Parkinsonism, Parkinson’s Disease

Last updated: April 17, 2019

PATHOLOGY

1. Depigmentation & neuronal loss (→ gliosis)
   - occurs normally with aging, but is greatly accelerated in parkinsonism.
   - degenerating cells in SN normally synthesize dopamine.
   - 60-85% nigral neurons are lost prior to development of symptoms.

2. Lewy bodies - pathologic hallmark of disease!1 - cosinophilic cytoplasmic inclusions in surviving neurons.
   - single or multiple, round to elongated; dense core surrounded by pale halo.
   - composed of neurofilament, tubulin, α-synuclein and ubiquitin.
   - also seen in Alzheimer's disease, Hallervorden-Spatz disease, ataxia-telangiectasia, rarely in patients without clinical neurological disease.

3. Pale bodies - composed of neurofilament interspersed with vacuolar granules.
   - also present in basal ganglia, cortex, brain stem, spinal cord.

Degenerative process is highly localized at illness beginning - area first affected is pars compacta in ventrolateral SN.

MACROSCOPY

Left: pale substantia nigra in PD. Right: normally pigmented substantia nigra.

Source of photo: "WebPath: The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD)

1. 4th most common neurodegenerative disease of elderly.
2. first reported by James Parkinson in 1817.
A. Normal substantia nigra.
B. Depigmented substantia nigra in PD.
C. Lewy bodies in substantia nigra neuron stain bright pink.

**MICROSCOPY**

Left: normal number of normally pigmented neurons in substantia nigra.
Right: decreased neurons and pigment in PD.

Left: rounded pink cytoplasmic Lewy body (H & E stain).
Right: immunoperoxidase staining with antibody to ubiquitin (demonstrates Lewy bodies more readily).

Surviving pigmented neuron in substantia nigra contains intracytoplasmic rounded eosinophilic inclusion (Lewy body, L).
In Parkinson’s disease (PD), there is loss of pigmented neurons from the substantia nigra and remaining neurons may be very sparse (A). Lewy bodies can be observed in residual neurons (A, inset) and are highlighted, together with Lewy neuritis, using α-synuclein immunohistochemistry (B). Lewy bodies and Lewy neurites may be present in significant numbers in the neocortex (C, frontal cortex). In multiple system atrophy (MSA), α-synuclein is primarily deposited in the form of glial cytoplasmic inclusions in oligodendrocytes (D, putamen) and may also form inclusions in neuronal cytoplasm and nuclei (arrow) (E, pontine nucleus). In progressive supranuclear palsy (PSP), tau forms aggregates in neurons and glia, giving rise to tufted astrocytes (F, caudate) and neurofibrillary tangles (G, pontine nucleus).

Characteristic feature of corticobasal degeneration (CBD) is the astrocytic plaque, formed from aggregated tau in the distal processes of astrocytes (H, parietal cortex). In CBD, tau also accumulates in neurons in the form of neurofibrillary tangles (H, inset a) and in oligodendrocytes as coiled bodies (H, inset b).

(A) Haematoxylin and eosin; (B–D) α-synuclein immunohistochemistry; (F–H) tau immunohistochemistry.
ETIOLOGY

Most actively studied hypothesis - **SELECTIVE OXIDATIVE STRESS**.

- **source may be:**
  1. *exogenous toxin* (e.g. such as MPTP, CO, manganese)
     - see p. Mov11 >
     - Gianni Pezzoli, MD and Emanuele Cereda, MD, PhD - Exposure to pesticides or solvents and risk of Parkinson disease - exposure to bug or weed killers and solvents increased risk of developing Parkinson's disease by 33-80%.
  2. *endogenous substance*; e.g. metabolism of dopamine generates numerous toxic byproducts (incl. H₂O₂, superoxide anions, -OH radicals) → lipid peroxidation, membrane disruption.
     - dopamine auto-oxidation generates superoxide radicals; dopamine metabolized by monoamine oxidase generates H₂O₂.
     - superoxide dismutase catalyzes conversion of superoxide to H₂O₂, which is converted by glutathione peroxidase and catalase to water; however, H₂O₂ can also react with ferrous iron to form highly reactive ·OH radicals.

- β₂-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Shuchi Mittal http://science.sciencemag.org/content/357/6354/891.full
  - Salbutamol, a β₂-adrenoreceptor, cuts the risk for PD by about a third.
  - On the other hand, propranolol, a β-blocker, is linked to a doubling of the risk for PD.

Supporting findings (in SN):
1. markedly reduced glutathione peroxidase (normally is reduced with oxidative stress).
2. increased elemental iron (facilitates formation of free radicals).
3. decreased or normal concentration of ferritin (iron-chelating protein) – i.e. no compensatory increase to handle free iron.
4. specific enzymatic activity defects in complex 1 of mitochondrial respiratory chain.

Actual precipitant (whether genetic, environmental, dietary, or multifactorial) remains to be determined.
No specific cause has been found.³

GENETICS

Isolated to be responsible for PD based on family based linkage analysis:
1. LRRK2 (PARK8) - autosomal dominant PD
   - leucine-rich repeat kinase 2 (LRRK2) - large, widely expressed, multi-domain and multifunctional protein (product of this gene is known as dardarin).
   - LRRK2 mutations are the common genetic cause of both familial and sporadic PD.
   - clinical features resemble those of late-onset sporadic PD
2. α-synuclein (SNCA) - autosomal dominant PD
3. parkin (PARK2) - autosomal recessive early-onset PD
4. UCH-L1 (PARK5)
5. PINK1 (PARK6) - autosomal recessive PD
6. DJ-1 (PARK7) - autosomal recessive PD
7. ATP13A2 (PARK9) - autosomal recessive PD
8. GLA
9. VPS35
10. EIF4G1
11. PARK16

Source of picture: Dr Janice Hölton, Queen Square Brain Bank for Neurological Disorders, London.
**CHOLINERGIC deficit**

- responsible for cognitive decline (present in up to 75% of patients 10 years after disease onset); the cell loss in nucleus basalis of Meynert is more pronounced than in Alzheimer’s disease!
- in a staging study of PD pathology, Braak et al. reported that basal forebrain pathology occurs simultaneously with nigral pathology, and the pathological change in the nucleus basalis of Meynert occurs early in PD.
- study by Kim 2011, indicates that the contribution of the substantia innominata atrophy to cognitive performance is greater in alpha-synucleinopathy-related cognitive impairments (PD, Lewy body disease) than in Alzheimer’s disease.

**DOPAMINERGIC deficit**

![](image)

black arrows – excitation; speckled arrows – inhibition.

