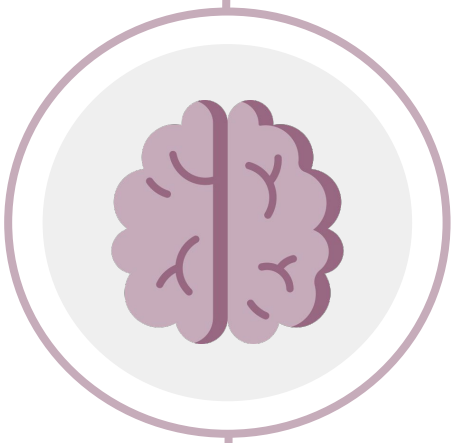
Parkinson's disease & movement disorders



Objectives :

- ★ Review etiologies for parkinsonism
- ★ Review motor and non-motor manifestations of PD
- ★ Discuss treatment options for Management of PD
- ★ Review features of atypical parkinsonian syndrome
- ★ Overview of hyperkinetic movement disorder

Editing file

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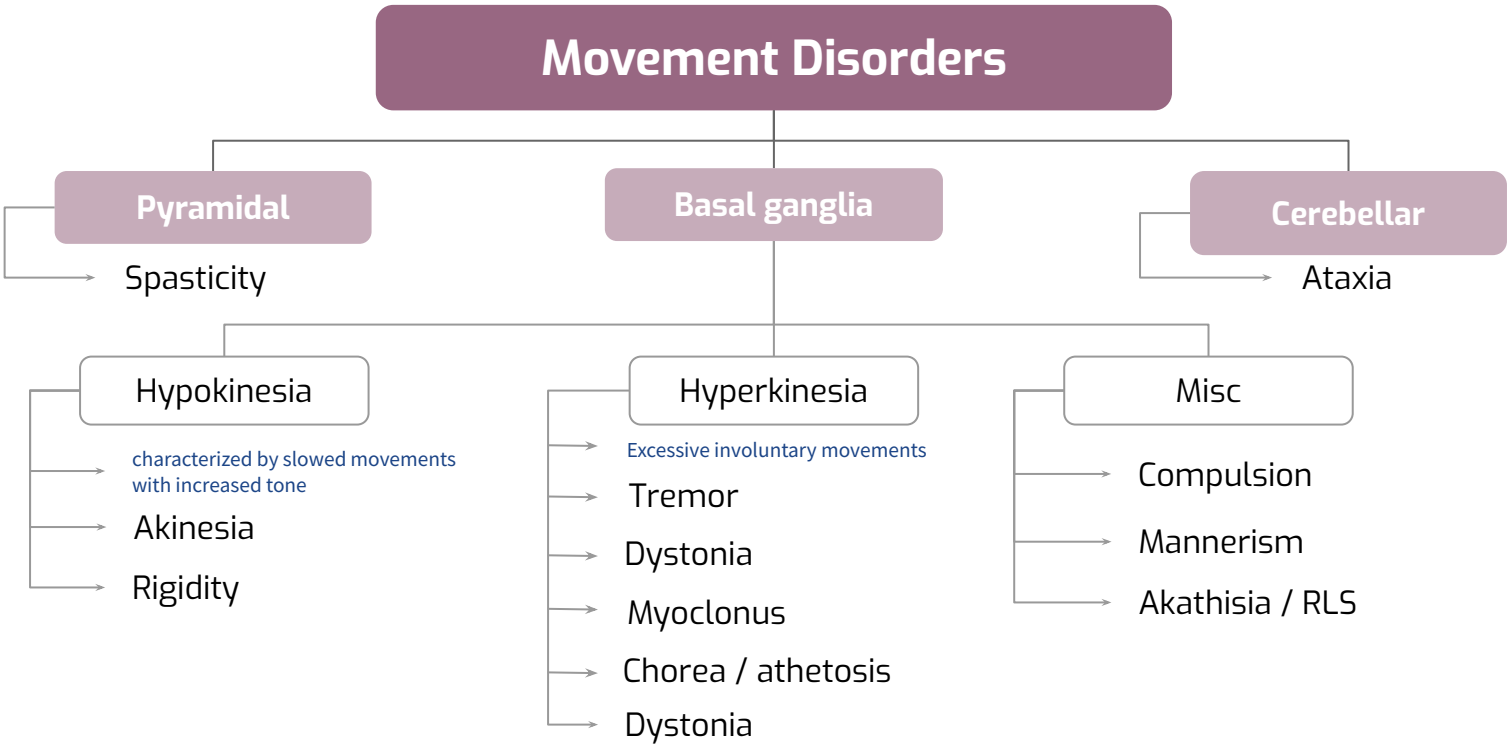
Introduction



Hypokinesia - Parkinsonism

Parkinsonism

Mnemonic: TRAP

- Is a **clinical motor syndrome** characterised by the presence of : **T**remor , **R**igidity (increased tone), **A**kinesia and **P**ostural instability .
- **Parkinsonism does NOT mean Parkinson's disease** but it is the **most common** cause.

