Neurocognitive disorders

Definition:

- The neurocognitive disorders (NCDs) comprise a group of conditions defined by a decline in the level of cognitive functioning, which composed into six domains that may be affected, include:

1. **Attention** .
2. **Function.**
3. **Learning and memory.**
4. **Language.**
5. **Perceptual-motor skills.**
6. **Social interaction**.

- The DSM-5 divides the NCDs into three main categories:

1. Delirium,
2. Mild NCDs.
3. Major NCDs (dementias).


DELIRIUM

Delirium

- **Delirium**: Acute state of confusion characterized by fluctuations in awareness, cognition, and attention.
- It is a **medical emergency,** associated with **high mortality!**
- Potentially reversible, Can advance to coma, seizures, or death.
- Consider delirium as acute brain failure!

- **EPIDEMIOLOGY**
  - Up to one-half of hospitalized elderly patients develop delirium.
  - Delirium often goes unrecognized (65–88% of the time).

- **ETIOLOGY:**
  - Almost any medical condition can cause delirium, ex: pneumonia, Meningitis, hypoglycemia...etc.

  - Substance intoxication delirium.
  - Substance withdrawal delirium.
  - Medication-induced delirium.
  - Delirium due to another medical condition.

  But the exact mechanism is unknown

- **RISK FACTORS**
  - Age > 65 years
  - Hearing or vision impairment.
  - Preexisting cognitive impairment
  - Prior history of delirium.
  - Severe or terminal illness

- **PRECIPITATING FACTORS:**
  - Polypharmacy, including the use of psychotropic medications
  - Infection.
  - Dehydration.
  - Organ failure.
  - Alcohol use or withdrawal.

- **CLINICAL MANIFESTATIONS**
  - Primarily a disorder of **attention** and **awareness**
  - Cognitive deficits **develop acutely** over hours to days.
  - deficits in **recent memory,** language, or perceptual disturbances (hallucinations).
  - Symptoms **fluctuate** throughout the day, typically worsening at night.

- There are three types of delirium based on psychomotor activity.

1. **Mixed type (most common)**: psychomotor activity may remain stable and may fluctuate rapidly between hyperactivity and hypoactivity.
2. **Hypoactive** ("quiet") type: Decreased psychomotor activity, **More likely to go undetected.**
3. **Hyperactive type** ("ICU psychosis"): Manifests with agitation and uncooperativeness. More common in **drug withdrawal or toxicity**.

Diagnosis

- A useful clinical tool for evaluation of a patient with suspected delirium is the **Confusion Assessment Method** (CAM).

- Feature 1: Acute onset in a fluctuating course.
- Feature 2: Inattention.
- Feature 3: Altered consciousness.
- Feature 4: Disorganized thinking.

- Delirium is diagnosed in a patient with **inattention** of **acute onset** and/or **fluctuating course** along with either **disorganized thinking** or **altered consciousness**.
- Once delirium has been diagnosed, the cause(s) should be sought.

TREATMENT

- **Treat the underlying cause(s)**
- Supportive care
- **Haloperidol** is the preferred agent and can be administered orally, intra-muscularly, or intravenously.
- Prevention of complications

Mild and Major Neurocognitive Disorders

Mild and Major Neurocognitive Disorders

- The non-delirium NCDs are characterized by a chronic cognitive decline that impacts functioning in daily activities.

- Major Neurocognitive Disorders:

1. Significant cognitive decline
2. Interferes with independence in daily living activities, ex: shopping, paying bills.
- Overtime can lead to total dependence

- Mild neurocognitive disorders:

1. Moderate cognitive decline
2. DOES NOT interfere with independence in daily living activities

Clinical scenario of Mild & Major NCDs

Scenario	Likely diagnosis
cognitive impairment + cogwheel rigidity + resting tremor	Lewy body disease Parkinson disease
cognitive impairment + fatigue + cold intolerance	hypothyroidism
cognitive impairment + vegan diet + paresthesias + diminished position and vibration sensation	Vitamin B12 deficiency
cognitive impairment + tremor + Kayser– Fleischer rings	Wilson disease

Diagnosis

- **Mini Mental State Exam (MMSE)**
  - is a screening test used due to its speed and ease of administration.
  - 5-15 minutes
  - Assesses orientation, attention/concentration, language, constructional ability, and immediate and delayed recall.
  - Perfect score: 30. Dysfunction <25

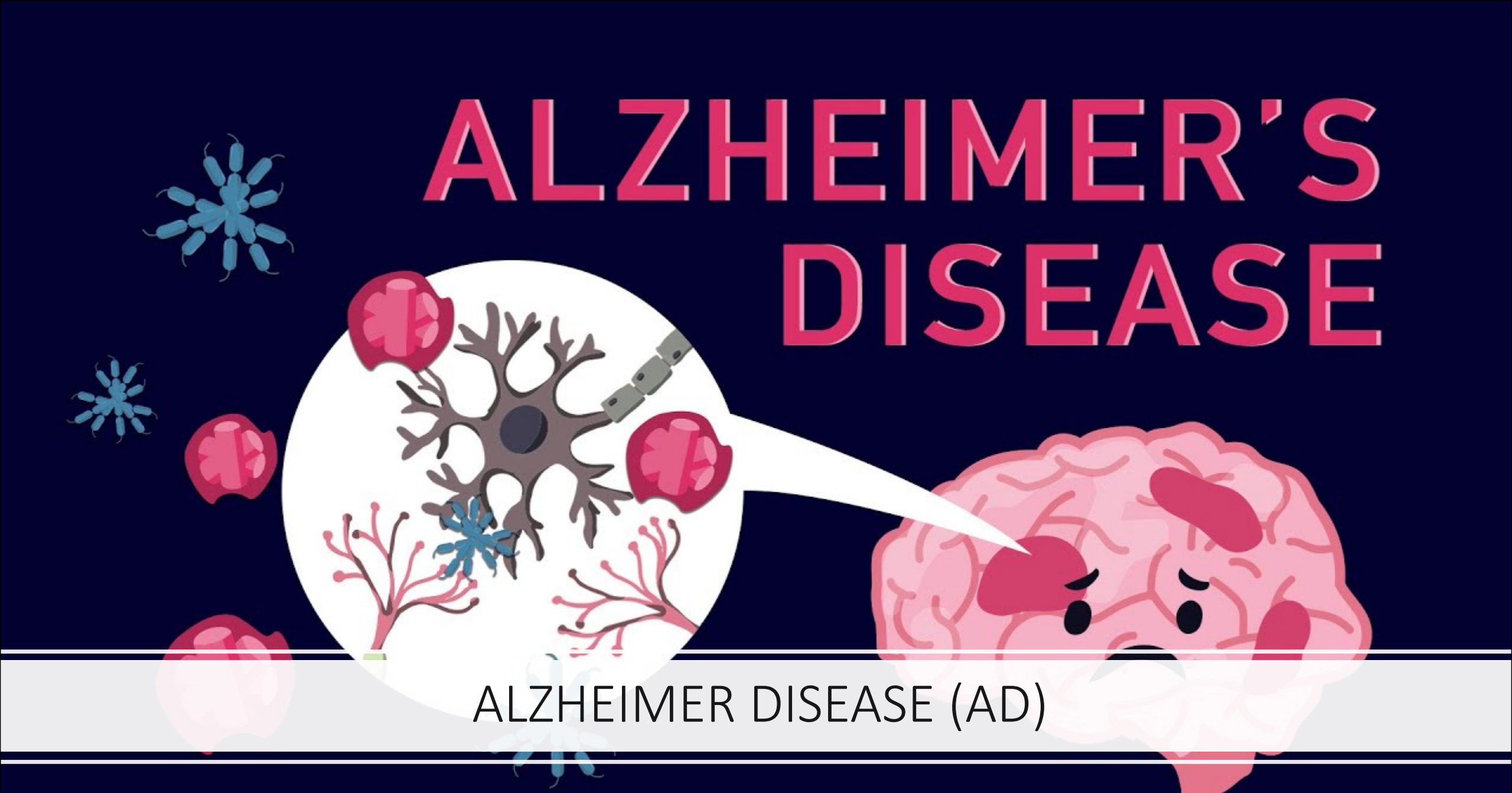
- **Mini-Cog**
  - Consists of three-item recall and clock-drawing tasks.

