Neurodegenerative disorders

#As age progresses... some neurons could die... but regeneration cannot occur.

If sufficient number of neurons die.
↓
some functions can stop
↓
disease.

Alzheimer.

- deficiency of Ach
↓
loss of memory. (dementia).

Parkinsonism

- deficiency of DA
↓
tremors

- **Alzheimer's Dementia**
  - occurs due to deficiency of Ach in the Basal nucleus of meinhart
  ↓
  responsible for memory.
  - So Ach deficiency
  ↓
  Memory loss.

m: to ↑ Ach, some use.
→ antiholinesterases.

① Ach ∈ # (DOC)

D – Donepezil
R – Rivastigmine
G – Galantamine

(DR GRG)

② mimantine.

we found that Glutamate.
↓ binding to its receptor.
NMDA.
↓ leads to
Excitotoxicity.
↓
which aggravates alzheimer's syndrome.

Mimentine – NMDA receptor blocker ☆

- used when not responding to Ach ∈ #
- used in moderate – severe alzheimers.
- 5mg is given.

③ A-β amyloid -antibody

Both above diseases doesn't stop the cause of degeneration / they can't stop degeneration.
→ the degeneration actually occurs due to deposition of Aβ amyloid.
Monoclonal Ab against ↑f
→ ADUCANUMAB.

Multiple Sclerosis.

- It is a demyelinating disease that causes neurological deficits.

MS if presents as:

acute neurological deficit : DOC – steroids.

Chronic

RRMS
- relapsing remitting {comes & goes}

↓

DOC:
- β-IFN
- Natalizumab
- Siponimod
- Glatiramer.

PPMS
primary progressive {steady worsens}.

- Ocrelizumab {MAb agint CD20}

Parkinsonism.

- there is Dopamine deficiency in Brain.

- tremors
- Rigidity
- Bradykinesia {slowed movmnts}

→ actually . DA & Ach are two opposite action Neurotransmitters.

→ and parkinsonism develops due to. Imbalance between Ach & DA:

Normally : Ach 100 — DA 100.

Imbalance.

DA 50

Treatment ?

- ↑ DA
- if that doesn't work, ↓ Ach.

↑ DA

tyrosine → Ty → DOPA → DA → DA

DA → metabolism.

① MAO
② COMT.

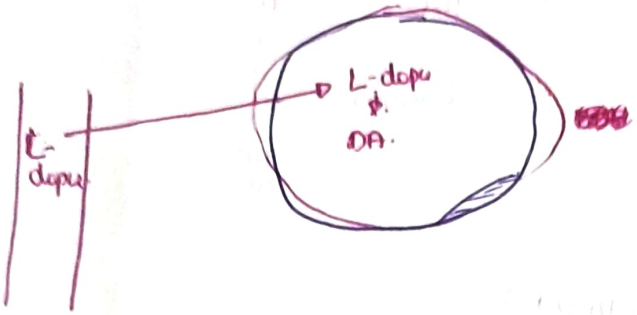
DA

for ↑ DA → we can give Levo dopa. ✓

but not dopamine as it can't cross BBB. ✗

ⓐ precursor of DA.
ⓑ Drugs ↑ DA release.
ⓒ metabolism ⊖
ⓓ ⊕ Receptors - dopamine agonist

ⓐ Levo-dopa



L- dopa.
↓ dopa - decarboxylase.
DA

But dopa-decarboxylase is present in periphery, and that too more active.

so if we give say,

100 L-dopa
- 99 dopamine is formed in periphery
- 1 dopamine in brain.

This can't cross B brain B. ✗

↓

But this dopamine will bind to

D_1 –	↓ BP.
β_1 –	↑ HR.
α_1 –	↑ BP.

in periphery

all part of Brain is not within Blood Brain Barrier

↓ areas outside are called → Circum ventricular Organs.

like CTZ (+)

↓

VOMITING

Solution ?

⊖ decarboxylase at periphery only. ★

↓↓

peripheral dopa decarboxylase Inhibitor.

↓ ↓

Carbi-dopa + LEVODOPA.