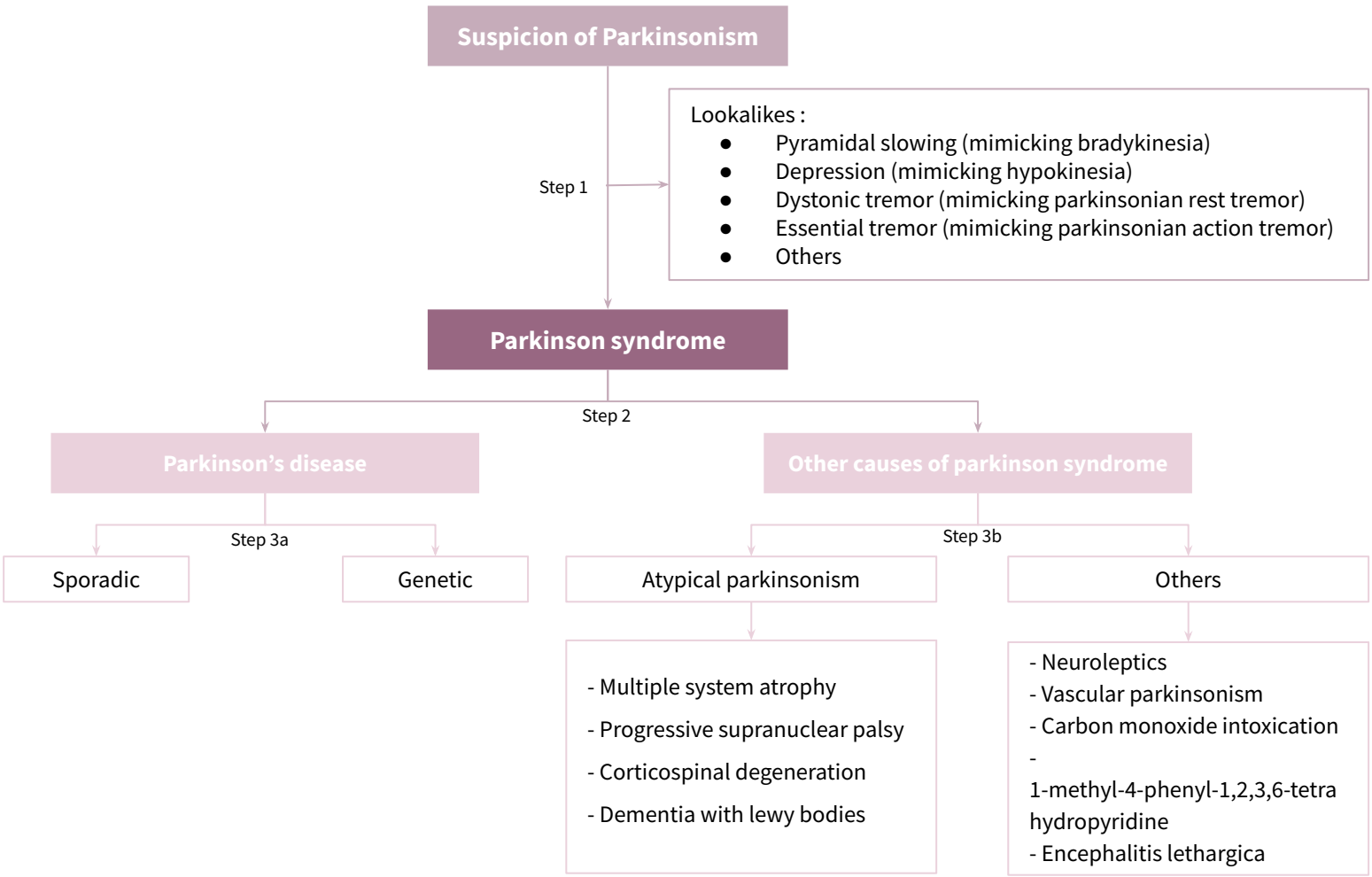
◀ DDx of Parkinsonism

1. Idiopathic parkinson's disease	
2. Atypical Parkinsonism	• Multiple System Atrophy (MSA) [1] • Progressive Supranuclear Palsy (PSP) : parkinsonism + difficulties in eye movement • Cortical Basal Syndrome (CBD) : Parkinsonism + features of cortical involvement
3. Secondary Parkinsonism	• **Drug induced** : Antipsychotic, the symptoms resolve when the medication is stopped, some other drugs can cause just a tremor without parkinsonism. • Vascular : Strokes that affect the basal ganglia that is involved in Parkinson's disease which is substantia nigra • Infectious : Toxoplasmosis • Metabolic : Wilson's and mercury poisoning • Immunologic, traumatic, structural
4. Heterodegenerative Parkinsonism (Rare)	• Aceruloplasminemia, Spinocerebellar ataxia, X-linked dystonia-parkinsonism

1. It is a disorder that has similar features of Parkinson's disease but also has other features (such as autonomic dysfunction) that make them different. These patients are always misdiagnosed with Parkinson's disease. It is worse than Parkinson's disease because it is **not treatable**

Parkinsonism *cont,*

◀ General approach to parkinsonisms



Idiopathic Parkinson's Disease

◀ Overview:

- Second most neurodegenerative disease,
- 1% of people over the age of 60,
- first described in 1817 by James Parkinson , describe it as "shaking palsy "
- clinical diagnosis
- no clinically available biomarker to indicate presents or to track disease progression

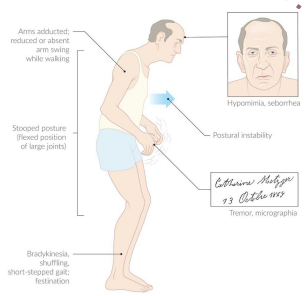
◀ Pathophysiology:

- pathological hallmarks of PD are the presence of neuronal inclusions called **Lewy bodies and loss of the dopaminergic neurons** from the pars compacta of the substantia nigra in the midbrain that project to the striatum of the basal ganglia
- Lewy bodies contain **tangles of α-synuclein and ubiquitin**, and become gradually more widespread as the condition progresses, spreading from the lower brainstem to the midbrain and then into the cortex.
- Degeneration also occurs in other basal ganglia nuclei.
- The extent of **nigrostriatal dopaminergic cell loss correlates with the degree of akinesia.**

Parkinson's disease

Clinical features

Motor symptoms



- These develop slowly and insidiously, and are often initially attributed to 'old age' by patients.
- Idiopathic PD is almost always more prominent initially on one side, a purely symmetrical tremor is probably something else but it can happen in PD.

- **Akinesia (bradykinesia):**
  - The cardinal clinical feature of parkinsonism and the main cause of disability.
  - Bradykinesia : slowness of movement , Slowness of initiation with progressive **reduction in speed and amplitude of repetitive action**
  - Decrement: movement become progressively smaller[1]
  - Hypomimia: decrease facial expression ; Facial immobility gives a **mask-like semblance** of depression , Frequency of spontaneous blinking diminishes, producing a ***serpentine stare***.
  - Hypophonia : soft speech
  - Micrographia : small handwriting
  - What distinguishes it from slowness of movement from other causes is a progressive ***fatiguing*** and ***decrement*** in amplitude and speed of repetitive movements.[1]
  - There is difficulty initiating movement
  - Upper limb is usually affected first and is almost always unilateral for the first years.

- **Tremor:**
  - An involuntary rhythmic **oscillatory** movement around a joint axis, example: if it's a hand tremor & you draw a line (the axis), then the hand will go above & below that line, usually at a similar amplitude & at a specific frequency.
  - **Parkinsonian tremor:**
    - The presenting symptom in 70% of patients, 4-6 Hz per second oscillations around the Wrist and finger
    - Initially it's **unilateral**[2] and **distal** (hand and wrist) , overtime become more proximal and over the contralateral side , spreading later to the leg on the same side and, after some years, to the opposite side.
    - **Predominantly at rest**[3], and reduces or stops completely when the hand is in motion.
    - **Re-emergence with maintained posture**; if you ask the patient to rise their hands and hold it out stretched, after few seconds you might see the tremor "re-emergence of tremor", it's different from action tremor where it comes out immediately as soon as hand is elevated, but if it has a latency "few seconds" its called re-emergence tremor.
    - Intermittent , tremor comes and go not present all the time
    - Described as ***pill-rolling*** because the patient appears to be rolling something between thumb and forefinger. It's made worse by emotion, stress, or mental concentration
    - Pronation/supination at the wrist
    - Worse with distractions or stress
    - Not always levodopa responsive

1. In finger tapping test: after about 5-10 seconds, you'll notice that the tapping kind of slows down or gets progressively smaller. In addition, the overall appearance of the patient e.g. moving slow, takes them long time to get up from the chair or changing their clothes or slowness in chewing food. e.g: if you ask the patient to open and close their hand initially it will be large but with time the movement will be smaller
2. If the tremor starts bilaterally then you have to look for other diagnoses
3. The patient will say that he has tremor while resting but once he moves his hand to get his phone the tremor stops.

