# Introduction to Parkinson's disease

4/23/2022

# History

- The earliest reference to 'shaking palsy’ in the Western medical literature is by Galen (AD 138-201)
- James Parkinson described the Shaking Palsy in 1817
- 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.

# Clinical Features

- Tremor
- Rigidity (not described in James Parkinson's original monograph On Shaking Palsy) Charcot late 1800s
- Bradykinesia – slow movements
- Postural instability-surprising may actually worsen on levodopa-evaluated by the pull test.
- Shuffling gait with festination

# Advanced disease

- Motor fluctuations
- Dyskinesia-choreiform
- Off symptoms-Freezing, panic attack like state.

# Non Motor symptoms

- Hallucinations-more likely in PDD and DLB
- Punding
- Dopamine dysregulation syndrome-compulsive shopping, etc.

# Medications

- Anticholinergics
- Dopamine agonists
- Levodopa
- MAOb inhibitors
- COMT inhibitors

# Anti-cholinergics

- Kampa Vata is a disorder described by Ayurvedic practitioners thousands of years ago
- Thought to be analogous to Parkinson's disease
- Herbal treatments include anticholinergics:
- Paraseekayavanee / henbane (dry fruit of Hyoscyamus reticulatus), which have hyoscyamine and scopolamine as active ingredients.
- Controversy about active ingredient in Mucuna pruriens plant, with some claims of levodopa content.

# Anti-cholinergics

- Treated mainly with anti-cholinergics until about the 1960's-1970's.
- Davidson, 3rd edn, 1956: mentions tinct belladonna, tinct stramonium (jimsonweed / devil's trumpet) and hyoscine hydrobromide and "newer synthetic preparations Artane, Lysivane and Pipanol." (*Stramonium* is originally from Greek, *strychnos* στρύχνος "nightshade" and *maniakos* μανιακός "mad")

# Anti-cholinergics

- Kampa Vata (About 2,000 B.C.)
- ***Datura stramonium***
- ***Jimsonweed aka loco weed***
- *Scopolamine prinicipal active drug*
- Difficult to dose teas or seeds from the plant
- Possible side effects: death, anti-cholinergic delirium

# Jimsonweed

- Also has atropine
- British soldiers at Jamestown trying to capture Nathaniel Bacon for seditious remarks about the king died after ingesting the plant.

# Datura Stramonium

## **Dhatura धतूरा**

# “Modern” anti-cholinergics

- Artane (trihexyphenidyl)– 1960s
- Cogentin (benztropine)

# Reserpine

- Dopamine initially thought of just as precursor to noradrenaline
- Brodie and others in 1950s investigated effects of reserpine
- Behaves as sympatholytic-depleting amines, but not as adrenolytic (not blocking receptors)
- Called reserpine phenomenon-led to development of theory of monoamines

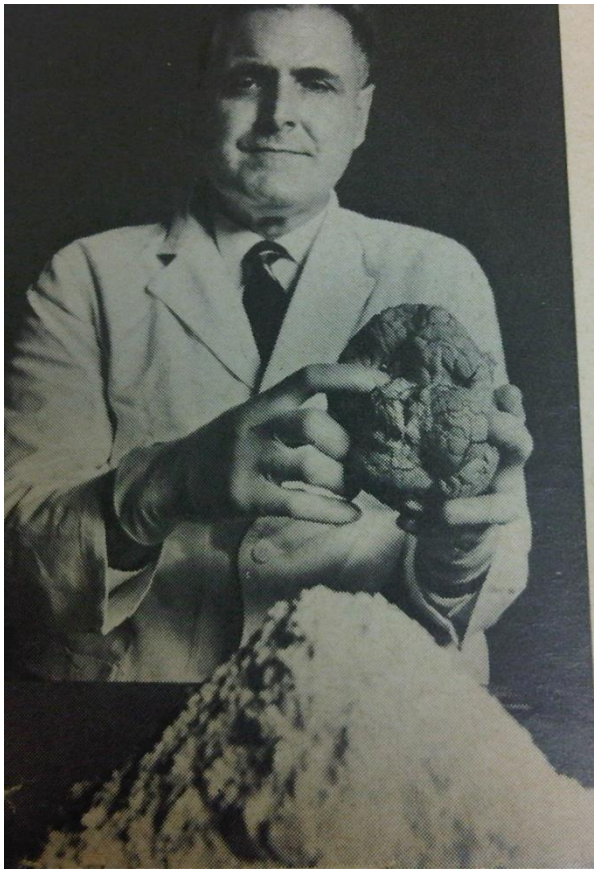
# Iproniazid

- Iproniazid (TB drug) can block the “calming effect” of reserpine and is instead a “psychostimulant” – Alfred Pletscher
- Kline-Rockland State Psych Hospital-Lasker Prize

