEVODOPA is not effective (dopamine receptors are occupied by offending drug) and may worsen underlying psychotic disorder!

MPTP-INDUCED PARKINSONISM

Best studied experimental model of parkinsonism!

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP):

- derivative of meperidine.
- by-product of synthesis of opioid (first developed during production of illicit heroin).
- opioid preparations heavily contaminated with MPTP led to several cases of parkinsonism in early 1980s (drug dealer in northern California supplied homemade "synthetic heroin").



- MPTP enters brain and is converted (by MAO-B in astrocytes) to *N*-methyl-4-phenyl-dihydropyridine ($MPDP^+$).
- $MPDP^+$ diffuses across glial membranes and extracellularly undergoes nonenzymatic oxidation and reduction to active metabolite *N*-methyl-4-phenylpyridinium (MPP^+).
- MPP^+ is taken up by plasma membrane transporters (that normally reuptake dopamine from synapses).
- internalized MPP^+ is concentrated in mitochondria → inhibits oxidative phosphorylation (by interacting with complex I of mitochondrial electron transport chain) → reduced metabolism of molecular oxygen → **increased formation of active radicals** → cell injury.

Intravenous injection → highly focused damage of **substantia nigra pars compacta** → **acute severe irreversible parkinsonism** (in humans and primates).
N.B. other neurons (including other dopaminergic neurons) are left intact!
Clinical syndrome is indistinguishable from PD and responds to LEVODOPA.

POSTENCEPHALITIC PARKINSONISM

- was most prominent sequela of pandemics of *ENCEPHALITIS LETHARGICA (von Economo disease)* that occurred between 1919 and 1926. see p. Inf9 >>
- today vanishingly rare.
- causative agent (was never established) affected mainly midbrain.
  other viruses (Coxsackie, Japanese B, western equine encephalitis) can cause parkinsonism!
- pathology - **NEUROFIBRILLARY TANGLES** in remaining nigral neurons.
- clinical features:
  1) parkinsonism similar to PD (but onset at young age with slower progression).
  2) ***oculogyric crises*** - forced, sustained deviation of head and eyes to fixed position for minutes to hours.
  3) grimaces, torticollis, torsion spasms, myoclonus, facial and respiratory tics, bizarre postures and gaits, behavioral disorders, ocular palsies may appear.
- treatment - ***limited tolerance to LEVODOPA*** (dyskinesias at low dosages); **anticholinergics** are tolerated well.

HEMIPARKINSONISM-HEMIATROPHY SYNDROME

Etiology - brain injury early in life (possibly even perinatally).

Relatively benign uncommon syndrome:

1. **HEMIPARKINSONISM** - begins in young adults and remains as hemiparkinsonism*; sometimes with unilateral dystonic movements; nonprogressive (or slowly progressive compared to PD).
   *sometimes becomes bilateral.

2. Ipsilateral **BODY HEMIATROPHY** (or contralateral **CORTEX HEMIATROPHY**) - completely unnoticed by patient (comparative examination of size of hands and feet may be necessary to diagnose condition)

Responds poorly to medications.

"LOWER-BODY PARKINSONISM"

1. **NORMAL PRESSURE HYDROCEPHALUS** - gait with shuffling short steps and loss of postural reflexes and sometimes freezing.
2. **VASCULAR PARKINSONISM** - resulting from lacunar disease: gait is profoundly affected, with short steps, freezing and loss of postural reflexes.
3. **IDIOPATHIC GAIT DISORDER OF ELDERLY**.

BIBLIOGRAPHY for ch. "Movement disorders, Ataxias" → follow this LINK >>