Parkinson's disease

◀ Clinical features

Motor symptoms

- **Rigidity:**
  - Resistance of the muscle to passive movement around a joint that is **independent of the velocity** of the movement,It is present throughout the range of movement.[1]
    - Use contralateral limb activation maneuvers, watch out for paratonia
  - Cogwheeling and reduce arm swing
  - Patient complaints:
    - Stiffness
    - Shoulder pain
    - Difficulty turning over in bed
  - Type of rigidity found in PD : *lead-pipe*" (stiffness throughout passive limb movement) , cogwheel (lead pipe superimposed with tremor)
  - Rigidity is related to extrapyramidal disorders, which means it doesn't involve the pyramidal system, but structures such as the basal ganglia.
  - Early axial rigidity think about PSP

- **Postural and gait changes:**
  - Impairment in the ability to recover one's balance :
    - Very stable early on , occurs in uneven surfaces , mild trapping
  - Pull test is used to test for postural instability
  - **Falls early** in the disease should trigger concern for **atypical Parkinsonism**(PSP, MSA) > not typical for Parkinson's disease. in typical PD falls almost never occurs before 5y.
  - A stooped posture is characteristic. Gait gradually becomes **shuffling** with small stride length, slow turns, freezing and reduced arm swing.
  - Postural stability eventually deteriorates, leading to falls, but this is a late-stage feature that should arouse suspicion of an alternative diagnosis if present during the first 5 years

- **Other Motor Abnormalities:**
  - Impaired finger dexterity (fine movement)
  - Flexed/ stooped posture
  - Freezing phenomena[2] > e.g: when the patient is walking he stops suddenly and can't move for a while then start moving again
  - Gait initiation difficulties; when they get up they can't start walking right away
  - Dyskinesias[3] : involuntary , erratic ,writhing movement of face, arms, leg or trunk
  - Motor fluctuations
  - Swallowing difficulties (later)

- Almost always presents with the typical motor symptoms of **tremor and slowness of movement** but it is likely that the **pathological process starts many years before these symptoms develop.**
- By the time of first presentation, on average **70%** of dopaminergic nigrostriatal cells have **already been lost.**

1. **Contrary to spasticity** which is a velocity dependent finding, it could be missed on exam if the limb wasn't moved quickly.
2. transient episodes, usually lasting seconds, in which the motor activity being attempted by an individual is halted
3. As a side effect of treatment

Parkinson's disease

◀ Clinical features - Nonmotor symptoms:

Prodromal pre-motor (pre-clinical) symptoms

- Patients develop a variety of non-specific non-motor symptoms during the approximately **7 years**, sometimes longer, **before the motor symptoms** become manifest. including:
  - Hyposmia (46%) : a slowly progressive loss of smell which might happen decades before Parkinson's develops (olfactory bulb is one of the first structures to be affected).
  - **Autonomic dysfunction**
    - Constipation (39%) (usually chronic in these patients even before the disease starts), Erectile dysfunction (28%), Urinary dysfunction / incontinence (30%) , and Orthostatic hypotension (21%).
  - REM sleep behavior disorder (28%) **(REMBD)** : "Rapid Eye Movement Behavior Disorder" - normally, while someone is sleeping & having dreams, their body paralyzes so they do not act out these dreams. Sometimes, REMBD even precedes Parkinsonism, & the patient starts to physically act out their dreams in bed, so their partner in bed might complain about that person yelling/punching them in sleep.
  - Insomnia (36%), Depression (43%), Anxiety (30%) , Fatigue (36%) and Hypophonia

Cognitive and psychiatric changes

- Memory impairment (later) is now recognized to be common in late stage PD (80%) :
  - MCI (15%)
  - Lewy body dementia
  - if cognitive impairment happens in the beginning or before the motor symptoms then it's probably lewy body dementia, but in Parkinson's disease the cognitive impairment happen at least after 1 year of pure Parkinson's disease which it will be called Parkinson's disease dementia.
- Hallucinations; especially **visual hallucinations** that usually happen later on in the disease. If they occur early, you could think of Lewy Body dementia. Sometimes, the hallucinations could be a side effect of medications.

speech and swallowing

- Speech becomes quiet, indistinct and flat. **Drooling** may be an embarrassing problem and swallowing difficulty is a late feature that may eventually lead to aspiration pneumonia as a terminal event.

◀ DDX for Parkinson Disease

- Atypical parkinsonism (MSA,PSP,CBD)
- Dementia with lewy bodies (DLP) : dementia occurs along with Parkinson's symptoms
- Dystonic tremor
- Essential tremor
- Frontotemporal dementia (FTD)
- NPH > present with magnetic gait
- Functional(Psychogenic) movement disorder.

Parkinson's disease

Risk factors

- **Age and gender:**
  - Prevalence **increases sharply with age**, particularly over 70 years. Ageing changes are likely to be an important factor in causation.
  - Prevalence is higher in **men** (1.5 : 1 male to female).

- **Environmental factors:**
  - small increased risk with rural living and drinking well water
  - **Pesticide exposure** has been implicated and pesticide-induced rodent models of PD exist
  - The chemical compound methyl-phenyl tetrahydropyridine **(MPTP)**, a **potent mitochondrial toxin**, causes severe parkinsonism, leading to suggestions that oxidative stress may be a factor leading to neuronal cell death in idiopathic PD
  - Studies consistently show that **non-smokers have a higher risk** of PD than smokers.

- **Genetics:**
  - Not usually familial but twin studies show there is a **significant genetic component in early-onset PD (onset before 40)**
  - Most of these are rare but together they account for a large proportion of early-onset and familial PD, and a small proportion (perhaps 1–2%), of sporadic late-onset cases.
  - Main significance of the ***PARK* genes is that they provide insights into the pathophysiological mechanisms** underlying PD that may be relevant to sporadic cases.

i **Box 26.51 Selected Parkinson's disease (PD) genes**

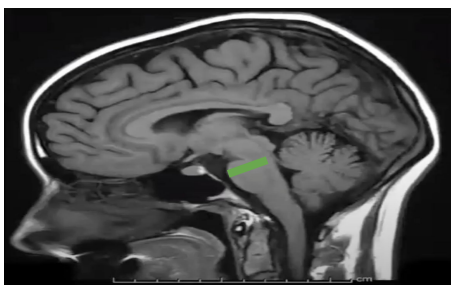
Locus	Protein	Inheritance	Comments
PARK1	α-Synuclein	AD	Rare but a major protein in Lewy bodies
PARK2	Parkin	AR	Responsible for most cases of juvenile PD and 20% of early-onset PD cases
PARK6	Pink-1	AR	Rare. Protein involved in mitochondrial function
PARK8	LRRK2 (a kinase of unknown function)	AD	Phenotype almost identical to sporadic PD. Found in 1% of apparently sporadic PD patients. High frequency in Jewish and North African Arab patients

AD, autosomal dominant; AR, autosomal recessive.