Positive screening	Negative screening
1. No items recalled after 3 minutes. 2. Only one to two items recalled with abnormal clock drawing.	1. All three items repeated correctly after 3 minutes. 2. One to two items recalled with normal clock drawing.

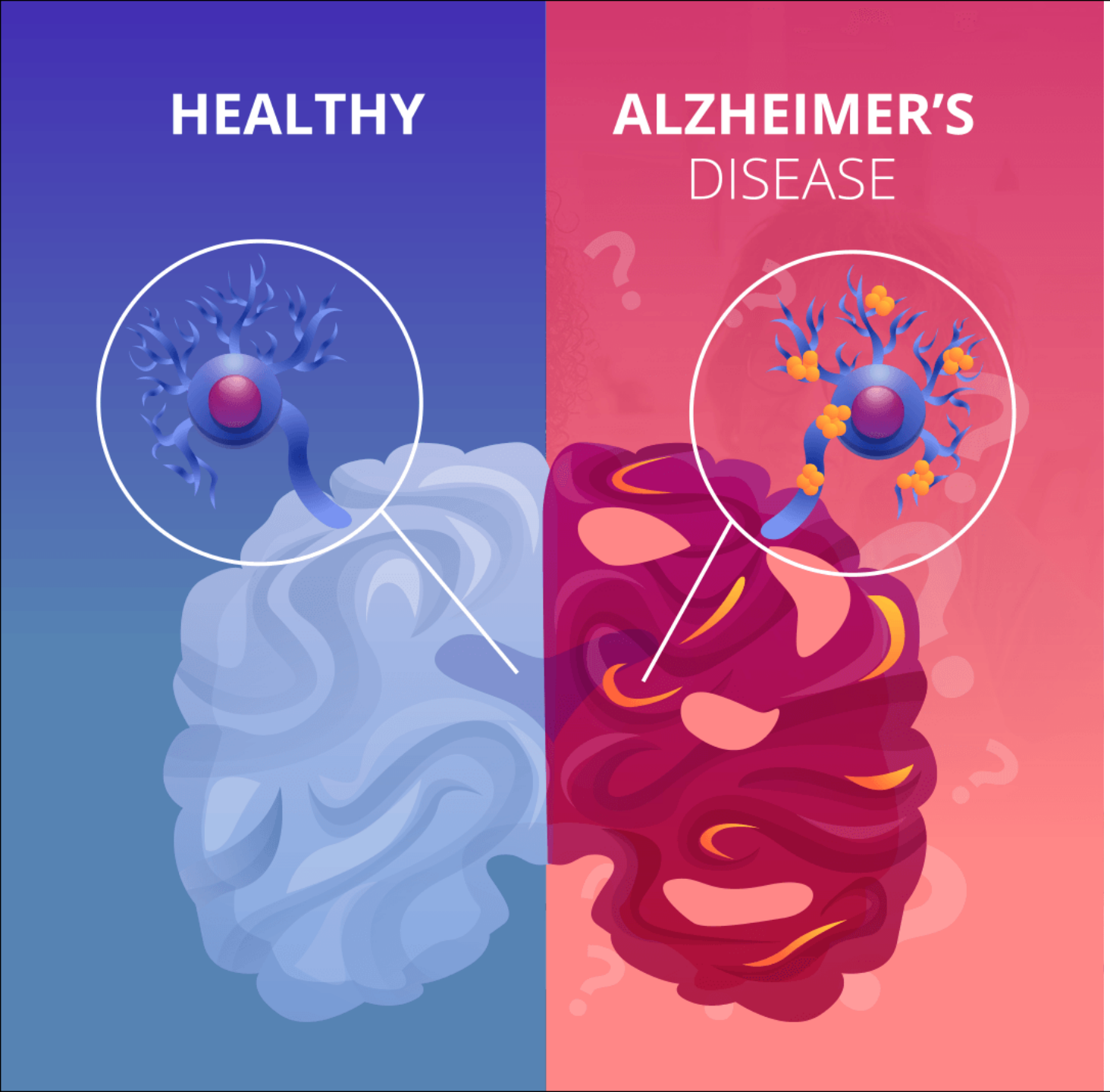
Major neurocognitive disorder

ACQUIRED DISORDER OF COGNITIVE FUNCTION THAT IS COMMONLY CHARACTERIZED BY **IMPAIRMENTS IN THE MEMORY, LANGUAGE, ATTENTION EXECUTIVE FUNCTION, SOCIAL COGNITION, AND/OR PERCEPTUAL MOTOR DOMAINS**.

MOST FORMS ARE ASSOCIATED WITH OLDER AGE.



ALZHEIMER DISEASE (AD)



Alzheimer disease

- Alzheimer disease is a progressive NCD and it is the **most common** underlying etiology of major NCDs (dementias).