DA neurons inhibit and ACh neurons excite GABAergic output from striatum:

- striatum acts via 2 pathways:
  - direct pathway inhibits GP\_i/SNr
  - indirect pathway stimulates GP\_i/SNr.
- normally, dopaminergic input activates direct pathway neurons that express D\_1 receptors and inhibits indirect pathway neurons that express D\_2 receptors; net effect is decreased stimulation of GP\_i/SNr.

**PARKINSONISM**

DOPAMINERGIC UNDERACTIVITY (less than 20% of normal) at nigrostriatal projection* → relative muscarinic cholinergic overactivity (ACh > DA) in striatum → increased GABAergic output from striatum (to indirect pathway).

*fibers to putamen are most severely affected.
Due to nigrostriatal deficiency:
- indirect D2-mediated pathway is activated → stimulation of GPi.
- direct D1-mediated pathway is deactivated → loss of inhibition on GPi.
- in addition, D1 receptors are compensatory increased (upregulated), whereas D2 receptors are reduced (downregulated).
- net effect – hyperactivity of GPi → thalamic inhibition → less cortical activation → HYPOKINESIA.

Direct lesioning of subthalamic nucleus / GPi / thalamus can relieve HYPOKINESIA.

N.B. D2 receptors are more important in mediating parkinsonian symptoms!

In concert, there appears to be altered phasic responsiveness by GPi to proprioceptive stimuli - numbers of responding cells increase, and receptive field becomes less specific → loss of directional effects and responses from multiple joints (account for rigidity and for altered timing and coordination of volitional movements in hypokinesia).

- other pigmented nuclei also degenerate: locus ceruleus → norepinephrine ↓
- dorsal raphe → serotonin ↓

EPIDEMIOLOGY

PREVALENCE 107-187 per 100,000 population.
- PD affects 1% of those ≥ 65 yr old.
- at least 1/3 of elderly exhibit some parkinsonian evidence.
- male : female ratio is 3 : 2.

RISK FACTORS:
1) family history of PD.
- one autosomal dominant pedigree (in Italy) - gene locus in 4q21.23 (Aα53Thr substitution in α-synuclein gene).
- one pedigree in Iowa – four copies (instead of normal two) of normal α-synuclein gene. α-synuclein (synaptic protein of undetermined function) is component of Lewy bodies!
- another autosomal recessive form (in Japan) - mutation of parkin (protein associated with ubiquitination) on chromosome 6.
- Lewy bodies are rich in ubiquitin!
- in general, familial cases are uncommon.
2) insecticide / herbicide exposure, rural residency, well water exposure
3) nut or seed eating 10 years prior to diagnosis.
4) essential tremor (PD and ET coexist relatively frequently!)
CLINICAL FEATURES

Mean age of clinical onset is 55 years, but range is very wide (20-80 years) and bell-shaped!

- onset is insidious
- young patients often present with tremor-predominant disease; elderly patients - with gait dysfunction and akinesia
- early in course, signs are usually asymmetrical (disease may be confined for one body side even for several years!) but eventually become bilateral and progressively worse.

vs. secondary parkinsonism or Parkinson-plus syndromes - almost always symmetric!

MOTOR FEATURES

- Parkinson's disease has both HYPOKINETIC and HYPERKINETIC features (“paralysis agitans”, “shaking palsy”)

1. POSTURAL TREMOR - Hyperkinetic feature
   - first symptom in 70% cases.
   - occurs in 80% patients with idiopathic PD.
   - rarely is seen in Parkinson-plus syndromes or secondary parkinsonism (except in drug-induced and MPTP-induced parkinsonism).

N.B. resting tremor helps distinguish idiopathic PD from other causes of parkinsonism!

- most patients also have postural tremor (re-emergence of rest tremor on coexistent essential tremor).

2. RIGIDITY - Hyperkinetic feature
   - tendon reflexes are normal.

3. BRADYKINESIA, AKINESIA
   - term “hypokinetic syndrome” is synonymous with “parkinsonism”

N.B. hypokinesia is not caused by rigidity!

- 1) slowing of activities of daily living.
- 2) difficulty in turning in bed / rising from deep chair / getting out of automobiles.
- 3) loss of gesturing, patient sits motionless.
- 4) rapid alternating movements are performed slowly with decreasing amplitude (DECELERATION).

5) masked faces (HYPOMIMIA) with rare blinking (staring expression).

PARKINSON'S DISEASE

- Decreased facial mobility
- Brisk reflexes
- A mask-like face may result, with decreased blinking and a characteristic stare. Since the neck and upper trunk tend to flex forward, the patient seems to peer upward toward the observer.
- Facial skin becomes oily, and drooling may occur.

- Local myopathic changes were suggested as a possible cause, but these may rather be a secondary phenomenon. Treatment is currently unsatisfactory in most cases. Occasional patients may benefit from intramuscular botulinum toxin injections or from deep brain stimulation.

- pathogenesis of this striking clinical sign is unknown. It is definitely not due to a primary disease (PD).

- In advanced disease → choking and aspiration.

6) speech abnormalities:
   - slow (HYPOPHASIA).
   - monotonous voice with lack of inflection (speech APOSYNODUSY).
   - not clear enunciation (DYSSOPHARIA).
   - do not separate syllables clearly - running words together (TACHYPHESIA).

7) failure to swallow spontaneously → saliva/drooling (DROOLENG).
   - patients can swallow properly when asked to do so, but only constant reminders allow them to keep swallowing.
   - DYSPAGIA in advanced disease → choking and aspiration.

8) slow small handwriting (MICROGRAPHIA).

9) “freezing” (motor block) - sudden transient (maximum several seconds) inability to perform active movements.
   - most often affects legs when walking. (see p. Mov7)
   - also can involve eye opening (taperocysis of lid opening), speaking (palilalia), writing.

- bradykinesia is commonly misinterpreted by patients as “weakness”.

- fatigue is common complaint (related to bradykinesia or rigidity).

- despite severe bradykinesia, patients may rise suddenly and move normally for short burst of motor activity (kinetasia paradoxica).

- patient eventually sits much of day and is inactive unless encouraged to exercise.

- camptocormia - abnormal, severe and involuntary forward flexion of the thoracolumbar spine, which becomes manifest during standing and walking and subsides in the recumbent position.
   - It was originally described as a psychogenic disorder, particularly in soldiers involved in long-term trench service during World War 1. It is becoming increasingly recognized as a prominent and disabling phenomenon during the course of Parkinson's disease (PD).