Diagnosis

Diagnosis is (clinical) made by recognizing physical signs and distinguishing idiopathic PD from other parkinsonian syndromes.

Investigations and Imaging is normal in typical PD.
However, in vascular Parkinson's you might see signs of vascular disease (stroke)



Normal brain.
Line: midbrain

Patients with suspected PD should be referred to a specialist without initiation of treatment.

Dopamine transporter (DAT) imaging using SPECT or PET makes use of a radiolabeled ligand binding to dopaminergic terminals to assess the extent of nigrostriatal cell loss. it is abnormal even in the early stages , but does not differentiate between the different forms of degenerative parkinsonism and so is not specific for PD

Parkinson's disease

◀ Management

Dopamine replacement with levodopa or a dopamine agonist improves motor symptoms and is the basis of pharmacological therapy.

Treatment of non-motor symptoms, such as depression, constipation, pain and sleep disorders, is also necessary and significantly improves quality of life.

01 02 03 04 05

01 Education about the condition is necessary and physical activity is beneficial and should be encouraged.

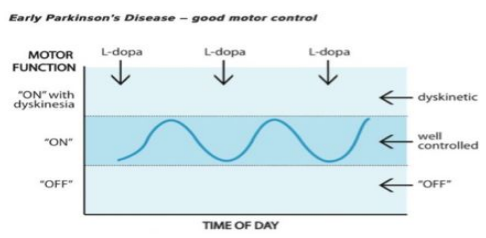
03 Dopamine replacement may not always be needed in early-stage PD and is only started when symptoms begin to cause disability.

05 Drugs for PD should not be stopped abruptly, as this can precipitate malignant hyperthermia

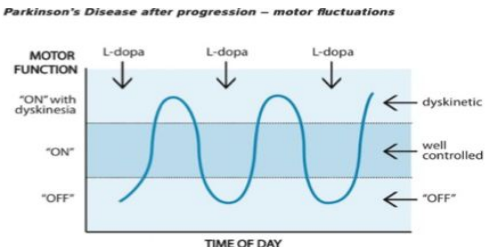
Pharmacological therapy

★ Levodopa/Carbidopa (LD/CD) (first line)

- **Mainstay of treatment**
- most effective form of treatment and all patients with PD will eventually need it.
- most effective for relieving akinesia and rigidity; tremor response is often less satisfactory and it has no effect on many motor (posture, freezing) and non-motor symptoms.
- Levodopa is the active agent, while Carbidopa prolongs the duration of levodopa by delaying its metabolism.
  - When administered orally, more than 90% is decarboxylated to dopamine peripherally in the gastrointestinal tract and blood vessels, and only a small proportion reaches the brain.
  - To avoid this,It is combined with a dopa decarboxylase inhibitor – benserazide (co-beneldopa) or carbidopa (co-careldopa) – to reduce the peripheral adverse effects (e.g. nausea and hypotension)
- **Side effects: Dyskinesias, hypotension, drowsiness and GI upset** (the most common) : nausea and stomach pain (GI upset gets better with time)



When you treat a patient with Levodopa, the medication has a fluctuating course known as "ON-OFF" phenomenon. ON time is when the drug is working well & symptoms are controlled. OFF time is when it is wearing off, & symptoms such as tremor, rigidity, & slow movement re-emerge. "ON with dyskinesia" happens when the levels of L-dopa are too high, leading to excessive movements (dyskinesia) as a side effect. These symptoms typically improve after the next dose is taken.
In early disease it's usually well controlled



In advanced disease, when the patient take the medication their levels peaks very quickly beyond the well controlled line where it start to give side effects which are (abnormal excessive movement "dyskinesia"), then it quickly drops and patient goes to an "OFF" phase as if there are not on any drug. That happens because the regulation becomes impaired in the nervous system, there is more neuronal loss and less receptors, & the absorption of the drug becomes more erratic.

Parkinson's disease

Dopamine agonists (Pramipexole, Rotigotine 'Patch' , Ropinirole)

- **May be used in combination with levodopa or as initial monotherapy in younger patients (below age 65–70)** with mild to moderate impairment
    - Originally introduced in the hope of delaying the initiation of LD and thus delaying motor complications
- Although less efficacious in symptom control than levodopa(Their role in the management of PD remains uncertain)and generally less well tolerated, DAs are associated with fewer motor complications over a 5-year period.
- ***Apomorphine:*** a potent, short-acting DA administered subcutaneously, It is used in advanced PD.
    - With the exception of apomorphine, all the agonists are considerably less effective than LD in relieving parkinsonism, have more adverse effects (nausea, vomiting, disorientation and hallucinations, impulse control disorders) and are more expensive.
- Non-ergot DAs (pramipexole, ropinirole, rotigotine, or apomorphine via transdermal patch) are used in preference to **ergot-derived** drugs, which may be associated with **fibrotic reactions**, including cardiac valvular fibrosis.
- **Domperidone is used as an antiemetic** when initiating DA therapy (other antiemetics should not be used, as they may worsen symptoms by blocking central dopamine receptors).
- **Side effects: impulse control disorder (**Ex. the patient is unable to resist impulses to participate in gambling or such activities**) and sleep attack**

other drugs

- **Monoamine oxidase (MAO)-B inhibitor:** *Selegiline , Rasagiline*
    - Reduces catabolism of dopamine in brain. It has a mild symptomatic effect.
    - **Side effect : insomnia, risk of serotonin syndrome**
- **COMT inhibitors :** *Entacapone , opicapone*
    - Prolongs activity of LD in blood, Not an agent by itself, it can be added instead of increasing the dose of L-dopa
    - **Side effect: Orange discoloration of urine , dyskinesias**
- ***Amantadine:***
    - Not used as frequently as before
    - Has a mild, usually short-lived effect on bradykinesia and is rarely used unless patients are unable to tolerate other drugs
    - More commonly employed as a treatment for LD-induced dyskinesias in advanced disease.
    - **Side effect: livedo reticularis, peripheral (leg) oedema, delirium (confusion in elderly)**
- **Anticholinergic: (e.g. orphenadrine, procyclidine, trihexyphenidyl)**
    - May help tremor but are rarely used in PD except in younger patients.
    - They have a high propensity to cause confusion and cognitive impairment in older patients.