- **Epidemiology:**
  - AD is the leading cause of dementia and the sixth most common cause of death in the US.
  - AD pathology is estimated to play a role in 60–90% of major NCDs.
  - Two-thirds of patients diagnosed with AD are women

- **Etiology:**
  - **Accumulation** of extra-neuronal ***beta*-amyloid plaques** and intraneuronal *tau* protein tangles is associated with progressive brain atrophy.
  - Approximately 1% of AD results from an autosomal dominant single-gene mutation (amyloid precursor protein, presenilin 1, or presenilin 2), which is associated with an early onset of symptoms.
- **Other risk factors:**
  - Age (strongest predisposing factor for regular AD)
  - Family history of dementia (strongest predisposing factor for early-onset AD)

Clinical Manifestations

The most common initial presentation is **short-term memory loss**, which insidiously progresses to dementia with deficits in other cognitive domains

1. Gradual progressive decline in **cognitive functions:**
    1. Short term memory
    2. Language impairment
    3. Temporal and spatial disorientation

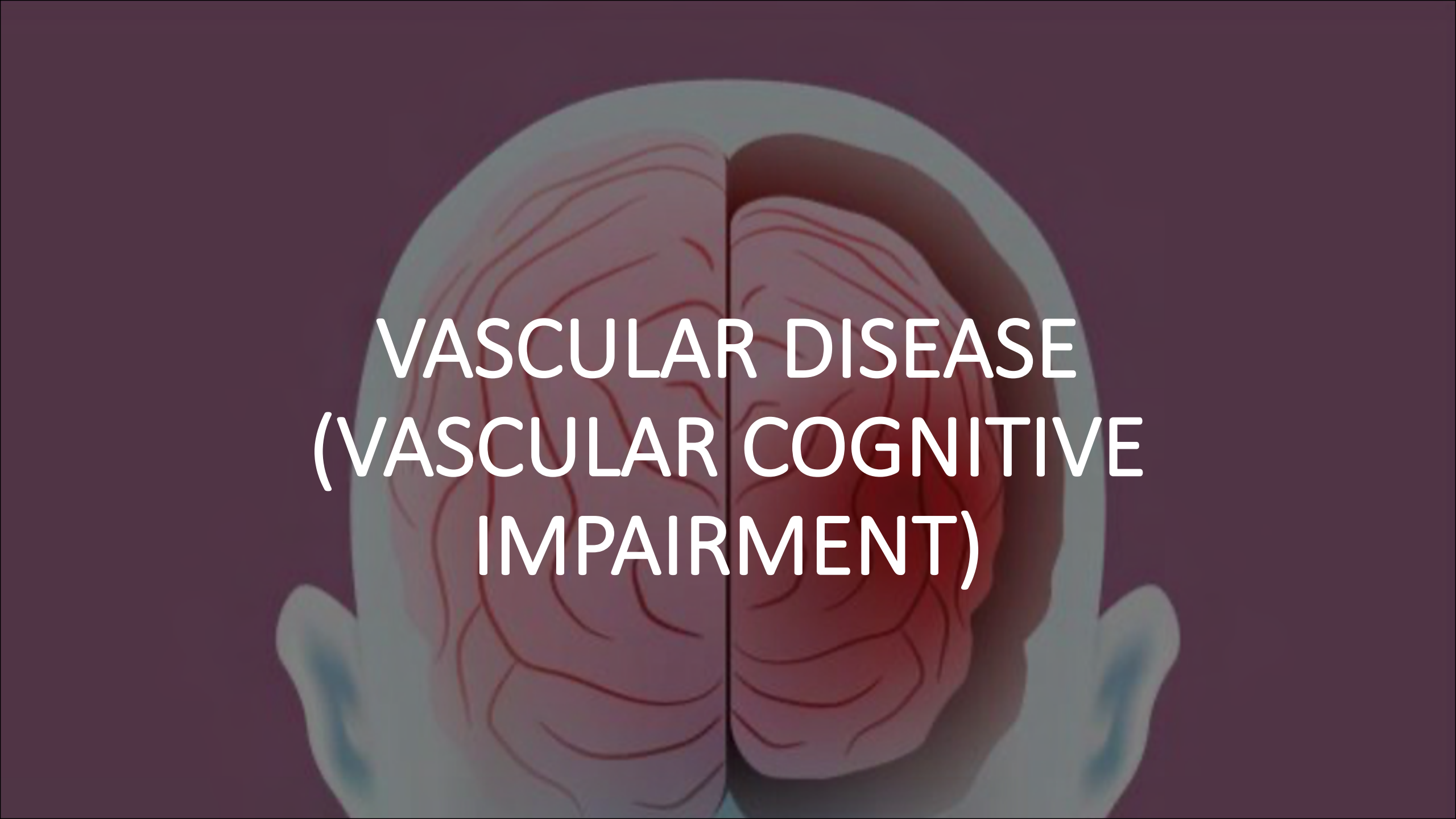
2. Non-cognitive Sx:
    1. Behavioral, ex: apathy, agitation
    2. Mood disorders
    3. Paranoia

Diagnosis

- Perform a comprehensive clinical evaluation
- A diagnosis of possible NCD due to AD is made based on the presence of characteristic clinical findings:
  - Insidious onset.
  - Gradual progression.
  - Impairment in one (mild NCD) or more (major NCD) cognitive
  - domains.
- Assess for reversible causes of cognitive impairment
- Obtain laboratory tests (for Vit B12, TSH) and neuroimaging (brain MRI) to assess for underlying causes of major neurocognitive disorder.

Treatment

- No cure or truly effective treatment.
- **Cholinesterase inhibitors** (e.g., donepezil, rivastigmine) may slow clinical deterioration.
- **NMDA receptor antagonist:** (e.g, memantine) patients with moderate-to-severe disease.
- Antipsychotic medications: to treat agitation and aggression.
- Supportive care



VASCULAR DISEASE (VASCULAR COGNITIVE IMPAIRMENT)

Vascular dementia

- Vascular dementia (VD) describes gradual cognitive decline caused by small or large vessel disease.

- **Epidemiology**
  - Second most common type of dementia (15–20% of cases)
  - Prevalence increases with age (~ 1–4% in patients ≥ 65 years).