# Levodopa

- Hornykievicz et al. contributed to initial experiments
- Ehringer& Hornykievicz 1960 showed basal ganglia dopamine deficiency in Parkinson's disease
- ***Birkmeyer*, *W. and O*. *Hornykievicz*, *1962***, Der L-Dihydroxy- phenylalanin(L-DOPA)-Effekt beim Parkinson-Syndrom des Menschen

# Miraculous White Powder



# Levodopa

- George Cotzias
- Cotzias GC (March 1968). "L-Dopa for Parkinsonism". The New England Journal of Medicine 278 (11): 630.
- Problems: dyskinesias, off-symptoms.
- Needs neutral amino acid transporter in the gut and also blood brain barrier! (hence a high protein meal interferes)

# MPTP

- 1976 when a 23 year old American chemistry graduate student in Maryland and apparent opioid addict took a shortcut to synthetising his own pethidine analogue, MPPP (Desmethylprodine) which is an analogue to meperidine developed by Hoffman La Roche in the 1940s.
- One byproduct was MPTP (I -methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which is not harmful itself, but the cation 1-methyl4-phenyl pyridinium (MPP+) is produced by MAO-B. Hence selegiline could prevent toxicity if given rapidly enough.
- MPP+ caused severe and pure Parkinsonism on the third day, which responded to levodopa till his cocaine overdose 18 months later.
- In 1982, seven people in Santa Clara County, California were diagnosed with Parkinsonism after having used MPPP contaminated with MPTP. Dr. J. William Langston tested MPP+ in the laboratory and developed an animal model of Parkinson’s disease.

# Dopamine agonists

- Calne 1974 Bromocriptine(dopamine agonist) effective

# Bromocriptine

- Caraceni et al. **Bromocriptine alone or associated with L-dopa plus benserazide in Parkinson's disease.** J Neurol Neurosurg Psychiatry. 1977 Dec;40(12):1142-6.
- Twenty-six patients affected by Parkinson's disease were treated with a 2-Br-alpha-ergocriptine (CB 154): 14 cases were given CB 154 alone, and 12 were given CB 154 along with L-dopa plus benserazide (Madopar). Both CB 154 and combined therapy (CB 154+Madopar) induced a significant improvement in total disability score, tremor, rigidity, akinesia, self-sufficiency, and some motor performance tests (dynamic tests).

# Newer dopamine agonists

- D3>D2
- Ropinirole (non-ergot)
- Pramipexole (non-ergot)
- Rotigotine (Neupro patch-non-ergot)
- Watch for sleep attacks, dopamine dysregulation syndrome-gambling, compulsive shopping.

# Other dopamine agonists

- Pergolide
- In March 2007, pergolide was withdrawn from the U.S. market for human use, after several published studies revealed a link between the drug and increased rates of valvular dysfunction.
- D2 agonist, weak D1 agonist, serotonin agonist

# Cabergoline

- Another ergot derivative
- Also found to be associated with valvular proliferation / heart damage

# MAOb inhibitors

- Birkmayer1962 showed response to deprenyl(selegeline) MAOB inhibitor
- Rasagiline also used currently
- ADAGIO trial, Olanow CW
- At 1 mg / day dosage, resagiline showed neuroprotection, but NOT at 2 mg/day dosage
- MAOb inhibition can facilitate serotonin syndrome
- Hypertensive crisis unlikely from MAOb unless Stilton cheese (high tyramine) is ingested.

# COMT inhibitors

- 1960s first generation COMT inhibitors shown to be effective
- Tolcapone was the first COMT inhibitor to be licensed but was withdrawn because of hepatic toxicity
- Currently, comtan / entacapone is used.
- reduces DOPA *O*-methylation in the gut, increases levodopa absorption, and prolongs half-life by reducing degradation of dopamine
- STRIDE-PD data re-analysis
- “The catechol *O*-methyltransferase inhibitor entacapone, used as an adjunct to levodopa in PD patients who do not experience motor fluctuations, does not improve Unified Parkinson's Disease Rating Scale motor scores but does improve a variety of quality-of-life measures.“ Olanow 2004

# Others

- Amantadine-unique mechanism. Can cause livedo reticularis. May be tried for tremor or dyskinesias… hit or miss medication
- Beta blockers-may be considered for treatment of tremor in tremor dominant PD

# Apokyn / Kynmobi

- Apomorphine
- Activates D1 and D2
- Short acting Injectable or sublingual for severe off symptoms
- Can be used to provide reliable “on” therapy for patients with dose failures