Strategies to manage motor complications

- Dose fractionation of levodopa increasing dose frequency
- Addition of the catechol-O-methyl transferase (COMT) inhibitor entacapone (200 mg with each levodopa dose) to prolong duration of action; this is also available as a combined preparation with levodopa and carbidopa
- Slow-release levodopa mostly used for overnight symptoms, as absorption is erratic and difficult to predict, so limiting effectiveness in control of daytime symptoms
- Avoidance of protein-rich meals (which impair levodopa absorption) and taking doses at least 40minutes prior to meals
- Apomorphine continuous subcutaneous infusion
- Deep brain stimulation and levodopa intestinal gel (discussed in the next slide)

Parkinson's disease

◀ Procedural treatment

Deep brain stimulation (DBS)

- Used in (LD/CD responsive patients only) as an **adjunct to treatment,** it doesn't replace medications, it helps in controlling the signs & symptoms.
- Stereotactic insertion of electrodes into the brain (they implant a device) has proved to be a major therapeutic advance in selected patients (usually under age 70) with disabling dyskinesias and motor fluctuations not adequately controlled with medical therapy.
- Targets include:
  - Subthalamic nucleus – response similar to levodopa with reduction in dyskinesia
  - Globus pallidus – improves dyskinesia but levodopa still required for motor symptoms
  - Thalamus – for tremor only.

L-dopa/carbidopa intestinal gel (LCIG) = Duodopa

- Continuous infusion of this gel into the small intestine via a jejunostomy using a patient-operated pump is effective for selected patients with severe motor complications. At present, it is used only where apomorphine or DBS are contraindicated, partly because of high costs.

Tissue transplantation

- Transplantation of embryonic mesencephalic dopaminergic cells directly into the putamen has produced mixed results but is potentially promising with research ongoing to refine the technique. Stem cells and gene therapy approaches are in development.

Physiotherapy, OT and physical aids

- Physiotherapy, occupational therapy and speech therapy all have a role to play in managing PD and reducing disability, speech and swallowing problems and falls. Walking aids are often a hindrance early on, but later a frame or a tripod may help. A variety of external cueing techniques may help with freezing.

Other akinetic-rigid syndromes

◀ Think of atypical Parkinsonism if :

- Early falls
- Absence of tremor
- Rapid progression
- Early Autonomic failure
- Poor levodopa response

Progressive Supranuclear Gaze Palsy (PSP) : (Steele-Richardson-Olszewski's syndrome)

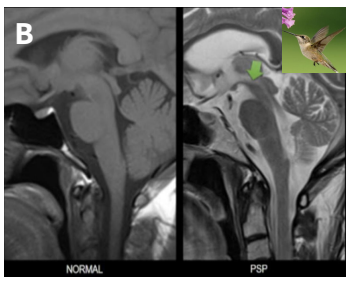
- **The most common** form of atypical parkinsonism 5% to 6%
- **Age of onset** > 63 to 66 years

Hallmarks of the disease:

- **Gait**:
  - Steph, Ford paste, with knee extended and arm abducted > "drunken sailor" or "dancing bear"
  - **Early falls**
  - Lateral deviation and step asymmetry, when turning tend to pivot
  - Prominent early postural instability
  - Axial rigidity and unexplained falls > first 2 years

- **Eyes sign:**
  - **Impaired vertical gaze and lateral supranuclear palsy** ; so the patient presents with Parkinsonism + the inability to look up & down (because there is degeneration in the part of the **midbrain** that is responsible for vertical gazing) whereas their ability to look right & left remains intact, postural instability with early falls, pseudobulbar palsy and dementia.
  - Slowed sccades and reduced OKN (V > H)
  - Square-wave jerk : Abnormal eye movement similar to nystagmus it is in the primary gaze not when they look to the side

- Progressive dementia and personality changes
- **Bulbar dysfunction** : dysarthria dysphagia, etc
- Mona Lisa stare or stone face (image A)
- **Hummingbird sign** : disproportionate atrophy of the midbrain and superior cerebellar peduncle (image B)
- Tau deposition is seen pathologically in the substantia nigra, subthalamic nucleus and midbrain.



◀ PSP Vs. IPD

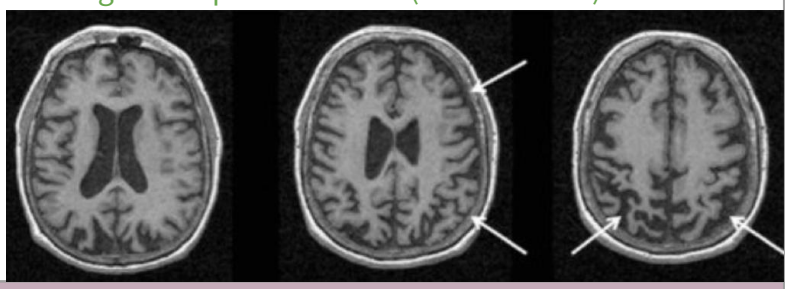
Table 1 : Comparison between idiopathic Parkinson disease and PSP[1,2]

Features	Idiopathic Parkinsonism	Progressive Supranuclear Palsy
Rigidity	Present	Present
Bradykinesia	Present	Present
Tremors	Universal	Rare
Asymmetric findings	Common	Rare
Ocular problems	Uncontrolled blinking Excessive watering of eyes Diplopia	Vertical gaze palsy (Supranuclear) Eyelid apraxia, Blepharospasm (Lid freezing)
Posture	Tend to fall forwards as if chasing centre of gravity	Tend to fall backwards due to head tilt backwards.
Pseudobulbar features	Absent	Common
Cognitive deficits	Common in advanced disease.	Noted in virtually all patients
Dysautonomia	Infrequent	Infrequent
Pathology	α- Synucleinopathy	Tauopathy
MRI brain	Not required with typical presentations. Useful to rule out other disorders like normal pressure hydrocephalus, mass lesions and vascular disease	Midbrain atrophy
Response to dopaminergic agents	Good	Poor

Other akinetic-rigid syndromes

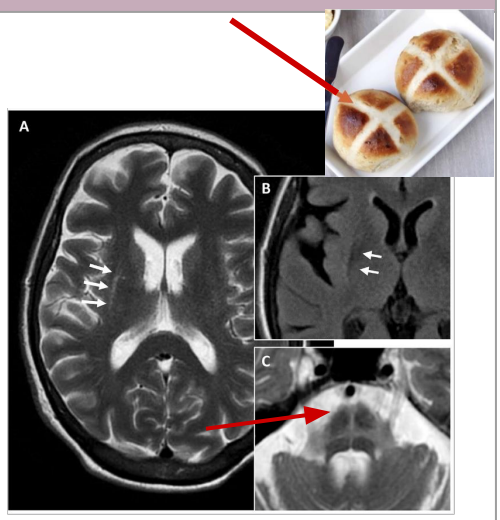
Corticobasal degeneration / Syndrome (CBS)