- clear correlation between camptocormia and levodopa treatment.
   - A few patients, the abnormal posture improved and in others it was unaltered or even became worse following levodopa administration. In a minority of fluctuating patients, there was a temporary deterioration during the "off" periods, but in most, the severity of camptocormia was unchanged during the "on" and "off" phases. In some patients it is associated with back pains, whereas in others it is painless. It occurs in sporadic PD as well as in postencephalitic and parkin-gen mutation PD and in other parkinsonian syndromes such as MSA.

- The pathogenesis of this striking clinical sign is unknown. It is definitely not due to a primary ventral redblood cell disease causing kyphosis as ankylosing spondylitis, as the bent spine does not allow recovery in one step. The muscles involved may be the abdominal, paravertebral or both. It may be due to a pecular dystonia or to an extreme form of rigidity.

- Local myopathic changes were suggested as a possible cause, but these may rather be a secondary phenomenon. Treatment is currently unsatisfactory in most cases. Occasional patients may benefit from intramuscular botulinum toxin injections or from deep brain stimulation.

4. POSTURAL INSTABILITY

- PRO-, LATERO-, RETRO- rotation (tendency to fall when center of gravity is displaced) — destabilizing fall, falls.

- pathophysiology may be related to bradykinesia and not to unique postural response deficit.

- specific PARKINSONIAN GAIT with FLEXED POSTURE

- "pull test" - examiner stands behind patient and, with advance warning, tug briskly on shoulders:
   - normal person can recover in one step.
   - patient takes several steps backward (retropulsion), possibly falling into examiner's arms.

- N.B. make sure examiner has a wall behind (helps to brace if heavy patient falls into you)

J.B. Lipppincott Company; ISBN 0781758599 >>
Diagnosis of definite Parkinson N.B. cases of presynaptic

Cognitive decline, up to dementia:
- to 96% of nucleus basalis of Meynert neurons are lost in both AD and PD dementia patients compared to age-matched controls (Candy et al. 1983, Erienne et al. 1986, Gaspar and Gray 1984, Whitehouse et al. 1983, 1981).
- strong correlations have been shown between NBM neuronal loss, resultant cortical cholinergic deficits and the degree of cognitive impairment in both diseases (Erienne et al. 1986, Gilmore et al. 1999, Perry et al. 1985).
- NBM cholinergic neurons are common, even early in disease! (e.g. sustained glabellar blink response - MYERS sign)
- APATHY: patient is slow in responding to questions (BRADYPHENESA) - correct answer can be obtained if patient is given enough time.
- 75% of patients develop dementia after 8 years, possibly rising to 83% at 20 years. It is hard to predict when dementia will appear but markers for its imminent appearance are falls and hallucinations.
- tremor predominant patients seem to have later onset of the dementia.
- 15–20% patients develop profound dementia (concurrent Alzheimer disease or diffuse Lewy body disease)*.
- *it is not known whether spread of Lewy bodies into cortex is feature of Parkinson disease progression or distinct entity.
- PD dementia is the "subcortical" type predominantly marked by a dysexecutive syndrome (characterized by impaired planning and concept formation) with significant deficits in attention and hallucinations.
- dementia limits tolerance of antiparkinsonian agents (because they increase confusion and produce psychosis; anti-dementia cholinergic treatment worsens parkinsonism!!)

Hypothetical schema of anatomical progression (dashed arrows) of pathology within the nucleus basalis of Meynert, with possible clinical pathological correlations.

3. Sleep disruption (fragmented sleep, frequent awakenings) - REM behavioral disorder.
4. Akathisia, restless legs syndrome
5. Sensory symptoms (= 50%) - pain (often misdiagnosed as arthritis / bursitis), burning, coldness, numbness, loss of sense.
6. Autonomic disturbances (due to dopamine depletion in hypothalamus) - orthostatic (especially in later stages); constipation, neurogenic bladder (inadequate bladder emptying), erectile dysfunction, hypotension.
7. 6-fold increased risk of skin melanoma.

DIAGNOSIS

Parkinson's disease = all four cardinal signs + brisk response to LEVODOPA!!
N.B. cases of presynaptic secondary parkinsonism (e.g. MPTP, postencephalitic) and many Parkinson-plus syndromes in early stages (e.g. multiple system atrophy) also respond to LEVODOPA.
Diagnosis of definite PARKINSONISM - at least two of following features (with at least one being either tremor at rest or bradykinesia/hyperkinesia):
(1) tremor at rest
(2) bradykinesia/hyperkinesia
Alternative diagnosis: bradykinesia + at least one (resting tremor, rigidity, postural instability)

There is no diagnostic test to confirm diagnosis! Diagnosis is clinical!

**CSF**
- CSF homovanillic acid*/ xanthine ratio may become future marker of disease activity.
- Aβ42 has a role in predicting cognitive decline in PD
- t-α-Syn: most promising marker; differentiates synucleinopathies from other neurodegenerative diseases and controls but is not specific
- t-tau and p-tau: inconsistent data, can help differentiate PD from AD and can be useful in combination with other markers
- NF-L: useful in differentiating PD from atypical parkinsonian conditions
- 4R-tau: possible marker of disease progression in PSP
- DJ1: potential role in discriminating MSA from PD

**IMAGING**
- structural imaging has limited role (except to exclude other diseases) - traditional MRI and CT are normal!
- functional imaging: PET with F-DOPA - activity of nigrostriatal dopaminergic system (correlation between fluorodopa uptake and striatal dopamine content); may allow preclinical diagnosis!

Overview of MRI methods used to study PD:
- Cortex - changes detected using voxel-based techniques, cortical thickness measurements and perfusion imaging.
- Brain connectivity: investigated using resting-state functional MRI (rs-fMRI) for functional connectivity and tractography for structural connectivity.
- Substantia nigra - changes detected using DTI (reduce fractional anisotropy - FA), relaxometry (increased R2* indicating increased iron load and more recently susceptibility-weighted imaging), magnetization transfer ratio (MTR reduced) and spectroscopy.
- Basal ganglia: studies showed no or mild changes in FA, R2* or MTR.
- Locus coeruleus area: reduced signal intensity was detected using neuromelanin imaging.

**DaTscan**
- ISOLUTANE DODINE-123 injection – FDA approved for use with SPECT in suspected parkinsonian syndromes.
- Schedule II controlled substance - high potential for abuse!!!
- abnormal distribution of dopamine transporters (DaT) in striatum in parkinsonian syndrome but are normal in other conditions, such as essential tremor and Alzheimer's disease.
- to decrease thyroid accumulation of I-123, block the thyroid gland at least 1 hour before administration of DaTscan; failure to do so may increase the long term risk for thyroid neoplasia.

