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REVIEW ARTICLE OF PARKINSONISM

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ABSTRACT

Parkinson is a second most common neurodegenerative disease in which degeneration of dopaminergic neurons will occur in substantia nigra and corpusstriatum parts of brains basal ganglia leads to loss of motor control Due to degeneration of dopaminergic neurons which leads totremors muscular rigidity bradykinesia is observed. Increased levels of acetylcholine and decreased levels ofdopamine Is observed in a patient with Parkinson disease.

Epidamology
In India more than one million cases are reported every year, mostly reported in patients above age 65 among whom the incidence is about 1 in 100 individuals.

Etiology: Accurate cause of Parkinson disease is unknown
{idiopathic}, However modern researches shown that genetic mutation in LRRK2, PARK7, PINK1, PRKN (or) SNCA genes leads to development of Parkinson disease, Environmental factors such as subject to specific toxins, chemicals, pesticides and herbicides and heavy metals leads to development of Parkinsondisease

- However genetic factors alone can't cause development of Parkinson disease, mutation of specific genes and subject of patient to toxic environmental factors leads to development of Parkinson disease.
- Exposure to agent orange and DDT cause development ofParkinson disease.

Pathophysiology
There are two hall marks for histopathologic features of idiopathic Parkinson disease, they are as follows

1. Depigmentation of dopamine producing neurons (loss of SNCnerves)
2. Presence of Lewy bodies (neuronal filamentous aggregates composed of the pre synaptic proteins alfa-synuclein) in the remaining SNC neurons.

Lewy bodies appear in degenerating neurons in association with adjacent gliosis in pre-clinical stage (asymptomatic) Lewy bodies present in medulla locus and coeruleus and raphe nuclei, olfactory bulb so in asymptomatic idiopathic Parkinson disease anxiety, depression and vision abnormality will be seen.

Dopaminergic projections from SNC to striatum is observed.

Synapse on two populations of dopaminergic receptors mediated efferent neurons which intense and mediate motor activity via a complex neuronal circuit involving extrapyramidalsystem.

The Dirct Pathway
Activation of D1 receptors stimulates inhibitory GABA transmit substance-P efferent to globus pallidus interna and substantia nigrin reticulate.

Globus pallidus interna and substantia nigra and pars reticulate are inhibitory to thalamus.

In idiopathic Parkinson disease reduced activity generate inhibition of thalamus.

The Indirect Pathwy
Activation of D2 receptor inhibits GABA and enkephalin efferent to GPE, this GPE projects GABA neuron to STN here excitatory glutaminergic project to GPI, GPI output is inhibitedon glutaminergic thalamic projection.

In idiopathic Parkinson disease reduced D2 action is greater inhibition of overall loss of presynaptic nigrostriatal dopamine neurons in idiopathic Parkinson disease results in inhibition of thalamus activity and activation of motor complex.

Signs and Symptoms (Clinical Presentations)
Motor Symptoms
The patient experiences decreased manual dexterity, difficulty arising from a seated position, diminished arm swing during ambulation, dysarthria (slurred speech), dysphagia (difficulty with swallowing), festinating gait (tendency to pass from a walking to a running pace),

flexed posture (axial, upper/lower extremities), "freezing" at initiation of movement, hypomimia (Reduced facial animation), hypophonia (reduced voice volume), and micrographic (diminution of handwritten letters/symbols)