- Predominant involvement of cortex and basal ganglia
- Average onset 60s , average survival of 7 years
- **Clinical features:**
  - **Apraxia**: they lose their ability to use tools/their hands to do stuff, so for example they can no longer use a hammer or a pen.
  - **Cortical Sensory loss** ; here, we are talking about the *non-elemental* sensations that take multiple sensory components in order for them to be interpreted into an image in the mind (for reference, elemental sensations include pin-prick, vibration, & position sense). Non-elemental sensations include:
  - **Marked limb asymmetry / Alien limb phenomena**: limb that acts in its own not under control of the patient
  - Limb dystonia/ myoclonus
  - Early dementia
  - Bulbar symptoms
  - **Cortical Impairment** (of the higher functions of the brain)
    - Astereognosis: when you place an object in the patient's hands & ask them to identify it without looking at it - just by moving it around.
    - Agraphesthesia: when you draw something on the patient's hand (ex: a number) & ask them to guess what it is.
- **Imaging**:
  - Asymmetrical atrophy of the cortex



Multiple System Atrophy (MSA) :

- Two variants : **MSA-P** (Parkinsonism) and **MSA-C** (cerebellar)
- **Onset:** late 50s , survival 6-9 years



- **Clinical features :**
  - Symmetric bradykinesia , **atypical tremor**, rigidity
  - Pyramidal tract/ cerebellar sign
  - Early **dysautonomia** (autonomic dysfunction)
    - Urinary / erectile dysfunction
    - Orthostatic hypotension
    - Constipation
  - Sever spastic **dysarthria**, dysphonia, or strider
  - Respiratory dysfunction : they can die from it
  - Pisa syndrome : that means they are deviated to one side
  - Pathologically α-synuclein positive glial cytoplasmic inclusions occur.
- **Imaging findings:**
  - **Hot cross bun sign**; Disproportionate atrophy and gliosis of the pons This is the pons. It has a cross passing through it, which is an abnormal finding, giving it the appearance of a bread bun which is why it's called the "hot cross bun sign" - this sign is due to the degeneration of fibers going through the pons. It's seen in multiple system atrophy. They might also have CB findings, probably due to the CB's connections to the brainstem.
  - Slit like hyperintensity of the putamen

Other akinetic-rigid syndromes

Clinical Presentation	Features[a]
Multiple system atrophy–parkinsonian type (MSA-P) (previously referred to as Shy-Drager syndrome or striatonigral degeneration)	Onset >40 years, duration <10 years, progressive parkinsonism poorly responsive to levodopa, with autonomic failure (induding orthostatic hypotension, impotence, bladder dysfunction)
Multiple system atrophy–cerebellar type (MSA-C) (previously referred to as olivopontocerebellar atrophy)	Ataxia; degeneration of ventral pons, olives, cerebellum; mild parkinsonism and cognitive decline

[a] Autonomic dysfunction, respiratory symptoms, and sleep disturbance can precede motor signs by months to years.

★ Drug induced Parkinsonism ★

ALWAYS ask about medication history, eg: **metoclopramide**, simply by stopping the offending drug, you help the patient. It is the most important thing to ask about.
Dopamine blocking or depleting drugs, particularly **neuroleptics** e.g. **haloperidol** (with the exception of clozapine), induce Parkinsonism or worsen symptoms in affected patients, and may precipitate symptoms in elderly patients in the presymptomatic phase (so **should be avoided** in pts with PD)

Vascular Parkinsonism

- Patients might have upper motor neuron signs on exam
- Vascular parkinsonism, similar to vascular dementia, results from multiple strokes in multiple areas leading to parkinsonian features

Wilson's disease

- Copper deposition occurs in the basal ganglia, the cornea and liver , where it can cause cirrhosis.
- All young patients (below age 50) with an akinetic-rigid syndrome or any hyperkinetic movement disorder, or with liver cirrhosis should be screened for Wilson's disease (check serum copper and ceruloplasmin).
- Neurological damage is reversible with early treatment

◀ Red Flags:

★ **If present, suspect conditions other than Parkinson's disease.**

- Neuroleptic or anti-emetic drug use. Most important red flag.
- Early/prominent autonomic dysfunction → think of: multiple system atrophy
- Limited eye movements → think of: progressive supranuclear gaze palsy
- Pyramidal, cerebellar or sensory symptoms → these could all be vascular parkinsonism, but it could be:
  - multiple system atrophy or vascular if there were pyramidal symptoms
  - multiple system atrophy if there were cerebellar symptoms
  - and corticobasal if there were sensory symptoms.
- Cognitive impairment → especially if it happens later on after well-established Parkinson's disease (Parkinson's disease dementia), however if it happens early we could think of Lewy body dementia
- Symmetrical presentation and absence of tremor
- Levodopa unresponsiveness (or poor response)
- Early falls (within first year)
- Additional neurological features.

Hyperkinetic disorders

- There are five hyperkinetic movement disorders. These can sometimes be difficult to separate from one another and may occur in combination.

1. Tremor:

- An involuntary **rhythmic oscillatory movement** of a body part(s)
- **Classified based on activation :**
  - **Rest tremor**
    - Parkinson disease
    - Drug-induced parkinsonism
    - Vascular parkinsonism
    - Multiple system atrophy and other degenerative causes of parkinsonism (eg, spinocerebellar ataxia types 2 and 3) - rare
  - **Action tremor**
    - **Kinetic tremor :**
      - Cerebellar disease (eg, demyelination, degeneration or secondary to toxins, stroke)
      - Holmes tremor
      - Wilson disease
      - Psychogenic (functional) tremor (commonly also present on rest and posture)
    - **Postural tremor ;** on maintained posture-position specific :
      - Enhanced physiologic tremor
      - Dystonic tremor
      - Toxins (eg, mercury)
      - Drugs (of abuse, coffee, many medications)
      - Metabolic disturbance
      - Neuropathy
      - Parkinson disease
      - Fragile X permutation (fragile X tremor-ataxia syndrome)
      - **Essential tremor :** described in the table below

What is it?	Hereditary, autosomal dominant, not associated with any brain/thyroid pathology or medications, therefore it is essentially a benign condition but impairing. 438
Character?	• Slowly progressive, bilateral, fast, low amplitude tremor, asymmetric mainly in the upper limbs action tremor, that disappears at rest • The head and voice are occasionally involved. • It is an important differential for Parkinson's, but there is no bradykinesia, rigidity, or dystonia. • You have to be careful with the cerebellar exam because a cerebellar tremor could look exactly like an essential tremor, so unless a person presents with a longstanding (~10 years) progressive history, we should do imaging to exclude any cerebellar lesions (such as strokes) that could cause this.
Worse with?	Physical activity, caffeine, stress, anxiety, Sympathomimetics (e.g. salbutamol)
Relieved by ?	May temporarily improve after alcoholic beverages
Treatment?	Propranolol (B-blockers are prescribed, they are used when needed and they significantly improve the tremor), primidone or gabapentin may help - Stereotactic thalamotomy and thalamic DBS are used in severe cases.