- **Etiology**:
  - VD may occur as a result of a prolonged and severe cerebral ischemia of any etiology

- Risk factors:
  - Hypertension
  - Diabetes mellitus
  - Smoking
  - Hyperlipidemia
  - Advanced age

- **Clinical manifestations:**

Due to large vessel

Multi-infarct dementia: typically, **stepwise deterioration**

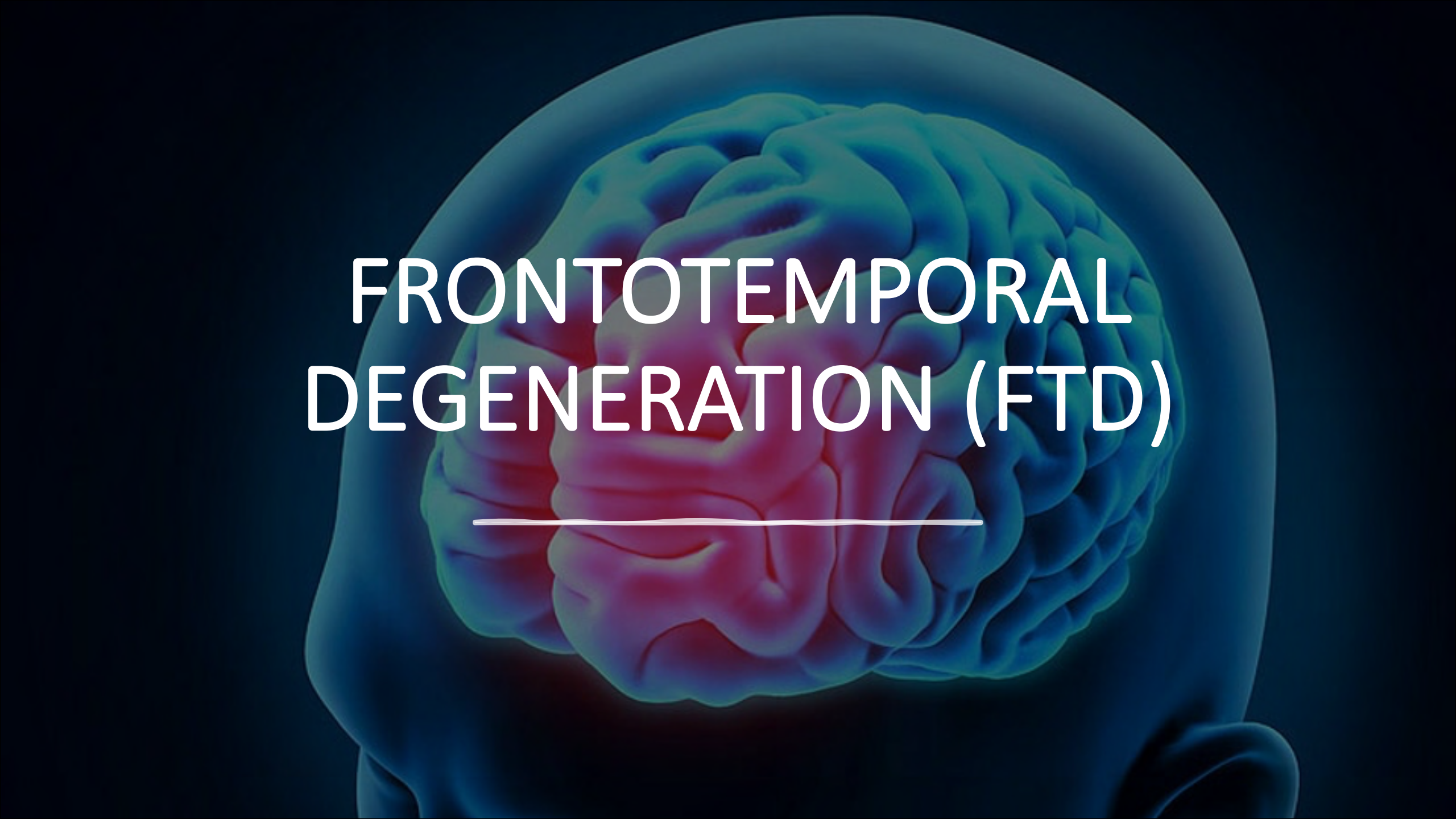
Cognitive impairment

Due to small vessel:

- Reduced executive functioning
- Impaired complex attention

Treatment

- No cure or truly effective treatment.
- Manage risk factors with a goal of preventing future strokes.
- Symptomatic treatment is similar to AD.



FRONTOTEMPORAL DEGENERATION (FTD)

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- Frontotemporal dementia (FTD) is a progressive neurodegenerative disease of the frontal and/or temporal lobe generally caused by mutations to proteins in the brain (e.g., Tau, progranulin).
- FTD includes a diverse group of clinical and pathological disorders that typically present between the ages of 45 and 65.
- Approximately 40% are familial, and 10% are autosomal dominant.
- Marked atrophy of the frontal and temporal lobes.

Etiology

- Generally associated with pathological intracellular inclusion bodies (Pick bodies) that are caused by **mutations in tau** (main protein component of Pick bodies)
  or **progranulin** (precursor of granulin, which regulates cell growth) proteins

• Clinical Manifestations

- Cognitive deficits in:
  - **attention**, **abstraction**, **planning**, and **problem solving**.

- **Behavioral variant:**
  - **Disinhibited** verbal, physical, or sexual behavior.
  - Decline in **social cognition** and/or **executive abilities**.

- **Language variant**
  - Difficulties with **speech** and **comprehension**.

- **Diagnosis:**

  - Definitive diagnosis cannot be made until autopsy.
  - FTD is **probable** if :

  1. frontotemporal atrophy is evident on structural imaging
  2. or hypoactivity is visualized on functional imaging in context of the characteristic clinical signs.

- **Treatment**
  - Symptom-focused.
  - Serotonergic medications (e.g., SSRIs, trazodone) may help reduce disinhibition, anxiety, , repetitive behaviors, and eating disorders.

HIV INFECTION

HIV INFECTION

- HIV is the most common infectious agent known to cause cognitive impairment.
- leads to a complex disease pattern that ultimately results in chronic immunodeficiency.
- HIV can be transmitted sexually, parenterally, or vertically.
- Infection is most common in the young adult population between 20 and30 years of age. The virus infects macrophages and other CD4+ cells, leading to the destruction of CD4 T cells

- **Risk Factors**
- History of severe immunosuppression.
- High viral loads in the CSF.
- Advanced HIV infection.

- **Clinical Manifestations**
  - Variable presentation depending on the part(s) of the brain affected.
  - Decline may be observed in executive functioning, attention, working memory, and psychomotor activity.
  - Psychiatric and neuromotor symptoms may also be present.