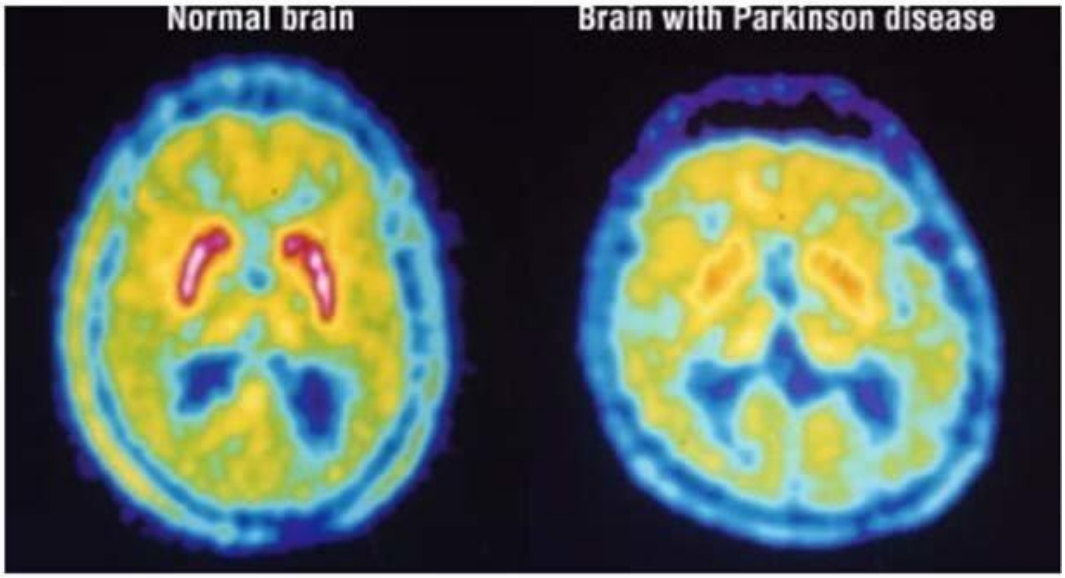
Autonomic and Sensory Symptoms

The patient experiences bladder and anal sphincter disturbances, constipation, diaphoresis, olfactory disturbance, fatigue, orthostatic blood pressure changes, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction,and sialorrhea (drooling).

Mental Status Changes

The patient experiences anxiety, apathy, bradyphrenia (slowness of thought processes), dementia, depression, hallucinosis/psychosis (typically drug-induced), and sleep sleep apnea, and rapid eye movement sleep behavior disorder)

DIAGNOSIS: Parkinson disease can be diagnosed by PET (positron emission tomography) scan, PET scan for the diagnosis of Parkinson disease can be done by injecting fluorodopa(F-18) which Is a radioactive trace for PET scan thathelp in visualizing the nerve endings of dopaminergic neurons



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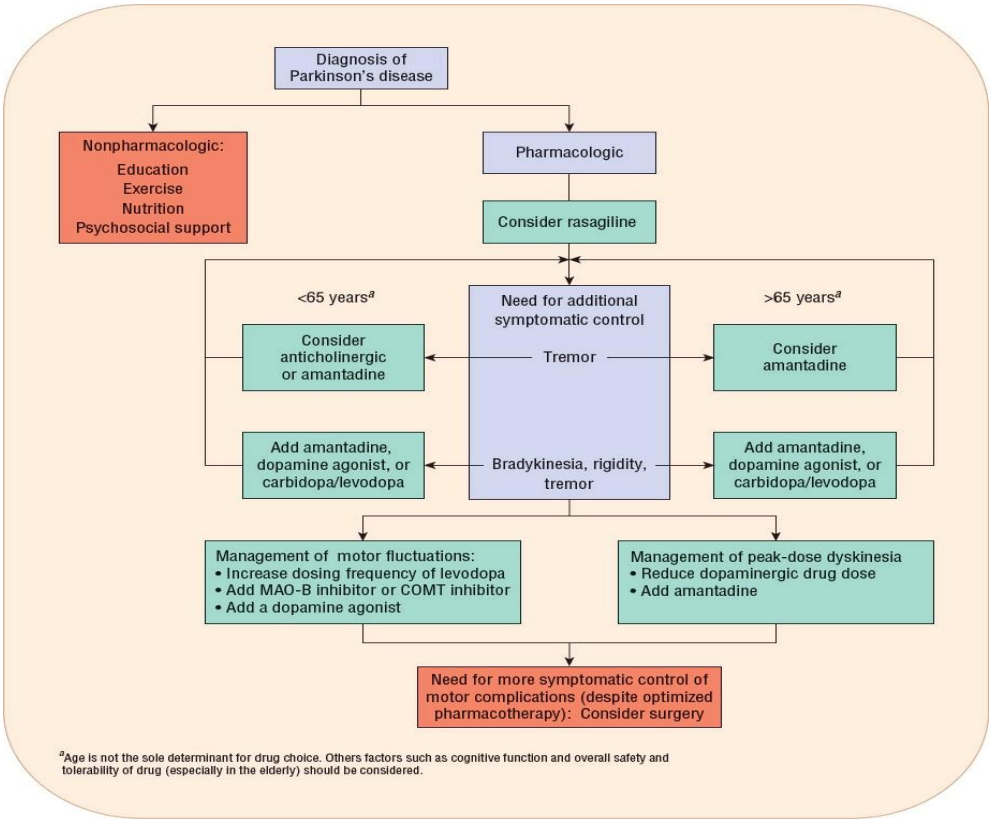
PET scan showing difference between normal brainand a patient with c