2. Dystonia:

- Is a movement disorder characterized by **sustained or intermittent muscle contractions** causing abnormal , often repetitive , movement, postures, or both . In a nutshell, it's the same movement happening persistently or repetitively, usually there's contraction of both agonist + antagonist muscles at the same time
- Dystonic movements are typically patterned (all the same) , twisting , and may be tremulous
- Often initiated or **worsened by voluntary action** and associated with **overflow muscle activation**[1]
- **Sensory trick** (Gestes Antagoniste): common action that improves dystonia
- Could be generalized or focal, could be lesional, drug or idiopathic
- Dystonia is most usefully classified by aetiology, into:
    - Primary dystonias – where dystonia is the only, or main, clinical manifestation (usually genetic)
    - Secondary dystonia – due to brain injury (trauma or stroke) , cerebral palsy or drugs for example
    - Heredo-degenerative dystonia – as part of a wider neurodegenerative disorder
    - Paroxysmal dystonias – rare, mostly genetic, attacks of sudden involuntary movements with elements of dystonia and chorea.

Inherited or acquired	Inherited (dystonia forms of proven genetic origin):
	Autosomal dominant
	Autosomal recessive
	X-linked recessive
	Mitochondrial
	Acquired (dystonia due to a known specific cause):
	Cerebrovascular (infarction or hemorrhage)
	Perinatal brain injury
	Traumatic brain injury
	Infection
	Drug
	Toxic
	Neoplastic
	Psychogenic
Idiopathic (unknown cause)	Sporadic
	Familial

- Ballismus :
    - A large amplitude choreiform movement, seen after **subthalamic strokes usually**
    - Hemiballismus describes violent swinging movements of one side caused usually by infarction or haemorrhage in the contralateral subthalamic nucleus.
- Treatment is difficult but botulinum toxin injections or DBS may be useful.

1. If the patient is writing with his right hand the same movement will happen also in the left hand

Hyperkinetic disorders

3. Chorea:

- Is a hyperkinetic movement disorder , characterized by involuntary continuous, **abrupt, rapid, brief , unsustained , jerky , irregular movements** that flow randomly from one body part to another
- **Associated features :**
  - Parakinesia (semi-purposeful camouflage)
  - Motor persistence (" darting tongue" , "milkmaid's grip ")
  - Pendular reflexes
  - Irregular ("dance-like") gait
- **Causes** :
  - **Genetic :** Huntington's disease (autosomal dominant disorder with progressive chorea, cognitive impairment and psychiatric features develop) and others
  - **Drugs :** anti-emetics, anti-epileptics
  - **Autoimmune :** sydenham's chorea , APLAS,SLE,Behcet
  - **Infections** : encephalitis, HIV, TB
  - **Vascular** : polycythemia vera , ischemic stroke
  - **Endocrine** : hypo/hyperglycemia , hyperthyroidism

4. Myoclonus:

- A **quick , involuntary muscle jerk** , can be either irregular or rhythmic (There are different types of myoclonus, some involve the entire body, others just parts of it. An example of physiological myoclonus that many of us have experienced before is when we are just about to go into sleep, & we get a strange dream of falling, so we suddenly wake up & our whole body jerks)
- **Can be either** :
  - Spontaneous
  - Action myoclonus : activated or accentuated by voluntary movement
  - Reflex myoclonus : activated or accentuated by sensory stimulation
  - E.g : hiccups , during sleep (these are physiological myoclonus)
- **Causes** :
  - Genetic : progressive myoclonus epilepsy
  - Hypoxia
  - Autoimmune
  - Infection : measles
  - Metabolic: liver failure (asterixis) , uermic encephalopathies
  - Drug induced
- Cortical myoclonus is usually distal (hands and fingers especially) and stimulus sensitive (spontaneous but also triggered by touch or loud noises) and caused by a wide variety of pathologies affecting the cerebral cortex; spinal and brain- stem myoclonus are caused by localized lesions affecting these structures.

5. Tics:

- Sudden , brief , intermittent, repetitive , non-rhythmic , **involuntary or semi-voluntary movements or muscle contraction**s (motor tics) or sounds (phonic tics) which abruptly interrupt otherwise normal motor activity and speech .
- **Can be preceded by a premotor urge** : regional or generalized sensory or mental phenomena or an urge that precede tics and are temporarily reduced by performance of tics .
- More common in children (boys > girls) > usually it goes away when they grow older but some adult still have it .
- stereotyped movements or vocalizations (may be temporarily suppressed)

Parkinson's disease (General information) :

- Parkinson disease is the most common hypokinetic movement disorder
- Onset is usually after age 50 years.
- Parkinson Disease Is Essentially A Clinical Diagnosis
- Lewy bodies (hyaline inclusion bodies) are a key neuronal finding in the brains of patients with Parkinson disease.
- Patients with tremor as a major symptom of Parkinson disease have a better prognosis than those who have bradykinesia as a predominant finding.

Clinical features:

- Pill-rolling tremor at rest(worsens with emotional stress) Tremor goes away when performing routine tasks.
- Bradykinesia—slowness of voluntary movements
- Rigidity is characteristic."Cogwheel Rigidity"refers to ratchet-like jerking, which can be elicited by testing the tone in one limb while the patient clenches the opposite fist.
- Poor Postural Reflexes;difficulty initiating the first step,andwalking with small shuffling steps; stooped posture
- Masked(expressionless)facies;decreased blinking.
- Dysarthria and Dysphagia,micrographia(small handwriting).
- Impairment Of Cognitive Function(dementia)in advanced disease.
- personality changes present in early stages.

