PARKINSON'S DISEASE

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PARKINSON'S DISEASE

- Parkinson's disease (PD) is the most common form of a group of progressive neurodegenerative disorders characterized by the clinical features of parkinsonism, including **bradykinesia, rest tremor, muscular rigidity, shuffling gait** and **flexed posture.**

- PD can be accompanied by a variety of **non-motor symptoms,** including **autonomic, sensory, sleep, cognitive,** and **psychiatric distrubances.**

EPIDEMIOLOGY OF PD

- PD affects ~1 million individuals in the United States (~1% of those older than 55 years).
- Its peak age of onset is in the early 60s (range 35-85 years), and the course of the illness ranges between 10 and 25 years.
- PD accounts for ~75% of all cases of parkinsonism; the remaining cases result from other neurodegenerative disorders, cerebrovascular disease, and drugs. Familial forms of known autosomal and recessive forms of PD (now numbering >10) comprise ~5% .

EPIDEMIOLOGY OF PD

- Although most patients with PD appear to have no strong genetic determinant, epidemiologic evidence points to a complex interaction between genetic vulnerability and environmental factors.
- Risk factors include a positive family history, male gender, head injury, exposure to pesticides, consumption of well water, and rural living.
- Factors associated with a reduced incidence of PD include coffee drinking, smoking, use of nonsteroidal anti-inflammatory drugs, and estrogen replacement in postmenopausal women.

CLINICAL FEATURES OF PD

- A diagnosis of PD can be made with some confidence in patients who present with at least two of the **three cardinal signs:**

1) REST TREMOR

2) RIGIDITY

3) BRADYKINESIA

- Masked facies, decreased eye blinking, stooped posture, and decreased arm swing complete the early picture. The onset may also be heralded by vague feelings of weakness, fatigue, aching, and discomfort.

MOTOR FEATURES OF PD

- **REST TREMOR,** at a frequency of 4-6 Hz, typically appears unilaterally, first distally, involving the digits and wrist, where it may have a *"pill-rolling"* character. Tremor usually spreads proximally and occasionally to the ipsilateral leg before appearing on the other side after a year or more.

It may appear later in the lips, tongue, and jaw but spears the head and neck.

Tremor is particularly important, as it is present in 85% of patients with true PD; a diagnosis of PD is particularly difficult when tremor is absent.

MOTOR FEATURES OF PD

- The most disabling motor feature of PD is **BRADYKINESIA,** which interferes with all aspects of daily living including rising from a chair, walking, turning in bed, and dressing.

Fine motor control is also impaired, as evidenced by decreased manual dexterity and *micrographia*. Soft speech (*hypophonia*) and *sialorrhea* are other troubling manifestation of (bulbar) bradykinesia.

THE EXTRAPYRAMIDAL SYSTEM
THE CEREBELLUM

- Motor activity is intricately controlled by the interactions of three major regions of the brain: the cerebral cortex, the cerebellum, and the basal ganglia.
- These regions influence the lower motoneurons either directly through the pyramidal system or indirectly through the extrapyramidal system.
- The pyramidal system consists of the corticonuclear and corticospinal pathways.

MOTOR FEATURES OF PD

- **RIGIDITY** is felt as a uniform resistance to passive movement about a joint throughout the full range of motion, accompanied by a characteristic "*plastic*" quality to the movement.

Brief, regular interruptions of resistance during passive movement, due to subclinical tremor, may give rise to a "*cogwheeling*" sensation.

MOTOR FEATURES OF PD

- **DYSTONIA** involving the distal arm or leg may occur early in the disease, unrelated to treatment, especially in younger patients. It can also be provoked by antiparkinsonian drug therapy.