- CT scan is done for anatomical detailing of Parkinsondisease
- FDA approved DaT scan which consist of a dye loflupane123 injection (or) phenyl tropane which is a radioactive pharmaceutical agent which is injected in to the patient veins in a procedure referred to as SPECT scan used in the diagnosis of Parkinson disease

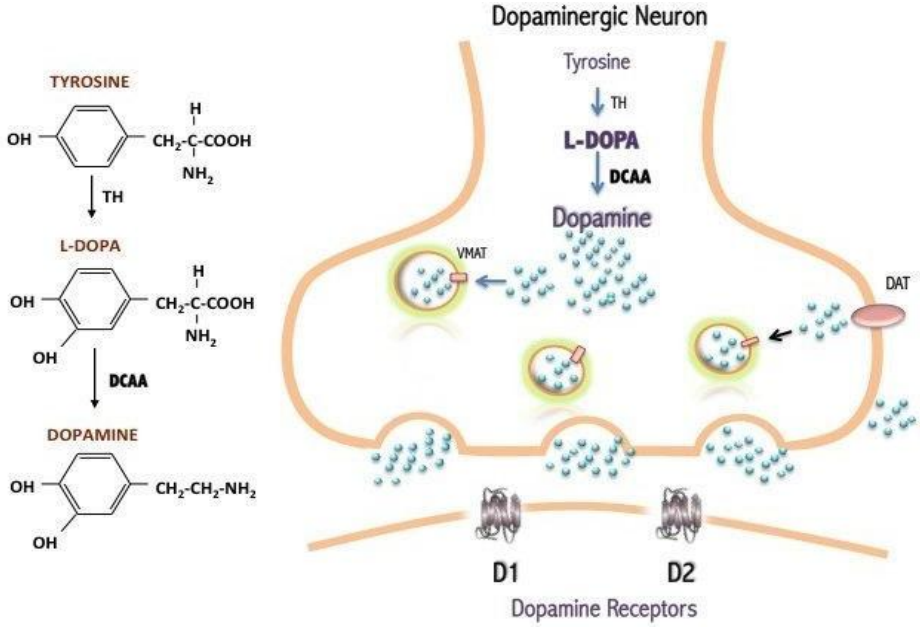
General Approch in the Treatment of Parkinson Disease

General, therapy begins with rasagiline if the symptoms don't attenuated addition of drug will be done, based on the age if the patient age is above 65 amantadine is used instead of anticholinergic because In patients with age above 65 cognitive impairments occur naturally so upon addition on anticholinergics will increase the severity of cognitive impairment so if the patient with age less than 65 anticholinergic drugs are given if there is no improvement the addition of L-DOPA is done along with other drugs.



Drugs Used In The Treatment Of Parkinson Disease

Synthesis of dopamine neurotransmitter



Tyrosine is a non-essential amino acid in from which dopamine is synthesized in nerve terminal of dopaminergic neurons, tyrosine is converted in to dopa by tyrosine hydroxylase and dopa is converted in to dopamine through dopa decarboxylase, the synthesized dopamine is stored in vesicles movement of dopamine in to vesicle occur through a transporter called VMAT2 (vascular Mono aminotransferase 2) upon production of impulse dopamine is released from the pre synaptic neuron into synaptic cleft and act on dopamine receptor and elicits it's actions, The released dopamine is catabolized by two enzymes MAO-B and COMT.

Treatment goals for increasing dopamine concentration

- In a patient with Parkinson disease low levels of dopamine is observed due to degeneration of dopaminergic neurons so the treatment is given in

such a way that concentration of dopamine should increased

- Concentration of dopamine can be increased by followingfour ways

1. By administering DOPA precursors.
2. By generating impulse to release dopamine from vesicle in tosynaptic space.
3. By inhibiting MAO-B and COMT enzymes. 4)By using dopa agonists.

1) DOPA precursors: Use of dopa precursor to increase the dopamine levels centrally, L-DOPA is the prodrug of dopamineL-DOPA is the most effective drug to improve life quality in patient with Parkinson disease.

Dopamine can't cross BBB (blood brain barriers) but L-DOPA can cross the BBB due to the presence of LAT (Large amino acidtransferase).