Normal (left) and abnormal (right) DaTscan results:

**EARLY DIAGNOSIS**
- test based on the smell of skin may allow the early diagnosis of Parkinson's disease. The study was inspired by a "super smeller" who detected a distinct odor on the skin of her husband, who had Parkinson's disease that was strongest both before he was diagnosed and toward the end of his life.
- The research is led by Perdita Barran, PhD, professor of mass spectrometry and director of the Michael Barber Centre for Collaborative Mass Spectrometry, University of Manchester, UK
Hoehn & Yahr (H&Y) Staging

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<th>Stage</th>
<th>Hoehn and Yahr Scale</th>
<th>Modified Hoehn and Yahr Scale</th>
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<tr>
<td>1.5</td>
<td>Unilateral involvement only with minimal or no functional disability</td>
<td>Unilateral involvement only</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral or midline involvement without impairment of balance</td>
<td>Bilateral involvement without impairment of balance</td>
</tr>
<tr>
<td>2.5</td>
<td>Bilateral disease: mild to moderate disability with impaired postural reflexes, physically independent</td>
<td>Mild bilateral disease with recovery on pill test</td>
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<tr>
<td>3</td>
<td>Severe disability; still able to walk or stand, unassisted</td>
<td>Milder moderate bilateral disease; some postural instability, physically independent</td>
</tr>
<tr>
<td>5</td>
<td>Confined to bed or wheelchair unless aided</td>
<td>Severe disability; still able to walk or stand, unassisted</td>
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The median time to transit H&Y stages:

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<th>Stage</th>
<th>Median Time to Transit (Months)</th>
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<tr>
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<td>4</td>
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**CLASSIFICATION, DIFFERENTIAL DIAGNOSIS**

I. Primary Parkinsonism

1. Parkinson's disease (PD) (≈ 80% parkinsonism cases)
2. Juvenile parkinsonism

II. Parkinsonism Plus Syndromes (10%-15%) - degenerative disorders in which parkinsonism is one of several neurological features (but usually no tremor). See p. Mov12 >

1. Progressive supranuclear palsy (PSP)
2. Multiple system atrophy (MSA) syndromes:
   1. striatonigral degeneration (SND)
   2. olivopontocerebellar atrophy (OPCA)
3. Shy-Drager syndrome (SDS)
4. Lysin-Origo (parkinson-dementia-ALS complex of Guam (PDACG))
5. Cortical-basal ganglionic degeneration (CBGD)
6. Progressive supranuclear atrophy
7. Dementia syndromes (Alzheimer disease, diffuse Lewy body disease) – additional features not typical of Parkinson's disease.
   1. motor response to antiparkinsonian therapy destroyed postsynaptic D receptors.
   2. overall worse prognosis – most patients are dead at 5 years after diagnosis.

N.B. Fast 5 years after PD diagnosis have greatest risk of misdiagnosis, after 10 years only true PD patients survive

III. Heredodegenerative Diseases (in which parkinsonism is manifestation) see p. Mov12 >

1. Hereditary juvenile dystonia-parkinsonism
2. Autosomal dominant Lewy body disease
3. Huntington's disease (HD)
4. Wilson's disease (WD)
5. Hereditary ceruloplasmin deficiency
6. Hallervorden-Spatz disease (HSD)
7. Olivopontocerebellar and spinocerebellar degenerations (OPCA and SCA)
8. Familial amyotrophy-dementia-parkinsonism
9. Dementia-parkinsonism-amyotrophy complex
10. Gerstmann-Straussler-Scheinker disease
11. Familial progressive subcortical gliosis
12. Labag (X-linked dystonia-parkinsonism)
13. Familial basal ganglia calcification
14. Mithochondrial cytopathies with striatal necrosis

**UPDRS**

- Made up of following sections:
  1. Motor examination (18 items)
  2. Motor experiences of daily living (13 items)
  3. Non-motor symptoms (8 items)

**Hoehn and Yahr Scale**

- Score 0 means normal
- For most patients, "mentation, behavior and mood" scores increase later in disease, but there is a subset for whom those symptoms develop early on.
- Too low emphasis on non-motor features of PD.
IV. Secondary (Acquired, Symptomatic) Parkinsonism see p. Mov. 11

1. Drugs (5% of all cases!): (a) dopaminergic receptor blocking drugs (neuroleptics, metoclopramide), reserpine, tetraenzamine, a-methyldopa, lithium, fluazinam, cinamantline, amiodarone.
3. Toxins (can cause acute parkinsonism?): MPTP, TTP, Cns, Mh, Mg, Cs, Cys, cyanide, methanol, ethanol.
5. Trauma: pugilistic encephalopathy.
6. Other: hemophagocytic-hemiparkinsonism, parathyroid abnormalities, hypothryoidism, hepatocerebral degeneration, brain tumor, paraneoplastic diseases, normal pressure hydrocephalus, noncommunicating hydrocephalus, syringomyosemencephaly, peripherally induced tremor and Parkinsonism, psychogenic disorders.

TREATMENT - MEDICAL

Treatment is lifelong!

Remaining as active as possible is important!

Some patients find Pilate’s exercises to be extremely helpful!

Strategies to increase dopamine activity in CNS → see p. Adb >>

N.B. orally administered dopamine: cannot cross blood-brain barrier!

Levodopa equivalent daily dose (LEDD)

<table>
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<th>Medication</th>
<th>Dose, mg</th>
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<td>Levodopa</td>
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<td>controlled-release levodopa</td>
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<tr>
<td>bromocriptine</td>
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<tr>
<td>pergolide</td>
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<tr>
<td>amantadine</td>
<td>100</td>
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<tr>
<td>carbidopa</td>
<td>253</td>
</tr>
<tr>
<td>Stalevo</td>
<td>80</td>
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</tbody>
</table>

L-DOPA (LEVODOPA):

- natural immediate precursor of dopamine that can cross BBB.
- most effective symptomatic treatment!
- quick response is guaranteed in nearly all patients! (most patients improve within few days, some with first dose).
- if response is nil or minor, disorder probably is not PD; adequate response, however, does not assure diagnosis of PD!
- bradykinesia & rigidity respond better than tremor (tremor may never respond satisfactorily?)
- action depends on surviving dopaminergic neurons (that must contain levodopa to dopainize);
- not a problem in early disease!
- during 3-5th year of therapy efficacy decline begins;
- after 5 years of therapy 75% patients start to experiment complications: fluctuations (irregular and unpredictable) responses to medications – "on-off" phenomenon, dyskinesias, lack of efficacy, etc. see below

ELLDOPA study - after only 40 weeks of treatment, both efficacy and levodopa-induced motor complications increased in a dose-dependent fashion in de-novo PD patients who were within 2 years of diagnosis:
- dyskinesias were reported in 16.5% of patients receiving 600 mg/day of levodopa, which was significantly greater than 2-3% reported in those receiving 150 mg/day or 300 mg/day.
- motor fluctuations were reported in 30% of patients in the 600 mg/day group, which was significantly greater than 13–18% reported with lower doses.