- **Diagnosis**
- Mild or major NCD attributable to confirmed HIV infection.
- Elisa, serology

- **Treatment**
- Antiretroviral therapy (ART) improves cognition in some patients.
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
  - e.g: abacavir

- Psychostimulants target fatigue, apathy, and psychomotor retardation.

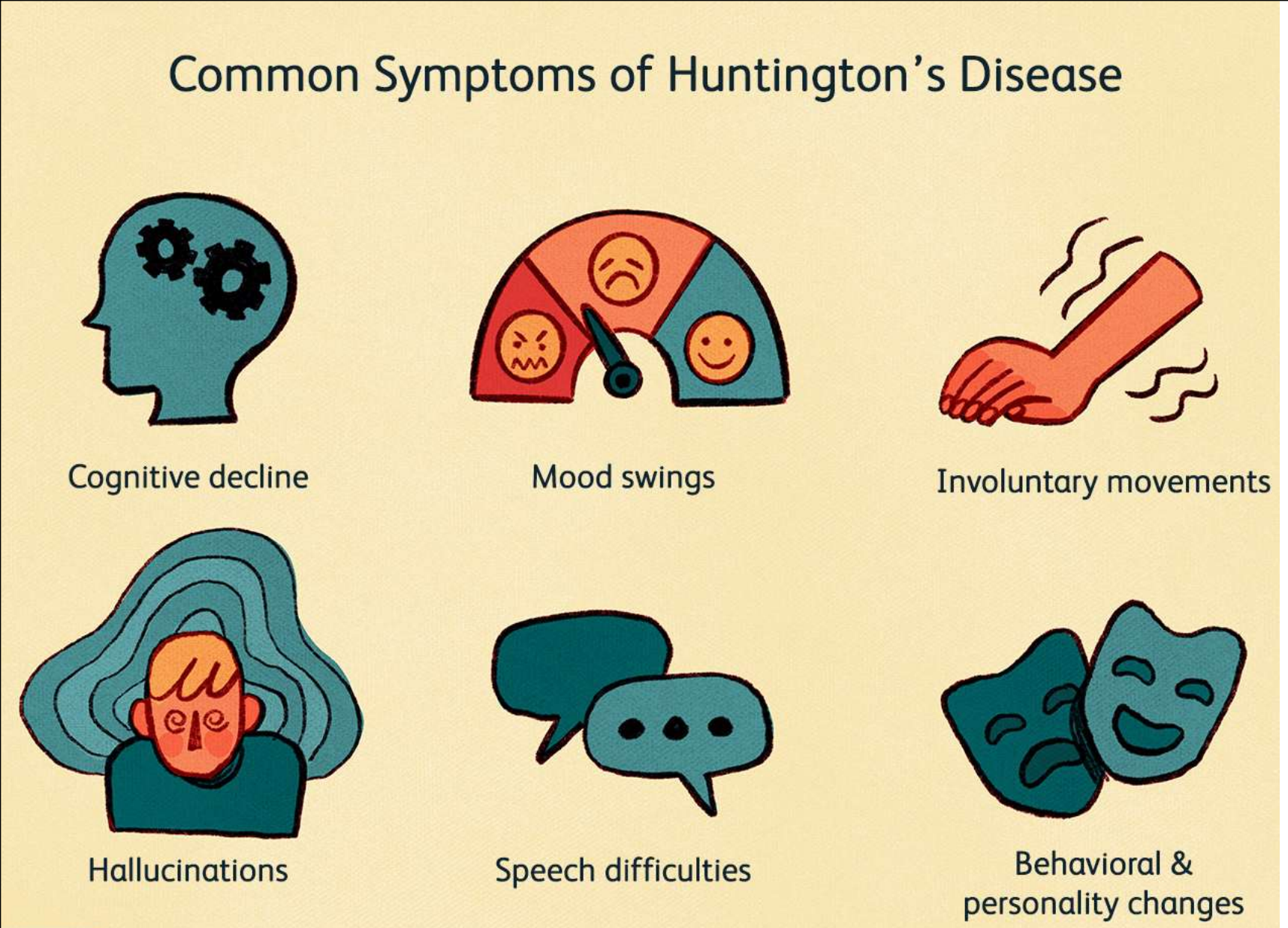
HUNTINGTON DISEASE (HD)

HUNTINGTON DISEASE (HD)

- Is a neurodegenerative movement disorder characterized by involuntary and irregular movements of the limbs, neck, head, and/or face (chorea).
- This autosomal-dominant inherited disease is caused by mutations (increased number of CAG trinucleotide repeats) in the huntingtin gene which eventually leads to the dysfunction of subcortical motor circuits.
- Symptom onset depends on the individual extent of the genetic abnormalities but usually occurs around 40 years of age.

- **Epidemiology:**
- **Peak incidence:** 40 years of age
- One of the most common hereditary diseases of the brain

- **Etiology:**
- **Increased number of CAG repeats,** in the huntingtin gene on **chromosome 4**
- Inheritance (Autosomal dominant)



Clinical Manifestations

Characterized by a triad of:

Motor symptoms.

- **Chorea and bradykinesia**

Cognitive symptoms

- **(decline in executive function)**

- **Psychiatric symptoms (depression, irritability, hallucinations)**

Diagnosis

PATIENT HISTORY

GENETIC TESTING (PCR)

IMAGING: CT, MRI. (RARELY USED)

Treatment

- **Hyperkinetic/choreatic movements**
  - Monoamine-depleting drugs (tetrabenazine)
  - Atypical (2nd generation) antipsychotics.(clozapine)
- **Depression**: SSRIs (e.g., citalopram)

PARKINSON DISEASE (PD)