BENSERAZIDE

- more L-dopa will enter Brain
- lesser peripheral side effects.

• what is on - off phenomenon?
& wearing off phenomenon?

→ after giving OA - how long will it work for → It will work for (2h)

So does that mean we will have to keep giving it every 2 hours?

⇒ No, we give L-dopa only 1 or 2 times per day... Still it will work for the whole day!! How?

⇒ the dopa we give... Neurons will store and then release according to need so that there is continued supply for many hours

⇒ But neurons are getting degenerated in parkinsonism.. so storage capacity will decrease with increased destruction of neurons

⇒ so initial 2-4 hours it will work.. then later it will work for only say.. 20 hours so 4 hours symptoms will come towards the end of day drug wears off

⇒ wearing off phenomenon.

• In Extreme cases ie, later parkinsons there will be little storage only.

ie, dopamine will only work for 2 hours.

for 22 hours - symptoms ✓

→ on & off.

which is better? on / off?

NONE!.

Cause in off — parkinsonism sign ✓

in on — since there is no storage.. there is flooding with dopamine.

↓

psychosis.

patient alters btwn

psychosis & parkinsonism.

ON - OFF

Never normal.

So here, we will give divided doses many times but not practical.. so we give, Other drugs for on-off phenomenon.

Drugs Releasing Dopamine.

AMANTADINE

actually an Antiviral drug. ★★

↓ Influenza A.

↓ treats dyskinesia.

- all other drugs causes dyskinesia
- how does it treat it?
- cause it acts by other mech too → NMDA blocker.

S/E

- ankle edema.
- Livedo reticularis - ### pink reticular pigmentation on skin.

MAO ⊖

MAO A

present at all places
- Brain
- Liver
- platelet etc..

- metabolises all monoamines
  ↓
  adrenaline, NA, DA, 5-HT
- Tyramine (drug ↓)
  pethidine

MAO-B

Brain ✓

DA metabolism ✓ mainly.

So we use,

MAO B ⊖

↓

Selective MAO B ⊖ in parkinsonism.

↓

SELEGILINE
RASAGILINE
SAFINAMIDE.

DA → MAO-B → free-radicals → Neuronal regeneration.
↓
metabolite

⇒ they are also Disease modifying drugs.

Thus reliefs.

COMT ⊖

ENTACAPONE ✓ used.

TOLCAPONE — ×× hepatotoxic — not used now

OPICAPONE —
↓
used for on-off phenomenon.

dopamine Receptor agonist

- **Ergot** : claviceps purpurea.
  - Bromocriptine
  - pergolide
  - ↓
  - ergot derivedes
  - intense vasoconstriction
  - ↓
  - periphery ⇒ numbness, tingling in extremity
  - ↓
  - (a) DRY GANGRENE. (good)
  - (b) Fibrosis.
- **Non-ergot**
  - Pramipexole, Ropinirole → DOC
  - safer
  - long acting.

DOC in parkinsonism

pramipexole

Ropinerole.

Most effective drug in Parkinson

L-dopa.

Pramipexole / R.

→ DOC for P.

→ can be used in - restless leg synd. ★
{Ekboom synd}.

✓ was DOC before
✓ now - gabapentine.

S/E

① Excessive daytime sleepiness.
actually useful as old people have insomnia.

② increase control of impulse disorders
↓
- compulsive shopping.
- Gambling.

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antipsychotics can cause Parkinsonism.
↓
drug induced parkinsonism

- antipsychotics are dopamine receptor blockers
- all the above drugs cannot act as receptors are blocked
- so tt is to ↓ Ach.

→ Antimuscarinergics ✓

② Ach #.

ⓐ Central Anticholinergic.

Benzhexol {Trihexi phenydil ; THP}

↓

DOC for Drug induced parkinsonism.

ⓑ First Generation Anti-histamine.

- Cross BBB ✓ } promethazine can be used but not DOC.
- Ach #
- H #

DOC for parkinsonism

Pramipexole.

most effective.

L dopa + Carbidopa.

DOC for drug induced

THP.