- L-DOPA is converted into dopamine by peripheral dopa decarboxylase the converted dopamine can't cross BBB sosystemic dopamine toxicity is observed which leads to stimulation of chemo toxic zone of the brain and induce vomiting which can be overcome by using D2 antagonists like domperidone and metoclopramide mostly domperidone is used because being lipid soluble it can easily cross BBB and act as antagonist on D2 receptor and suppress the stimulation of chemo toxic zone and suppress vomiting , peripheral dopa decarboxylase inhibitors are given to avoid the conversion of L- DOPA to dopamine systemically.
- Peripheral dopa decarboxylase inhibitors which include
- Carbidopa
- Benserazide

These two drugs are used to inhibit the action of peripheral dopa decarboxylase on L-DOPA thus systemic concentration of L-DOPA is increased which can easily cross BBB and converted in to dopamine by central dopa decarboxylase which is present only in the brain and spine.

- L-DOPA is administered through orally and it get absorbed into systemic circulation from small intestine, protein rich food should be avoided when the patient is on L-DOPA medication.
- Prolong use of L-DOPA causes dyskinesia of limbs, trunks and tongue this can be treated by medicating the patientwith amantadine and levetiracetam
- L-DOPA causes mydriasis (pupillary dilation) which increase the ocular pressure which result to the damage of optic nerve which leads to complete loss of vison so L- DOPA is contraindicated in the patients with glaucoma.
- Sudden stop of using L-DOPA medication result in development of neuroleptic malignant syndrome.
- L-DOPA is given carefully to the patients with acute pepticulcers and malignant melanoma.
- L-DOPA is absorbed from small intestine in to systemic circulation, The absorption is decreased when L-
- DOPA is taken along with protein rich food, there will be a competition between large neutral amino acids like leucine and iso leucine and L-DOPA to cross intestinal barrier and reach systemic circulation and transport across BBB and show therapeutic action.

Intractions

Concomitant administration of L-DOPA and MAO inhibitors such a phenelzine can produce hypertensive crisis due to enhance production of catecholamines which include nor adrenaline and adrenaline and dopamine.

Anti psychotics are contraindicated In Parkinson patients because they block dopamine receptors and produce Parkinsonsymptoms.

Patients with cardiac diseases should be monitored when using L-DOPA because there are high chances of developing arrythmia's when L-DOPA is used by cardiac disease patients.

Mortar Complications Of L-Dopa

Long term use of L-DOPA therapy associated with variety of complications, approximately 10% of idiopathic Parkinson disease patients may develop involuntary movements.

Complications starts with in six months of starting L-DOPAtherapy if excessive dose used initially.

1) End of Dose Wearing Off (mortar fluctuation)

The term off and on refers to period of poor movements (I.e. is return of tremor and rigidity) and good movement respectively.

MOA

Increasing loss of neuronal storage capacity for dopamine as well as the short half-life of L-DOPA, initially exogenous L- DOPA is taken up by remaining presynaptic neurons convert itto dopamine that is stored in vesicles with progressive loss of neuron and storage capacity and synthesis patient becomes more dependent on exogenous L-DOPA hence, peripheral pharmacokinetic properties of L-DOPA become an important determinant of central dopamine synthesis.

- In advancing IPD administration of s single carbidopa\L-DOPA progressively shortens frequent administration.
- It is also replaced by other drugs like COMT inhibitors or MAO-B inhibitors or dopa agonist
- Offen, off episodes occur during night and patient will awaken in off state for this bead time administration of DOPA agonist or SRD example: carbidopa CR can improve functioningupon awaking and reduce nocturnal off episodes.

2) Dealyed on and No On Responce

It is the result of delayed gastric emptying or decreased

absorption in duodenum.

Treatment
Orally disintegrating tablet formulation on empty stomach decreases gastric disintegration time and facilities gastric emptying additionally SC administration of apomorphine used arescue therapy form this.

3) Freezing
Freezing or sudden, episodic inhibition of lower extremity motor function and interfere with ambulation and increase riskof fall.

Patient fell that their feet got stuck to the floor especially (door ways, turn stiles).

There is no specific therapy, psych therapy along with walkingdevices and sensory cues are helpful.

4) Off-Period Dystonia
Dystonia occurs at lower extremities and often occurs in mornings so, bead time administration of sustain released product (ropinirole CR), use of baclofen, botulinum toxin andcholinergic.

5) Dyskinesia
- In voluntary choreiform movements involving usually neck,trunk and upper\lower extremities
- It occurs at peak striatal dopamine levels or too much striatal dopamine receptor stimulation and less commonly during riseand fall of L-DOPA effects.
- Generally, dose reduction will attenuate dyskinesia but reverses Parkinson's symptoms so, a counteract amantadinewill be given
- In severe cases surgery will be done (DBS).