Parkinson disease

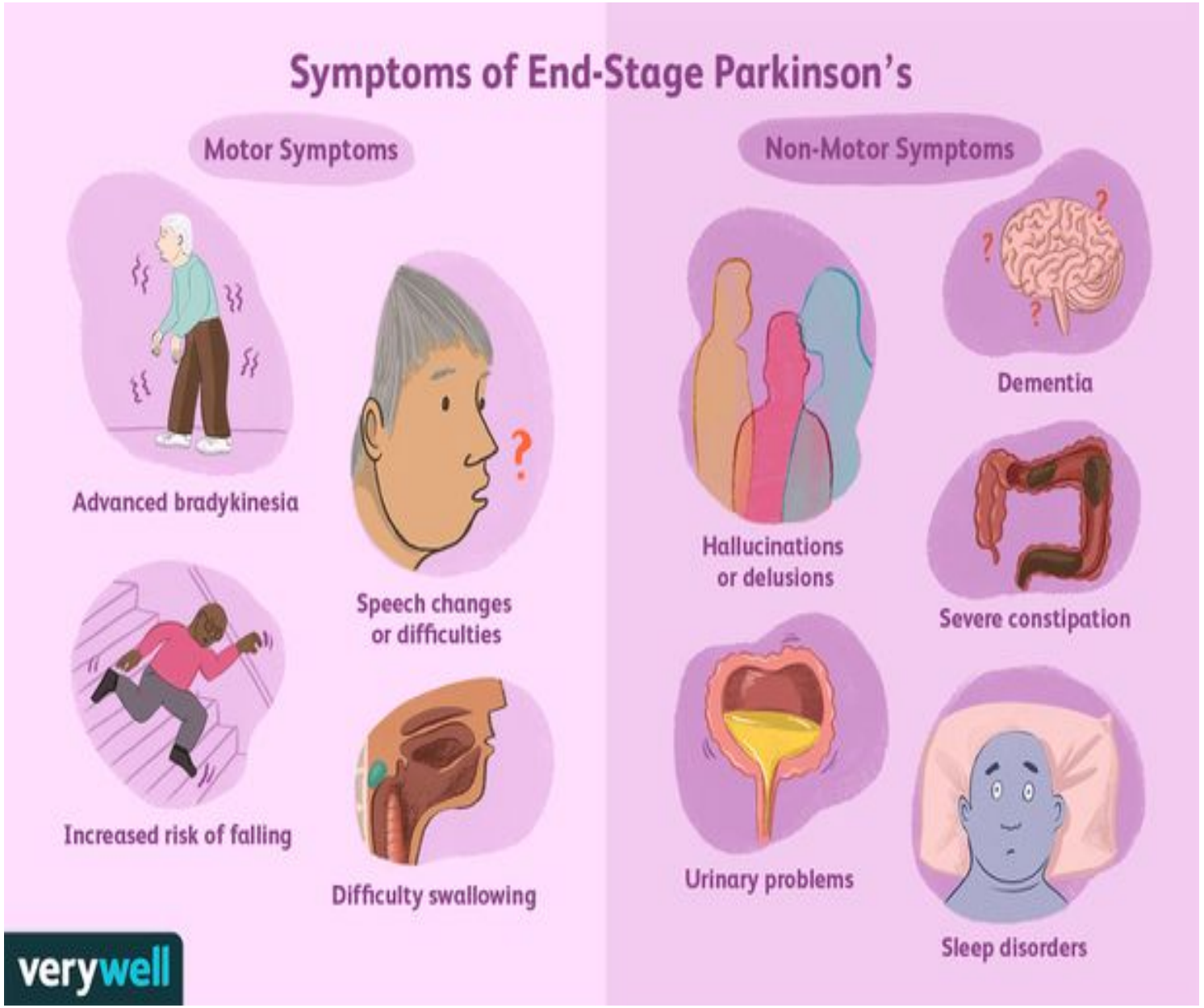
- Parkinson disease (PD) is a neurodegenerative condition that involves the progressive **depletion of dopaminergic neurons in the basal ganglia**, particularly the substantia nigra.

- It's the second most common neurodegenerative disorder following Alzheimer disease

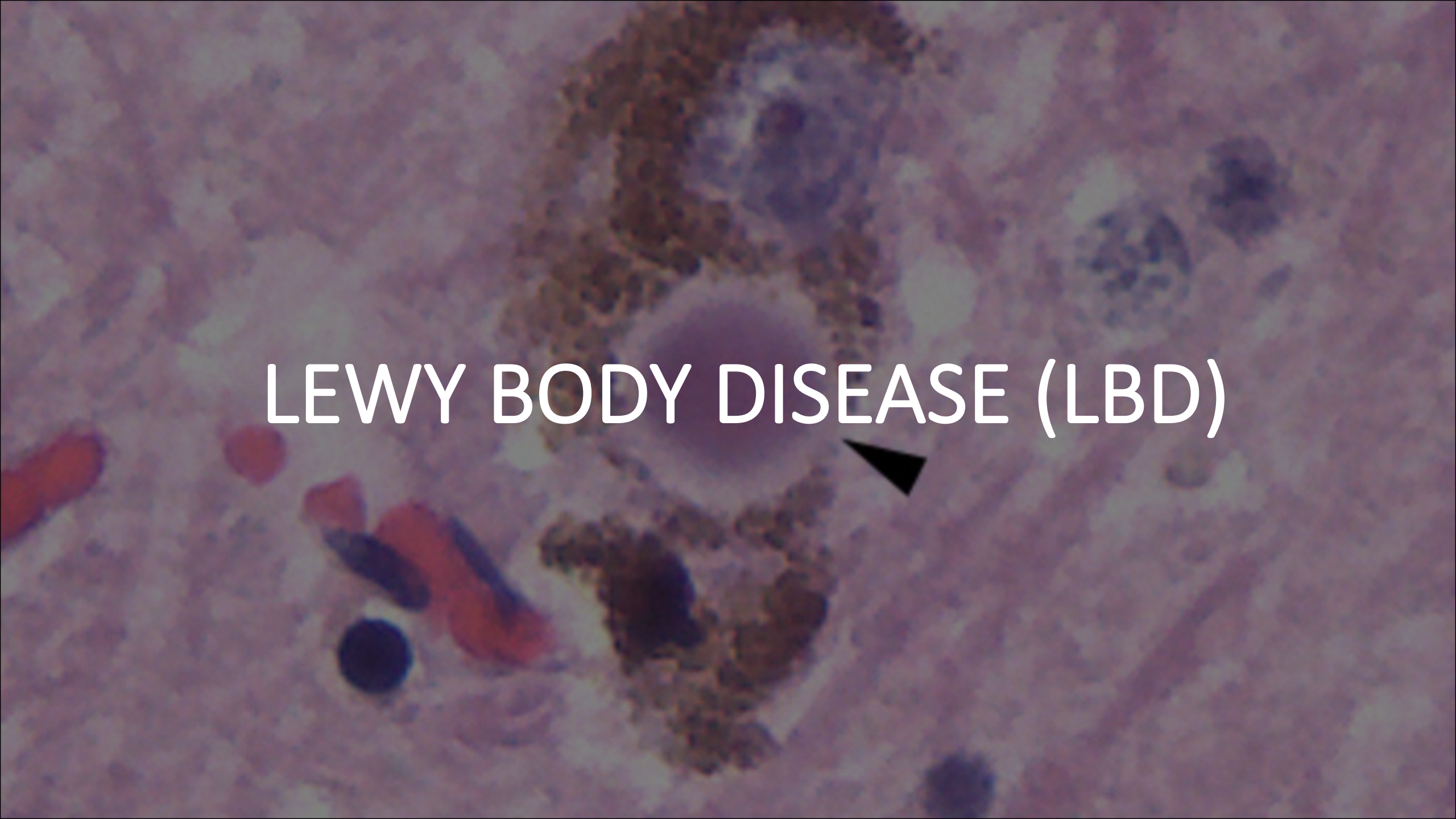
Age of onset: ~ 60 years in sporadic cases