- **GAIT DISTURBANCE** with *shuffling short steps* and a tendency to turn en bloc is a prominent feature of PD. *Festinating gait*, a classic sign of parkinsonism, results from the combination of flexed posture and loss of postural reflexes, which cause the patient to accelerate in an effort to "*catch up*" with the body's center of gravity. *Freezing of gait*, a feature of more advanced PD, occurs commonly at the onset of locomotion (*start hesitation*), when attempting to change direction or turn around, and upon entering a crowded room or narrow space such as a doorway.

MOTOR FEATURES OF PD

- **ABNORMALITIES of BALANCE and POSTURE** tend to increase as the disease progress. Flexion of the head, stooping and tilting of the upper trunk, and a tendency to hold the arm in a flexed posture ehile walking are common, as are changes in the posture of the fingers, hand and arm.
- **POSTURAL INSTABILITY** is one of the most disabling features of advanced PD, contributing to falls and injures and leading to major morbidity and mortality. Patients are also at risk for hip fractures, which are associated with osteoporosis and vitamin D deficiency.

NON-MOTOR FEATURES OF PD

- Non-motor aspects of PD include:

DEPRESSION and **ANXIETY,**

COGNITIVE IMPAIRMENT,

SLEEP DISTURBANCES,

SENSORY ABNORMALITIES and **PAIN,**

LOSS OF SMELL (*anosmia)*

DISTURBANCES OF AUTONOMIC FUNCTION

PATHOGENESIS OF PD

- Nearly all forms of parkinsonism result from a reduction of dopaminergic transmission within the basal ganglia.
- The discovery of dopamine in the brain, the demonstration of its depletion in PD, and the success of dopamine replacement therapy by its precursor, ***levodopa,*** are all major landmarks in the field of neurology.

PATHOGENESIS OF PD

- In PD, *nigral* dopamine neurons and other cells die from a combination of factors, including:

  (1) genetic vulnerability;
  (2) oxidative stress;
  (3) proteasomal dysfunction;
  (4) abnormal kinase activity; and
  (5) environmental factors, most of which have yet to be identified.

PATHOGENESIS OF PD

- The biochemical consequence of dopaminergic cell loss in the *substantia nigra pars compacta* (SNpc) is gradual denervation of the *striatum*, the main target projection for SNpc neurons. Other target regions of these neurons include *the intralaminar* and *parafascicular nuclei of the thalamus, the globus pallidus,* and *the subthalamic nucleus* (STN). Dopamine denervation of the putamen, the motor portion of the striatum, leads to many of the motor symptoms of PD. Symptoms develop when striatal dopamine depletion reaches 50-70% of normal.

TREATMENT OF PD

- Pharmacologic restoration of dopamine transmission is the basis for symptomatic drug treatment of PD.

Bradykinesia, tremor, rigidity, and abnormal posture respond well to symptomatic therapy early in the course of the illness. In contrast, cognitive symptoms, hypophonia, autonomic dysfunction, and imbalance tend to respond poorly.

Primary motor disability in PD is often aggravated by secondary disability resulting from physical deconditionning following a sedentary lifestyle. Prevention of secondary disability requires a consistent program of physical exercise.

TREATMENT OF PD

- As a general principle, patients should be treated as soon as symptoms begin to interfere function in any way.
- The concern that symptomatic therapy should be delayed as long as possible since the available compounds are effective for only a limited number of years is unfounded.
- Early initiation of therapy is often necessary to maintain an adequate level of physical and mental activity.

TREATMENT OF PD

- Another common concern, that dyskinesias will develop sooner if levodopa is introduced “too early”, is also unfounded.
- In animal models of PD, forced exercise (e.g., treadmill running) at moderate intensities appears to promote neuroprotection in dopamine neurons.
- From a practical standpoint, dopaminomimetic therapy should be initiated as soon as the patient’s symptoms begin to interfere with quality of life.