2) By Generating Impuls To Release Dopamine fromVesicles
Amantadine
- Amantadine Is an anti-viral medication with mild antiParkinson activity.
- Amantadine is used against influenza-A
- Amantadine a weak non-competitive antagonist of NMDA receptors and which increase the release of dopamine andprevent its reuptake.
- Amantadine has anticholinergic and anti-glutaminergicproperty
- Amantadine is an anti-cholinergic so it causes xerostomia (dryness of mouth) and may cause constipation.

Adverse Effects
- Xerostomia
- Constipation
- Orthostatic hypotension
- Ankle edema
- Levido reticularis

3) By Inhibiting Mao-B and Comt Enzymes
- Dopamine is metabolized by MAO-B (mono amino oxidase-B) and COMT (Catechol-o-methyl transferase) enzymes, by inhibiting the action of these enzymes can inhibit the metabolism of dopamine thus concentration of dopamine is increased in the synaptic cleft.
- MOA-A and MOA-B are the enzymes which are required forthe metabolism of catecholamines which include 5-HT, adrenaline, nor-adrenaline, dopamine.
- MOA-A enzyme has grater affinity for catabolism of hydroxylated amies which include serotonin (or) 5-HT and nor-adrenaline.
- MOA-B enzyme has greater affinity for catabolism of non- hydroxylated amines which include benzylamine
- Dopamine and tyramine are catabolized by both MAO-A andMAO-B.
- The concentration of MAO-A and MAO-B enzymes are available in different concentrations in different parts of the body, MAO-A is present in GIT tract, placenta and liver, MAO-b enzyme is present in brain, platelets and liver.
- In the treatment of Parkinson disease only MOA-B are given because MOA-B is the only enzyme which is responsible for the catabolism of the dopamine in the brain.
- When dopamine is catabolized by MAO-B it results in the formation of free radicals which leads to degeneration of brains dopaminergic neurons, by using MAO-B inhibitors formation of free radicals are inhibited so eventually degeneration of dopaminergic neurons are inhibited.
- Most commonly used MAO-B inhibitors in Parkinson treatment include, Selegiline (or) deprenyl which selectively
- block the MAO-B enzyme thus catabolism of dopamine isinhibited.
- Dopamine is metabolized by COMT through methylation to form 3-O-methyl dopa, catabolism of dopamine by COMT pathway is minor metabolism pathway in the breakdown f dopamine, when L-DOPA is given along with carbidopa a significant concentration of 3-O-methyldopa is formed which competes with L-DOPA for active transport in to the cental nervous system by crossing BBB.
- By using COMT inhibitors we can decrease the concentration of 3-O-methyldopa and can increase the central uptake of L- DOPA which leads to increased concentration of dopamine in the brain.
- Tolcapone and entacapone are nitro catechol derivatives that selectively and irreversible block the catabolism of dopamine by COMT enzyme, tolcapone causes fatal hepatitis so entacapone is used mostly in the treatment of Parkinson disease.

Adverse Effects
- Diarrhea
- Postural hypotension

- Nausea
- Anorexia
- Dyskinesia
- Sleep disorders

4) Dopamine receptor agonists

- Dopamine receptor agonist are used in the treatment ofParkinson disease.
- Dopamine receptor agonists are classified into two types1) Ergot derivatives
- Bromocriptine
- Pergolide

2) Non-ergot derivatives

- Ropinirole
- Pramipexole
- These agents have long duration of action on dopaminereceptors when compared to dopamine
- Dopamine agonists are more effective in patients when compared to L-DOPA, bromocriptine and pergolide are potentD2 agonist.
- Ergot alkaloids have vasoconstriction action so they are alsoused in the treatment of migraine, pergolide is more potent than bromocriptine
- When dopamine act on dopamine receptor it elicits some actions like Vaso dilation the same actions are elicited by theaction of ergot alkaloids on dopamine receptor.
- Use of ergot alkaloids may cause hallucination, confusion, delirium, nausea and ortho static hypotension, use of ergot alkaloids may develop serious cardiac problems particularly in the patients with the history of cardio vascular diseases such as MI
- Ergot derived drugs may cause pulmonary fibrosis

Non-Ergot Derived Dopamine Agonist

- Pramipexole, ropinirole are non-ergot derived
- Dopamine receptor agonists used in the treatment of Parkinsondisease.
- Non-ergot derived dopamine receptor agonists are used in thetreatment of advanced Parkinson disease, in the patients with advanced Parkinson disease non-ergot derived dopamine receptor agonists are added along with L-DOPA to decrease thedose of L-DOPA
- Unlike ergot alkaloids non-ergot derive drugs have very lessside effects.

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