Clinical Manifestations

- **Motor**: rigidity, resting tremor, bradykinesia, and postural instability.
- **Psychotic symptoms**: visual hallucinations and paranoid delusions.
- **Cognitive:** executive dysfunction and visuospatial impairments.
- Depression, anxiety, personality changes



- **Diagnosis**
  - Diagnosis of PD requires the presence of **bradykinesia** and either **tremor** or **rigidity**.
  - Associated with asymmetry of motor symptoms and favorable response to dopaminergic therapy.
  - Mild or major NCD is attributed to PD if **cognitive decline appears after the onset of motor symptoms** and no other underlying etiology is identified.
- **Treatment**
  - ■ Motor symptoms are most commonly treated with **carbidopa-levodopa** and/or **dopamine agonists**.



LEWY BODY DISEASE (LBD)

Lewy body dementia

- Dementia with Lewy bodies is a less common type of dementia. It is closely related to both Alzheimer's disease and Parkinson's disease.

- Lewy bodies are tiny clumps of protein that develop inside nerve cells. They prevent the cells from communicating properly by disrupting the important chemical messengers between them, eventually causing the cells to die.

Clinical Manifestations

- **CORE FEATURES:**
  - **Waxing and waning** of cognition
  - **Visual hallucinations**
  - **Rapid eye movement** (REM) **sleep behavior disorder (**violent movements during sleep in response to dreams)
  - Development of **extrapyramidal signs** (Parkinsonism)

- Indicative biomarkers:
  - REM sleep without atonia (RWSA) demonstrated via polysomnography.
  - Evidence of reduced dopamine receptor uptake in the basal ganglia via SPECT or PET

Diagnosis

- Definitive diagnosis can only be made with autopsy.

- **Possible** NCD with Lewy bodies: Only one core feature without evidence from indicative biomarkers OR one or more indicative biomarker(s), but no core clinical features.

- **Probable** NCD with Lewy bodies: Two or more core features OR one core feature and one or more indicative biomarker(s).

Treatment

- **Cholinesterase inhibitors** for cognitive and behavioral symptoms.
- **Quetiapine** or **clozapine** for psychotic symptoms.
- Levodopa-carbidopa for Parkinsonism.
- Melatonin and/or clonazepam for REM sleep behavior disorder.

PRION DISEASE

PRION DISEASE

- A form of subacute spongiform encephalopathy caused by proteinaceous infectious particles (prions).
- Most cases occur sporadically.
- The most common type is **Creutzfeldt–Jakob disease**.
- Up to 15% are familial (autosomal dominant).

Clinical Manifestations

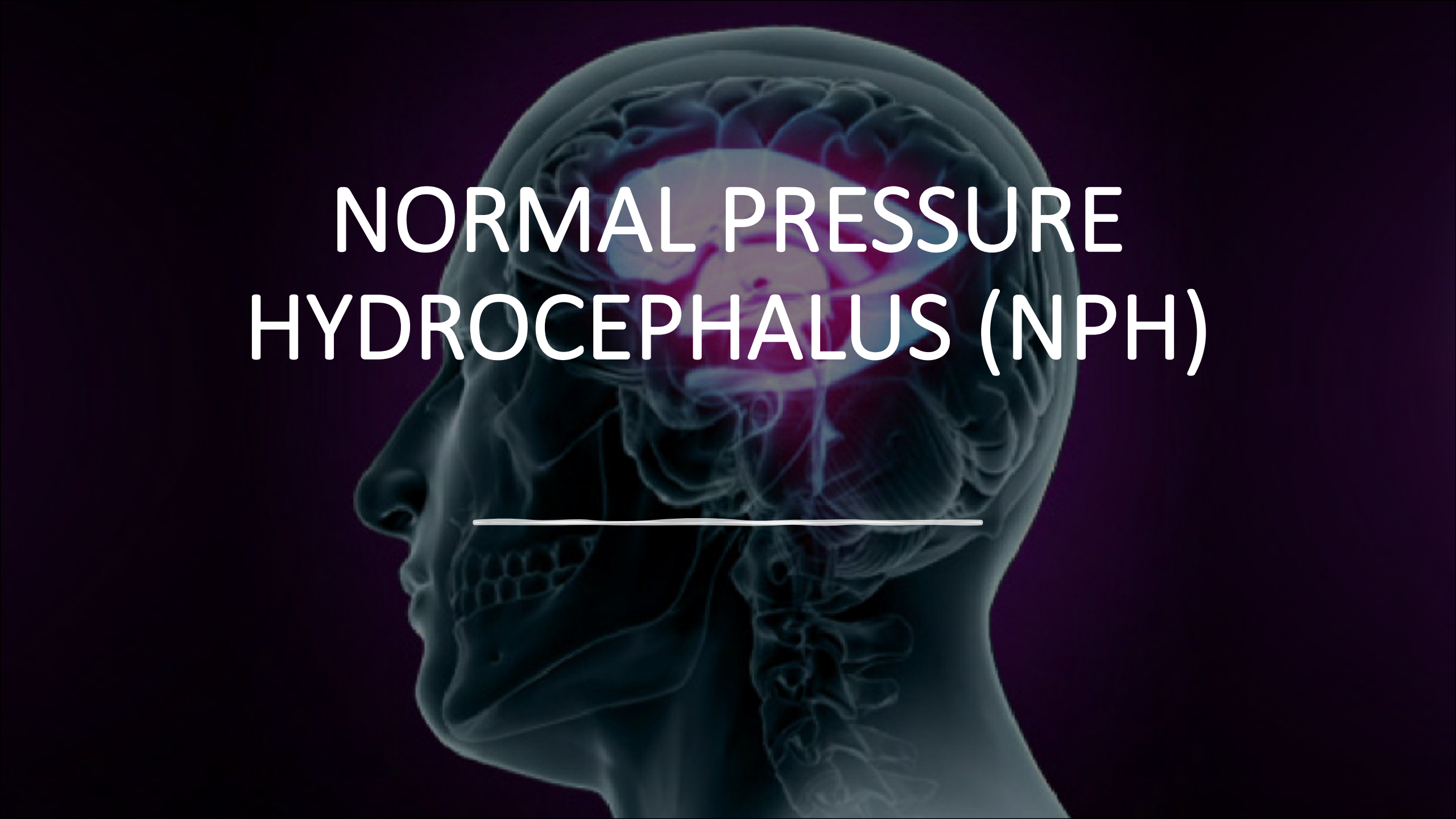
- rapidly progressive cognitive decline
- Difficulties with concentration, memory, and judgment.
- Myoclonus in 90% of patients
- Ataxia, nystagmus, and hypokinesia