Pharmacokinetics
- absorbed rapidly from small intestine;
- N.B. must be taken on empty stomach (at least 45 min before meals!)
- large neutral amino acids (e.g. Leu, Be) compete with levodopa for absorption from gut and transport across BBB.
- commercial dietary preparation with carbohydrate: protein = 7 : 1 is available.

- large doses are required because 99% of levodopa dose is rapidly decarboxylated to dopamine in GI tract and peripheral tissues → peripheral side effects.

CARBIDOPA - peripheral (does not cross BBB) inhibition of dopa decarboxylase when co-administered with LEVODOPA, more LEVODOPA remains available for CNS; LEVODOPA dose can / must be lowered 4.5-fod! → less peripheral side effects!)

= 75-100 mg/d of CARBIDOPA is needed for effective peripheral blockade.

SINEMET®: fixed combination LEVODOPA: CARBIDOPA (1:10 and 1:4); i.e. 10/100, 25/100, 25/525 mg; available in controlled-release formulation (SINEMET CR®) 50/200 mg.

DUODOPA - intestinal gel for continuous infusion;
• start on 10/100 mg ≤2/d or 25/100 mg ≤3/day with or after meals (to decrease nausea) → increase dosage gradually every other day (for every 4 days) until desired therapeutic effect is reached or side effects occur.
• most patients require 25/250 mg ≤3x/day.
• before concluding that LEVODOPA is ineffective, reasonable test dose of 2000 mg/d should be given.

INBRIJA® - levodopa oral inhalation formulation - FDA approved for OFF episodes in PD patients taking a carbidopa/levodopa regimen.
• can be used up to five times daily.
• breath-actuated - does not need to be pressed or manipulated in coordination with inhalation (inhaled makes a unique "whir" sound so the user knows the inhaler is working and the medicine is being delivered).

Adverse effects

Peripheral side effects (α and β – adrenergic):
1) nausea & vomiting (stimulation of emetic center in area postrema [outside BBB]);
   H: more CARBIDOPA, add DOMPERIDONE (dopamine receptor antagonist that does not enter CNS).
2) tachyarythmias, orthostatic hypotension
3) mydriasis
4) brownish saliva and urine (melanin from catecholamine oxidation)
5) positive Coombs’ reaction.
6) intracranial pressure

Central side effects
1) dyskinasias (usually choreic, but sometimes dystonic; dose-related, reversible) – most important side effect
2) visual & auditory hallucinations, vivid dreams (due to dopamine in mesolimbic, mesocortical systems)
3) depression, anxiety – due to breakthrough of central amines.
4) hyperprolactinemia (due to dopamine) in lactotroph function

Drug interactions

PERGOLIDE increases peripheral metabolism (atrophy decarboxylase) is pytoxine-dependent, no effect if CARBIDOPA is used.

MAO inhibitors – enhanced catecholamine production → hypertensive crisis.

Neuroleptics – antagonistic action.
Withdrawal must be gradual over 4 days (otherwise – fever, rigidity, confusion, neuroleptic malignant syndrome).

Motor response patterns - short T2 OFF (1-2 hours) causes plasma LEVODOPA fluctuations.

Early stages of LEVODOPA therapy, smooth improvement throughout day (no dose-timing variations); response is evident in morning despite lack of medication throughout night; dose skipping is without loss of effect.

• mechanism – prolonged storage of dopamine from exogenous LEVODOPA in residual nigrostriatal nerve terminals, prolonged postynaptic effect.

Later stages of LEVODOPA therapy, motor fluctuations and dyskinasias begin - correlate well with plasma LEVODOPA levels.

• mechanism – downregulation hypersensitiveness of dopamine receptors → dyskinetic effects, shortened duration of response.

First manifestation of FLUCTUATIONS – slow "wearing off" (end-of-dose deterioration in mobility – i.e. return of parkinsonian symptoms in less than 4 hours after last dose); treatment is based on smoothing out plasma concentration curves:
   a) controlled-release forms
   b) titration - having patient sip very small quantities of Sinemet dissolved in carbonated water or ascorbic acid solution every 30-60 min throughout day. An acidic solvent is required to dissolve levodopa and to prevent auto-oxidation of drug.
   c) combination with dopamine agonist (T can be longer than that of LEVODOPA or pergolide or COMT inhibitor.

Patterns of DYSKINESIAS:
 a) typically IDI pattern (peak-dose dyskinesias) improvement → "peak dose" dyskinesias → improvement:
   • treatment: reduce doses and make them more frequent.
 b) 15% patients have DID pattern (diphasic dyskinesias): initial dyskinesia (within few minutes after levodopa ingestion) → improvement (for 2-4 hours) → recurrence of dyskinesia (usually dyskinesia);
   • treatment: increase doses or switch to pergolide (low doses of levodopa are left as adjunctive).

Chronic LEVODOPA therapy - motor fluctuations become less predictable – "on-off", random, abrupt, temporary, not related to timing of LEVODOPA intake.
• for example: normal function may change to frozen akinetic state in as little as 15 seconds (sudden "off").
• mechanism – loss of presynaptic DA storage capacity, postynaptic receptor alterations.
• treatment: a) combination with dopamine agonist
   b) APOMORPHINE c/f (FDA approved for "off" periods!)
   c) consider DBS.
• d) recent finding - AMANTADINE (at higher doses than classic) can reduce dyskinetic and motor fluctuations in late-stage disease when given as adjunct to LEVODOPA/ DBS treatment that occurs during "off" ("off-freezing") - feature of parkinsonism itself; "on-freezings" remain terminal.
• "off" dyskinesias may appear during "off" states (e.g. painful "off" dystonia). A combination of drugs may affect the CNS and relieve symptoms of parkinsonism or other disorders.
• treatment: a) combination of flexures and dyskinesias occur: good "on" for parts of day; intermittently disabled by dyskinesias or "offs" - narrow therapeutic window for levodopa. Increasing patient rapidly from severe dyskinesias to severe akinetic "offs" with only brief "on" state.
• motor "offs" are often accompanied by changes in mood (depression), thought (bradyphrenia?), and sensory symptoms.
**End-stage - response to dopamine agonists is inadequate to allow patient-assisted activities of daily living.**

- mechanism - combined loss of presynaptic dopaminergic neuron + postsynaptic striatal dopamine receptors.