Management

- **No cure**—goals are to delay disease progression and relieve symptoms.
- **Carbidopa-levodopa (Sinemet)—drug of choice for treating parkinson's symptoms.**
  - show an"on–off"phenomenon(over the course of the day) during treatment, which leads to fluctuations in symptoms. This is due to dose– response relationships. It often occurs in advanced disease.
- **Dopamine-receptor agonists(bromocriptine,pramipexole).**
  - May control symptoms and delay need for levodopa for several years.
  - Initiate one of the seagents when you have established the diagnosis.You may use levodopa and one of these agents at the same time.
  - Pramipexole Is The Most Commonly Used.
  - These can be useful for sudden episodesofhesitancyorimmobility(described as "freezing")
- **Anticholinergic Drugs.**
  - Trihexyphenidyl And Benztropine.
    - These may be particularly helpful inpatients withtremor as amajor finding.Do not use in older patients or demented patients.
- **Selegiline**
  - Inhibits monoamine oxidase B activity(increased dopamine activity) and reduces metabolism of levodopa
  - An adjunctive agent, and is often used in early disease. It has mild symptomatic benefit.
- **Side Effects.**
  - Dyskinesias (involuntary, often choreic movements) can occur after 5 to 7 years of therapy. This is a major concern, and may warrant delay in initiating carbidopa-levodopa for as long as possible.
  - Nausea/vomiting, anorexia, HTN, hallucinations

Akinetic disorders

Progressive supranuclear palsy

Overview

Hallmarks of the disease:

- **Gait**:
  - Drunken sailor or "dancing bear", **Early falls ,** Lateral deviation and step asymmetry, , Prominent early postural instability and Axial rigidity
- **Eyes sign: Impaired vertical gaze and lateral supranuclear palsy**
- **Bulbar dysfunction** : dysarthria dysphagia, etc
- Imaging : **Hummingbird sign** : disproportionate atrophy of the midbrain and superior cerebellar peduncle

Corticobasal Syndrome (CBS)

Overview

- **Clinical features:**
  - **Apraxia**, **Cortical Sensory loss**, **Marked limb asymmetry / Alien limb phenomena**:
  - **Cortical Impairment**
    - Astereognosis and Agraphesthesia
- **Imaging**: Asymmetrical atrophy of the cortex

Multiple System Atrophy (MSA)

Overview

- **Clinical features :**
  - Symmetric bradykinesia , **atypical tremor**, rigidity
  - Pyramidal tract/ cerebellar sign
  - Early **dysautonomia** (autonomic dysfunction)
    - Urinary / erectile dysfunction
    - Orthostatic hypotension
    - Constipation
  - Sever spastic **dysarthria**, dysphonia, or strider
- **Imaging findings: Hot cross bun sign** and Slit like hyperintensity of the putamen

Hyperkinetic disorders :

Tremor

- An involuntary **rhythmic oscillatory movement** of a body part(s)
- Classified based on activation: **(rest tremor; PD) or (action tremor)**

Dystonia

- **Sustained or intermittent muscle contractions** causing abnormal , repetitive , movement or postures. .They are typically patterned , twisting , and may be tremulous
- **Worsened by voluntary action** and improved with **Sensory trick** (Gestes Antagoniste)

Chorea

- **abrupt, rapid, brief , unsustained , jerky , irregular movements**
- **Associated features :** Parakinesia, Motor persistence and Pendular reflexes

Myoclonus

- A **quick , involuntary muscle jerk** , can be either irregular or rhythmic

Tics

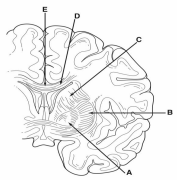
- Sudden, **involuntary or semi-voluntary movements or muscle contraction**s (motor tics) or sounds (phonic tics)
- **Can be preceded by a premotor urge**

Lecture Quiz

Q1: A left-handed 79-year-old man presents with a troublesome resting tremor of his left hand. The tremor is evident in his writing. He has also noticed his writing is smaller than it used to be. He complains he has difficulty turning in bed to get comfortable and his wife complains that he sometimes kicks her in the middle of the night. When he gets out of bed in the morning he feels a little woozy, but this resolves after a while. On examination, he blinks about three times a minute and his face does not show much emotion. Glabelar tap is positive. He has a slow, shuffling gait. He has difficulty stopping, starting and turning. He holds his feet slightly apart to steady himself. When you pull him backwards, he is unable to right himself and stumbles back. Which of the signs and symptoms is not commonly associated with parkinsonism?

A, Posturalinstability
B. Rapid eye movement (REM) sleep disturbance
C. Hypomimia
D. Broad-basedgait
E. Autonomicinstability

Q2: A 55-year-old woman has received treatment for years to manage a chronic, progressive disease. Since her mid-40s the patient has had difficulty initiating movements. She has a shuffling gait, an expressionless face, and tremor in her hands and fingers at rest. Over the years she has tried many medications but with little relief of her symptoms, and instead has experienced severe adverse effects. She is referred for possible ablation surgery. The neurosurgeon explains the different pathways involved in initiation and inhibition of movement, the foundation of her disease. The neurosurgeon explains that by nullifying or accentuating some of the pathways, some of her symptoms may be alleviated. The introduction of an ablative lesion into which structure labeled in the image would be expected to improve this patient's bradykinesia?



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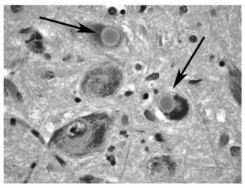
A- A
B- B
C- C
D- D

Q3: The high-power micrograph shown in the image demonstrates a key histologic finding obtained from the brain of a 75-year-old man at autopsy. In the years leading up to his death, the patient had exhibited the gradual onset of motor symptoms including bradykinesia, resting tremor, shuffling gait, and stooped posture. His medical history was otherwise unremarkable. Which of the following best describes the pathology underlying this patient's disease process?

A- Cortical atrophy associated with b-amyloid plaques, neurofibrillary tangles, and decreased cholinergic activity
B- Defective copper transport leading to the accumulation of copper in tissues
C- Loss of γ-aminobutyric acidergic neurons causing atrophy of the caudate nucleus
D- Loss of pigmented dopaminergic neurons in the substantia nigra
E- Malignant tumor cells derived from the neural crest leading to metastatic disease of the brain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Q4: What is the most common cause of parkinsonism?

A- Idiopathic
B- Drug-induced Parkinsonism
C- Vascular Parkinsonism
D- Dementia with Lewy bodies

Q5: Which migraine drugs worsen Parkinson disease?

A- Prochlorperazine
B- Metoclopramide
C- Chlorpromazine
D- All the above

Answers: Q1:D | Q2:A | Q3:D | Q4:A | Q5:D

Answers Explanation File!

GOOD LUCK !

***This work was originally done by* 438 Medicine team:**

Team Leaders

- *Raghad AlKhashan*
- *Amirah Aldakhilallah*
- *Mashal AbaAlkhail*
- *Nawaf Albhijan*

Member : Ghalia Alnufiea- Teif Alotaibi

Note taker : Lama Alassiri

***Edited by* 439 Medicine team:**

Team Leaders

- *Shaden Alobaid*
- *Ghada Alabdi*
- *Hamad Almousa*
- *Naif Alsulais*

Member : Nouf Alsubaie

Note taker : Abdurahman Aldweesh

CONTACT US THROUGH OUR EMAIL :
MEDICINE439@GMAIL.COM