Diagnosis

- Definitive diagnosis requires analysis of brain tissue obtained via biopsy or autopsy
- A diagnosis of probable CJD requires:
  - Rapid progression of cognitive decline.
  - At least two of the following typical clinical features:
    - Myoclonus.
    - Visual or cerebellar signs.
    - Pyramidal or extrapyramidal signs.
    - Akinetic mutism.
- Supportive findings from at least one diagnostic modality:
  - CSF positive for 14-3-3 proteins.
  - Lesions in the putamen or caudate nucleus on MRI.

Treatment

- Supportive
- No effective treatment exists.
- Most individuals die within 1 year of diagnosis.



NORMAL PRESSURE HYDROCEPHALUS (NPH)

NPH

- NPH is a potentially reversible cause of cognitive dysfunction.
- Enlarged ventricles (on imaging) with a **localized elevation** of cerebrospinal fluid (CSF) pressure but **normal opening pressures** on lumbar puncture.
- The etiology is either **idiopathic** or secondary to obstruction of CSF reabsorption sites due to infection (meningitis) or hemorrhage (subarachnoid or intraventricular).

Clinical manifestations

- **Gait disturbance** (“Wobbly”).
  - Most likely to be the first manifestation.
  - Slow with short steps.
  - Broad-based with outwardly rotated feet.

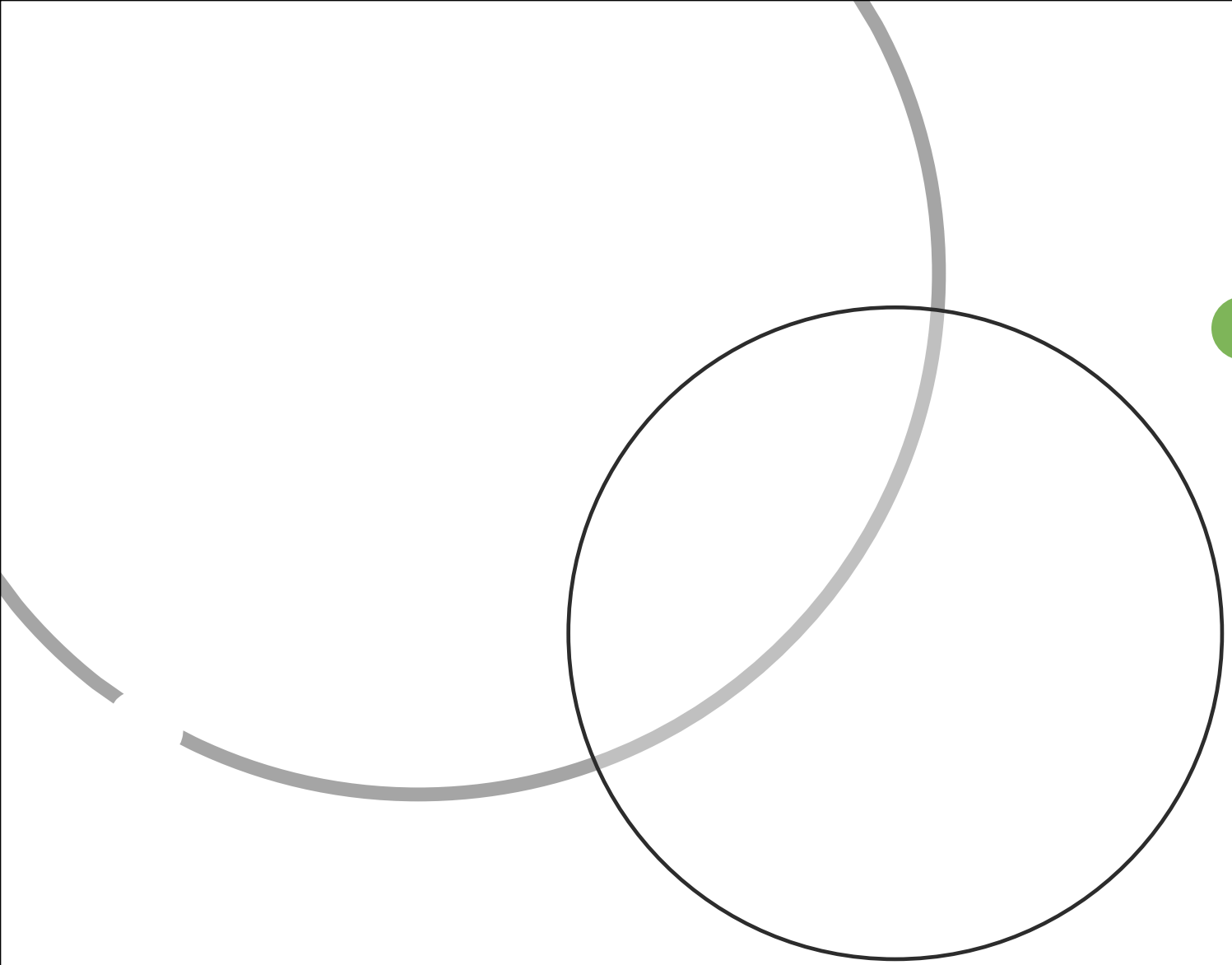
- **Urinary incontinence** (“Wet”).
  - May begin as urinary urgency.
  - In later stages, apathy may contribute

- **Cognitive impairment** (“Wacky”).
  - Insidious onset.
  - Executive dysfunction.
  - Psychomotor retardation.

- Neuroimaging shows enlargement of ventricles out of proportion to cortical atrophy.

Treatment

- Placement of a shunt (usually ventriculoperitoneal) may improve symptoms.
- Cognitive impairment is least likely to improve.



Thank you

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