### OUTCOMES (after ≥ 5 years of LEVODOPA therapy):

1. Smooth, good response (only 25%)
2. Troublesome fluctuations (43%)
3. Troublesome dyskinesias (19%)
4. Toxicity at (sub)therapeutic dosages (4%)
5. Total / substantial loss of efficacy (8%)

**N.B.** 75% patients have serious complications after 5 years of LEVODOPA therapy.

Two alternative opinions about fact that onset of LEVODOPA-induced complications is related to duration of LEVODOPA therapy:

- Levodopa therapy hastens advent of problems - rationale to withhold LEVODOPA as long as possible ('dopa-sparing' strategy) = it is right!
- It is part of natural course of disease - start LEVODOPA early to obtain maximal improvement in quality of life.

N.B. eventually all patients end up taking LEVODOPA and will then continue on it for rest of their lives.

**PD-MED trial** - patients started on levodopa versus levodopa-sparing therapies have very similar long-term outcomes.

Fox SH “Don’t delay, start today’': delaying levodopa does not delay motor complications.” Brain. 2014 (Jan)

Physicians should not be afraid of using levodopa (in low doses) to treat patients early in the course of Parkinson’s disease. Withholding the most effective anti-parkinsonian drug for fear of motor complications seems inappropriate.

### COMT INHIBITORS

**TOLCAPONE** - selective COMT inhibitor (central & peripheral).

- normally, metylation (by COMT) of LEVODOPA to 3-O-methyl-levodopa is minor catechol pathway; however, if CARBIDOPA is administered, significant 3-O-methyldopa concentration is formed; 3-O-methyldopa competes with LEVODOPA for active transport into CNS; TOLCAPONE prevents this!
- used only with LEVODOPA + CARBIDOPA.
- reduces “on-off” frequency.
- taken usually without regard to food.

### ADVERSE EFFECTS:

1) increased levodopa-related adverse effects
2) diarrhea – most common side effect!
3) fulminating hepatic necrosis (regularly follow liver enzymes) – WRITTEN PATIENT CONSENT is needed before starting treatment.

### ENTACAPONE

- only peripheral COMT inhibitor, hepatic failure not described.
- CARBIDOPA/LEVODOPA/ENTACAPONE is not good treatment option for early PD.

### STRIDE-PD study - dyskinesia were significantly more frequent with CARBIDOPA/LEVODOPA/ENTACAPONE, and they developed significantly earlier than with CARBIDOPA/LEVODOPA; there were no significant differences in motor fluctuations or motor function in the two groups, but dopaminergic adverse events were more common with CARBIDOPA/LEVODOPA/ENTACAPONE.

### FIRST-STEP study – early PD patients were randomized to either CARBIDOPA/LEVODOPA or CARBIDOPA/LEVODOPA/ENTACAPONE – there were no significant differences in the incidence of motor fluctuations or dyskinesia; however, UPDRS activities of daily living and motor scores favored CARBIDOPA/LEVODOPA/ENTACAPONE group.

### D-RECEPTOR AGONISTS

- All activate D2 receptors!
- only minority benefit adequately from D agonist alone.
- D agonists do not work if LEVODOPA does not work!
- relatively long T1/2 – used to smooth out motor fluctuations with LEVODOPA therapy.
- some specialists start D agonists in early phases (before LEVODOPA); others introduce D agonists after LEVODOPA dose has reached 300-600 mg/d or when LEVODOPA-related fluctuations emerge.

### SIDE EFFECTS:

1. *Parkinson's disease (Parkinson’s disease):*
   - D1-predominant hypotension, syncope
   - 2) daytime sleepiness (21%)
   - 3) impulse control disorders (17% vs. 7% on other anti-Parkinson’s medications – DOMINION study)

*SUDDEN ONSET OF SLEEP, WHICH CAN OCCUR WHILE DRIVING, HAS BEEN REPORTED in 1% of patients taking dopamine agonists.

### BROMOCRIPTINE, PERGOLIDE – ergotamine derivatives.

- used together with LEVODOPA (little effect if patient does not respond to LEVODOPA).
- dose is increased gradually over 2-3 months.

### SIDE EFFECTS:

- LEVODOPA, but mental & cardiovascular problems are more severe, whereas dyskinesia is less prominent.

*can produce peripheral vasospasm (erythromelalgia)*

**PERGOLIDE is withdrawn from market due to cases of serious heart valve damage**

### PRAMIPEXOLE (Mirapex®), ROPINIRELLE (Requip®) – non-ergot compounds.

- effective as first-line (in levodopa-naive patients) and as adjuncts (in advanced parkinsonism patients).
- side effects – ergotamine-derived D agonists (except – no risk of vasospasm); risk for heart failure with PRAMIPEXOLE.
- eliminated by kidneys.

### ROPINIRELLE is extensively metabolized (vs. PRAMIPEXOLE).

### DOPAMINE INTERACTIONS:

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>inhibits tubular secretion of organic acids</th>
<th>increases T1/2 of PRAMIPEXOLE by 40%</th>
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<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>inhibit metabolism of ROPINIRELLE.</td>
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### CABERGOLINE - potent D2-agonist with T1/2 = 65 hours.

**PRKINSONISMS, PRKINSON’S DISEASE**

** Mov10 | [13]**
4. APOMORPHINE (Apokyn®) – injectable (s.c. only) D agonist.
   - short-acting (T½ = 30-60 min).
   - FDA approved for “rescue” from acute unpredictable “off” periods.
   - may lower BP!
   - may cause drowsiness.
   - start dose 2 mg; max dose 6 mg.
   - strong emetic – antiemetic should be started 3 days prior to initial dose of apomorphine and continued at least first 2 months of therapy:
     a) TRIMETHOBENZAMIDE (300 mg id)
     b) DOMPERIDON (peripheral D receptor blocker).
   - N.B. contraindicated use with 5-HT antagonists (ondansetron, granisetron, dolasetron, etc.) – risk of profound hypotension and loss of consciousness!

5. ROTIGOTINE (Neupro®) - non-ergoline D/Dh/Dc dopamine agonist.
   - transdermal delivery system - applied once daily to intact skin - continuously delivers drug over 24-hour period
   - available in three strengths: 2, 4, and 6 mg/24 hours.
   - FDA approved for early-stage idiopathic Parkinson’s disease.
   - adverse effects - falling asleep (sometimes without warning), hallucinations, skin reactions at application site.

