NOTES
DEMENTIA

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Acquired, progressive cognitive impairment
- Involving one/more cognitive functions
  - Memory, concentration, language, learning, praxis, judgment, executive functions, social cognition
- Previous functional-level deterioration; consciousness remains intact

CAUSES

- Increasing age; most important risk factor
- Alzheimer disease
- Vascular dementia including multi-infarct dementia, Binswanger's disease
- Lewy body dementia (DLB)
- Frontotemporal dementia (e.g. Pick disease)

COMPLICATIONS

- Inability to function independently in everyday life
- Debilitated state infections (death secondary)
- See mnemonic for summary

MNEMONIC: DEMENTIA

Common causes of Dementia

Diabetes
Ethanol
Medication
Environmental (eg CO poisoning)
Nutritional
Trauma
Infection
Alzheimer's

SIGNS & SYMPTOMS

- Memory loss, difficulty retaining new information
- Language impairment
- Executive dysfunction
  - Difficulty in handling complex tasks, concentration loss, poor judgement
- Visuospatial ability impairment
- Apraxia (inability to perform an action)
- Behavioral disturbance
- Personality change

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Reveals microinfarcts indicative of vascular dementia

OTHER DIAGNOSTICS

- Mental status examination
  - Identify cognitive impairment with standardized mental status scales
- Montreal cognitive assessment (MoCA), mini-mental state examination (MMSE)
- Neuropsychological testing
  - Quantitate cognitive impairment degree/ domains involved (e.g. animal-naming test)
- Post-autopsy brain biopsy

TREATMENT

- Treatment/control of reversible causes

MEDICATIONS

- Acetylcholinesterase inhibitors
  - ↑ acetylcholine (brain's primary neurotransmitter) levels; used for Alzheimer disease, DLB
- Memantine
  - N-methyl-D-aspartate (NMDA) receptor antagonist (neuroprotective, disease-modifying drug) for advanced dementia

ALZHEIMER'S DISEASE (AD)

osms.it/alzheimers-disease

PATHOLOGY & CAUSES

- Neurodegenerative disease; beta amyloid plaque, neurofibrillary tangle formation → impaired neuronal signaling, neuron apoptosis
- Most common form of dementia
- Sporadic (95% of cases), typically > 60 years old
  - Early AD onset unusual, mostly familial
- Amyloid precursor protein (APP)
  - Normally located in neuronal membrane
  - Growth, neuron-repair contributor
  - Abnormal APP degradation via beta secretase (normally degraded by gamma, alpha secretase) → APP cut into insoluble fragments → create beta amyloid plaque → AD results
  - *Beta amyloid plaque pathology:* signalling obstruction → deposits around vessels (amyloid angiopathy), ↑ hemorrhage risk → initiates inflammatory response
- Tau proteins
  - Intracellular microtubule-associated proteins
  - In AD, Tau proteins become pathologically hyperphosphorylated → aggregate, stop supporting microtubules → form neurofibrillary tangles → obstruct neuronal signaling → neuron apoptosis

RISK FACTORS

- ↑ age (> 60 years old → risk doubling every five years)
- Family history
- Trisomy 21 (Down syndrome)
- Gene mutations affecting APP, presenilin 1 and 2 (gamma secretase subunits)
- Apolipoprotein E-e4 alleles (ApoEe4)
  - ApoE normally breaks down beta amyloid, e4 alleles encode less effective ApoE
- History of hypertension, dyslipidemia, cerebrovascular disease, altered glucose metabolism, brain trauma

COMPLICATIONS

- Complete debilitation, dependence on others
- Debilitation → dehydration, malnutrition, infection
- Death occurs 5–10 years after symptoms onset

MNEMONIC: RONALD

Features of AD

Reduction of Ach
Old age
Neurofibrillary tangles
Atrophy of cerebral cortex (diffuse)
Language impairment
Dementia (MC in elderly)/ **D**own's syndrome

SIGNS & SYMPTOMS

- Insidious onset, symptom progression

Early stages

- Initial symptom
  - (Commonly) recent memory impairment; inability to acquire, remember new information
- Executive dysfunction
  - Impaired reasoning, handling complex tasks, concentration/motivation loss, difficulty making/executing plans, poor judgement
  - Impaired visuospatial skills
  - Reduced insight into cognitive deficit (anosognosia)
  - Sleep disturbance

Intermediate/later stages

- Behavioral, psychological symptoms
  - Apathy, social disengagement, irritability, agitation, aggression, wandering, psychosis (hallucination, delusion)
- Motor task completion
  - Difficulty (dyspraxia)/inability (apraxia)
  - Impaired language function (e.g. word-finding deficit)
  - Remote memory loss
  - Seizure
  - Motor signs (e.g. pyramidal signs)