LEVODOPA FORMULATIONS USED IN TREATMENT OF PD

AGENTS	LD DOSE EQUIVALENCY	AVAILABLE STRENGTHS (mg)	INITIAL DOSING	COMMENTS
Carbidopa/ levodopa IR 25/100	**100 mg (levodopa anchor dose)**	**10/100 25/100 25/100**	**25/100; 0.5-1 tab tid**	**Usual range = 300-800 mg/d with typical schedules being q8h to q 3h.**
Carbidopa/ levodopa CR 50/200	**150 mg**	**25/100 50/200**	**50/200; 1 tab bid to tid**	**Increased bioavailability with food. Splitting the tablet negates the CR properties. Usual schedule is q8h to q4h.**
Carbidopa/ levodopa/e ntacapone 25/100/200	**120 mg**	**1275/50/200 25/100/200 37.5/150/200**	**25/100/200; 1 tab bid to tid**	**Do not split tablets. May combine with Sinemet IR. Usual schedule is q8h to q4h.**
Parcopa	**100 mg**	**25/100 25/250**	**25/100; 1 tab tid**	**Can be used as regular or supplemental rescue doses in cases of regular dose failure. Orally dissolved without water.**

IR, immediate release; CR, controlled release; LD, levodopa (with carbidopa)
Carbidopa/levodopa/entacapone = Stalevo.

TREATMENT OF PD

- ***Motor fluctuations,*** also known as ***"on-off"*** phenomena, are the exaggerated ebb and flow of parkinsonian signs experienced by many patients between doses of antiparkinsonian medications.
- ***Dyskinesias*** refer to choreiform and dystonic movements that can occur as a peak dose effect or at the beginning or end of the dose (diphasic dyskinesias). More than 50% of patients with PD treated over 5 years with levodopa will develop these complications.

DOPAMINE AGONISTS USED IN TREATMENT OF PD

AGENTS	DA EQUIVALENT TO ABOVE LD ANCHOR DOSE	AVAILABLE STRENGTHS (mg)	INITIAL DOSING	OTHER CONSIDERATIONS
Non-ergot alkaloids **Pramipexole**	**1 mg**	**0.125, 0.25, 1, 1,5**	**0.125 mg tid**	**Renal metabolism; dose adjustments needed in renal insufficiency. Occasionally associated with "sleep attacks."**
Ropinirole	**5 mg**	**0.25, 0.5, 1, 2, 3, 4, 5**	**0.25 mg tid**	**Hepatic metabolism; potential drug-drug interactions. Occasionally associated with "sleep attacks."**
Ropinirole extended release **Rotigotine**	**Availability pending.**	**2, 4, 6**	**2 mg/24 h**	**Available as transdermal patch**
Ergot alkaloids **Bromocriptine**	**2 mg**	**2.5, 5.0**	**1.25 mg bid to tid**	**Rare reports of pulmonary and retroperitoneal fibrosis. Relative incidence of sleep attacks not well studied.**

LEVODOPA AUGMENTATION STRATEGIES IN TREATMENT OF PD

- ***MAO-B Inhibitors.*** These are selective and irreversible inhibitors of the catabolic breakdown of dopamine; they work by inhibiting MAO-B at the synapse. SELEGELINE (1989).RASAGILINE and ZYDIS SELEGELINE (2006).

- ***COMT Inhibitors.*** The cathechol-O-methyltransferase (COMT) inhibitors ENTACAPONE and TOLCAPONE blocks the enzymatic degradation of levodopa and dopamine.

- **Anticholinergics** and **amantadine** are appropriate adjuncts to dopamino-mimetic therapy.

SURGICAL TREATMENT OF PD

- The most common indications for surgery in PD are intractable tremor and drug-induced motor fluctuations or dyskinesias.
- ***Pallidotomy*** and ***thalamotomy.***
- ***Deep brain stimulation.***
- ***Neurotransplantation and Other Surgical Approaches***
  – fetal cell transplantation
  – carotid body cells; stem cells; encapsulated and genetically engineered cells capable of producing levodopa, dopamine, and/or trophic factors.

THE END