<table>
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<th>Agonist</th>
<th>D1 receptor</th>
<th>D2 receptor</th>
<th>D3 receptor</th>
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DOPAMINE RELEASE STIMULATORS & RE-UPTAKE BLOCKERS & NMDA ANTAGONISTS

AMANTADINE - enhance dopamine release & blocks reuptake + N-methyl-D-aspartate (NMDA) glutamate antagonist
   - action depends on surviving dopaminergic neurons.
   - also has some anticholinergic properties.
   - efficacy is less than LEVODOPA, but adverse effects are also less frequent. Best tolerated of all PD medications!!
   - pitting edema and tremor rarely (purple-pink skin mottling, particularly below knees) - does not require drug discontinuation.
   - agitation, confusion, hallucinations; at high doses may induce acute toxic psychosis.
   - bradykinesia & rigidity respond better (more effectively than ANTITRANSPLANTOIDS), little effect on tremor.
   - mostly used to abolish dyskinesias so often can be stopped after DBS.

ROPOXIDOL (AMANTADINE extended-release) - first and only medicine approved by FDA for dyskinesias in PD patients receiving levodopa-based therapy, with or without concurrent dopaminergic medications.
   - It is 274 mg amantadine (equivalent to 340 mg amantadine HCI) taken once-daily at bedtime.
   - well absorbed orally, excrusted unchanged in urine.
   - response is seen within days, requires little or no dose titration.
   - tolerance develops within few months if used alone (rather than as adjunct) so it is not usually good choice for first drug (i.e. initiating therapy). MAO-B INHIBITORS

Both selegiline and rasagiline have been studied as potential neuroprotective agents; however, at this time there is insufficient evidence to consider either of them to be definitely neuroprotective.

DEPRENYL + SELEGILINE - selective* inhibitor of MAO-B (dopamine catabolism).
   - does not inhibit MAO-A (tyramine, norepinephrine, serotonin catabolism) – little potential for hypertensive (“cheese”) crisis.
   - substantially reduces required LEVODOPA-dose; in general, indicated only to increase duration of LEVODOPA response.
   - early use slows (up to 50%) parkinsonism progression (by reducing free radicals formation, drug prevents experimental MPTP toxicity).
   - Selegiline skin patch (Embrall®) is FDA approved for major depression. see p. Psy15 >>

N.B. antipsychotic TOCOPHEROL had no effect in delaying need for levodopa in controlled trials!

RASAGILINE (Azilect®) – potent, irreversible inhibitor of MAO-B
   - whether selective for MAO-B is not established.
   - indication - initial monotherapy (1 mg x 1/d) or as adjunct to LEVODOPA (0.5-1 mg x 1/d).
   - early use 2.5 mg, can be administered with or without food.
   - dosing need not be modified in presence of LEVODOPA.
   - should be discontinued at least 14 days prior to elective surgery (if surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously).
   - contraindicated with some analgetics (meperidine, tramadol, methadone, propoxyphene), dexmethylphenidate, other MAO inhibitors, sympathomimetics.
   - necessary restriction of tyramine-rich foods! see p. Psy15 >>

MAO-B INHIBITORS, & EXCLUSIVE GLUTAMATE RELEASE INHIBITORS

SAFINAMIDE (Xadago®)
   - oral, once a day adjunctive therapy for any stage of PD.
   - dual mechanism of action - enhancement of the dopaminergic function (potent reversible inhibition of MAO-B and of dopamine uptake) + inhibition of the excessive release of glutamate.
   - results from Phase III studies, MOTION and SETTLE, confirmed that safinamide significantly improves motor function in early PD patients on a single dopamine agonist at a stable dose (MOTION study) and significantly improves motor fluctuations in mid-to-late stage PD patients on levodopa and other PD drugs at a stable dose (SETTLE study). Both short (6 months) and long term (18-24 months) treatment with safinamide has shown statistically significant improvement in Quality of Life.
   - FDA approved (March 21, 2017): as adjunctive treatment for patients with Parkinson’s disease who experience ‘off’ episodes while taking levodopacarbidopa.

*does not inhibit MAO-A (tyramine, norepinephrine, serotonin (potent reversible inhibition of MAO-B).
- risk of serotonin syndrome - should not be used in patients with severe liver problems or those taking dextromethorphan, an MAO inhibitor, an opioid, St. John's wort, and certain antidepressants (such as serotonin-norepinephrine reuptake inhibitors, tricyclics, tetracyclics, and triazolopyridines), or cyclobenzaprine.

### Antimuscarinics

**BENZTROPINE, TRIHEXYPHENIDYL** (Artane®, Biaperiden) – all are similar.

- block cholinergic overactivity in striatum.
- only adjuvant role in antiparkinsonism therapy (at any stage of disease).
- tremor responds best! (general indication – tremor not relieved by dopaminergic therapy in young patients)
- adverse effects – usual central & peripheral antimuscarinic actions
  - can cause forgetfulness and even psychosis (avoid in those > 70 yrs).

### Antihistamines with anticholinergic action (e.g. DIPHENHYDRAMINE) are weak antiparkinsonian agents.

### OTHER SYMPTOMATIC TREATMENT

Psychosis (esp. frightening visual hallucinations – common with chronically used dopaminergic drugs)

1) stop all drugs except LEVODOPA (lower its dose)
2) CLOzapine (selective D3 antagonist - few extrapyramidal side effects).
3) PAMAVANIRIN (Nalgupil) - FDA approved to treat hallucinations and delusions associated with psychosis experienced in Parkinson's disease

### Depression, sleep fragmentation – AMITRYPTILINE (tricyclic antidepressants and SSRIs are safe!)

MAO inhibitors are not recommended with LEVODOPA.

### Dystonic cramps - BACLOFEN.

Restless legs syndrome – opioids (propoxyphene, oxycodone, codeine).

### Constriction – high-fiber diet and adequate fluid, CHAPRESE.

### TREATMENT - SURGERY

In 1953, by accident, J. Cooper cut anterior choroidal artery during surgery on Parkinsonian patient and was forced to ligate it to prevent hemorrhage; unexpected and remarkable relief of tremor and rigidity on contralateral side led to more widespread use of this procedure, though mortality was approximately 10% (Cooper 1953)


- Surgery was the only effective treatment of PD until 1960s, when Cotzias introduced treatment with levodopa based on the pioneering work of Arvid Carlson.

- Drawbacks of ablative surgery, when contrasted with strikingly beneficial effects of levodopa, were responsible for almost total disappearance of ablative lesions until recognition of long-term side effects of levodopa (mainly motor fluctuations and dyskinesias) triggered renewed interest in surgical methods, but now with no or little tolerance for complications.

### DESTRUCTIVE SURGERY

**Operative (surgical) techniques – see p. Op360 >>**

- Lesioning of GPi / thalamus / subthalamic nucleus can relieve HYPOKINESIA.
  - surgery fails to improve most advanced cases (those who are unable to walk at any time).
  - surgery worsens dementia (but does not produce it); ≥ moderate dementia is contraindication.
  - surgery does not help patients who fail to respond to LEVODOPA.

### Targets

1) THALAMUS, MACROCELIAR PART OF VIM [VENTRALIS INTERMEDIOUS] NUCLEUS → improved severe contralateral tremor.
   - does not improve bradykinesia, rigidity, and dexterity.
   - Although tremor is the most visible of symptoms of PD, it is not the most disabling (difficulties in advanced parkinsonism are essentially related to akinesia and rigidity)
   - bilateral operations result in dysarthria in 15-20% patients.

2) GPi, POSTEROLATERAL PART → improved dyskinesia (contralateral > ipsilateral) and fluctuations; indicated if tremor responds to medications; preferred target for patients with cognitive issues.
   - *site of afferent excitatory fibers from subthalamic nucleus.

3) SUBTHALAMIC NUCLEUS, BILATERAL → pallidotomy (or even better! esp. for gait disturbances)
   - Procedure of choice for uncontrollable fluctuations!
   - Better than GPi if tremor does not respond to medications.
   - STN is in strategic position to influence the whole net output of basal ganglia! May be first therapy proven to be neuroprotective if applied in earliest stages of disease;
   - hyperactive subthalamic nuclei promote glutamate excitotoxicity, accelerating dopaminergic cell death in substantia nigra (DBS removes source of toxic glutamate input → preservation of dopaminergic cells → slowed PD progression).

4) PEDUNCULOPONTINE TEGMENTAL NUCLEUS (PPT).
   - STN vs GPi: at 16 months, motor function is improved similarly in both STN and GPi groups, however, STN group declines significantly faster than GPi group on Mattis Dementia Rating Scale and on other neurocognitive measures.
CONSTRUCTIVE SURGERY

- to provide new cell source of dopamine at striatal level.

CELL TRANSPLANTATION

1) autotransplantation of adrenal medullary tissue or fetal body works for a while, but long-term results are disappointing.

2) fetal ventral mesencephalic (inferred) transplantation to postcommissural putamen; it is proven that transplanted cells can survive up to 16 years:


Summary of studies above:
- long-standing graft survival was demonstrated in all 7 patients at post-mortem, ranging from 9 to 16 years after transplantation.
- grafts contained numerous tyrosine hydroxylase (TH) positive dopamine neurons, in the order of 10,000 to 100,000 per graft.
- grafts were well integrated and provided reinervation of the host striatum.
- grafts in 4 of the 7 patients reported were found to have Lacy-body-like pathology, typical of PD, as demonstrated by immunostaining with alpha-synuclein, phosphorylated alpha-synuclein, and ubiquitin (only 1.5% of grafted neurons contained Lacy-body-like pathology, whereas the remaining grafted neurons were healthy looking).
- solid grafts were found to elicit a stronger host immune reaction than cell suspension grafts, as demonstrated by the presence of activated microglia.
- clinically, clinical outcome was highly variable, ranging from little if any demonstrable benefits to marked improvements; in measures of PD function (incl. UPDRS motor “off” medication scores, ‘off’ time and dyskinesias, and substantially reduced antiparkinsonian medication requirements) with benefits lasting for over a decade.
- variable clinical benefits were found to correlate with the variation in graft size at post-mortem.
- no adverse events such as graft-induced dyskinesias.


• 40 patients randomized to receive either bilateral solid tissue putaminal transplants of fetal ventral midbrain tissue from two embryos per side or sham surgery.
• no immunosuppression was given.
• study failed to meet its primary endpoint of clinical improvement (however, a treatment effect was observed in younger patients).
• trial was concluded after only a year – too early for the growth and integration of human fetal dopamine neurons and the development of functional effects (e.g. several more patients showed clinical improvement after the conclusion of the trial, 2–3 years after transplantation surgery).
• ‘off’ dyskinesias were observed in 15 % of the patients.

Growth factors / neurotrophins

- infusion into ventricular CSF or brain tissue itself.
- e.g. gene therapy – injecting virus that carries gene to produce growth factor SECRETION

TREATMENT – LIFESTYLE

EXERCISE

Review of 39 exercise trials conducted in 1827 PD patients at various stages of disease
- most studies reported short-term benefits from exercise, particularly for gait, balance, and disability based on UPDRS scores.
- there is no definitive evidence that one form of exercise is more beneficial than another.
- print study (4-6 new patients diagnosed within 1 year, examined D2 receptor availability using [18F]Fallypride PET, postural control, and motor function after intensive treadmill exercise, three weekly for 8 weeks in n = 21 patients with no exercise (n = 21):
- results indicated that dopamine D2 receptor availability was increased and postural control was improved in 2 patients undergoing intensive exercise compared with those that did not exercise.

TREATMENT – ALGORITHM

All patients
- Education, physical-exercise therapy, good nutrition.
- No clinically significant disability.

SIDE EFFECTS or RASHES
(“delays need for LEVDOPA by < 9 months!”)

All symptomatic drugs can induce side effects – should be delayed until symptoms become more pronounced!

Refer to study centers (for trials of new neuroprotective strategies)

Clinically significant disability

Job security threatened or health endangered – controlled-release LEVDOPA (at lowest effective dose)
Job security NOT threatened and health NOT endangered (try to delay LEVODOPA – so-called “dopa-sparing” strategy):

a) young and tremor-predominant disease: anticholinergic or AMANTADINE
b) older: dopamine agonist, AMANTADINE
c) very elderly (≥ 80): LEVODOPA

Above patients with progressive disability

add LEVODOPA

if effect prolongation is needed - add SELEGILINE (if not currently taking it) or COMT inhibitor
consider surgery

De novo patients – strategies:

a) LEVODOPA may be initial treatment of choice in patients who are currently employed or because of other aspects of their lifestyle, need maximum control of their symptoms, but rather than increasing dosages above 600 mg/day, another agent such as dopamine agonist / MAO-B inhibitor could be added in attempt to delay onset of motor complications.

b) begin treatment with MAO-B inhibitor / dopamine agonist, particularly in younger patients, and add LEVODOPA as needed to maintain control of symptoms.

PROGNOSIS

- disease slowly progresses - if untreated, patient eventually becomes wheelchair-bound and bedridden.
- MORTALITY: prior to levodopa advent - three times normally expected mortality.
- after advent of levodopa - almost same as age-matched control population without disease.
- patients are more likely to die from infection (e.g. aspiration pneumonia) than from cancer (compared to age-matched controls).

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