Advanced

- Complete debilitation, dependence on others, urinary/fecal incontinence

DIAGNOSIS

- Diagnosis of exclusion

DIAGNOSTIC IMAGING

CT scan/MRI

- Exclude other dementia causes
- Brain scans show diffuse cortical (especially hippocampus) atrophy, gyri narrowing, sulci widening, ventricle enlargement

MNEMONIC: ALZHEIMER'S

Characteristics of AD

Anterograde amnesia
Life expectancy increase in population shows increased prevalence
Zapped (loss of) acetylcholinergic neurons
Hereditary disease
Entire hippocampus affected
Identified by neurofibrillary tangles
Mutation in amyloid genes
Entorhinal areas degenerate first
Retrograde amnesia
Senile plaques at synapse

OTHER DIAGNOSTICS

- Mental status scale clinical assessment (e.g., MoCA, MMSE)
- Neuropsychological testing
  - Confirm cognitive impairment diagnosis
- Post-autopsy brain biopsy
  - Shows characteristic beta-amyloid plaque, neurofibrillary tangle

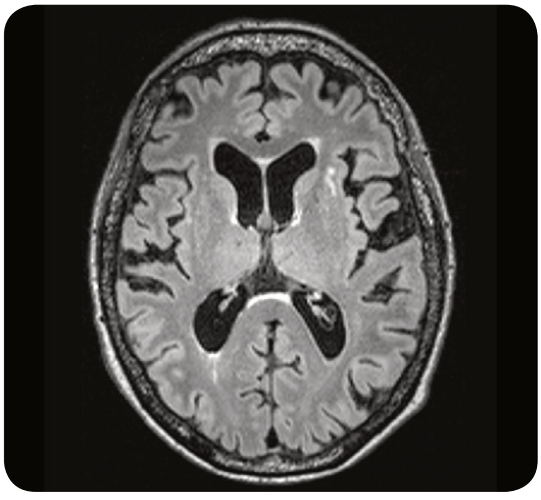

Figure 72.1 An MRI scan in the axial plane demonstrating prominent sulci and gyri in an individual with Alzheimer's disease.

TREATMENT

- No cure

MEDICATIONS

- Acetylcholinesterase inhibitors
- Vitamin E supplementation may provide benefit
- Memantine (advanced stages)

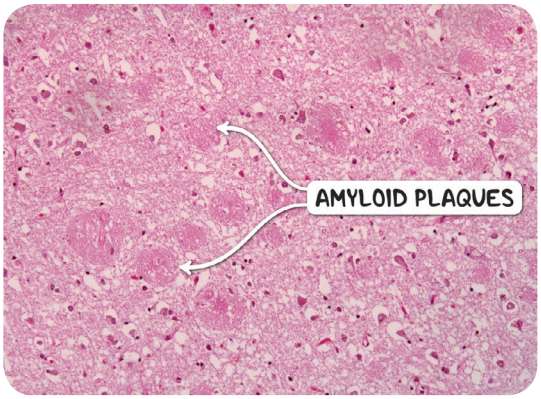

Figure 72.3 A histological section of brain from an individual with Alzheimer's disease demonstrating multiple amyloid plaques.

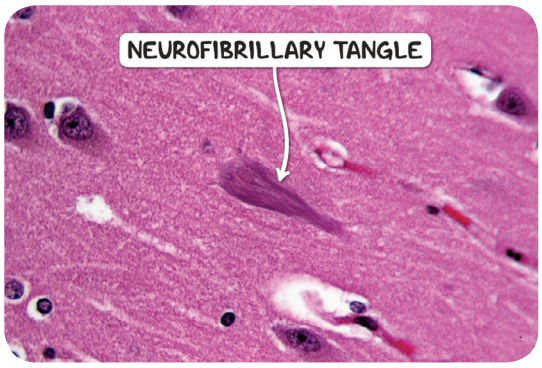

Figure 72.2 A histological section of the hippocampus from an individual with Alzheimer's disease demonstrating a neurofibrillary tangle.

LEWY BODY DEMENTIA

osms.it/lewy-body-dementia

PATHOLOGY & CAUSES

- Degenerative disease
  - Early dementia, visual hallucinations onset; later parkinsonian clinical feature onset, presence of Lewy bodies
- Occurs at 50–85 years old (typically)
- More rapid cognitive decline than AD

CAUSES

- Alpha-synuclein protein aggregation in neurons (particularly cortex, substantia nigra) forming Lewy bodies, → apoptosis

COMPLICATIONS

- Persistent psychotic symptoms, especially visual hallucinations
- Depression
- Complete debilitation, dependence on others
- Debilitation infection often → death; life expectancy ↓
- Neuroleptic-agent sensitivity
  - Adverse effects (parkinsonism) ↑ severity, symptom exacerbation

SIGNS & SYMPTOMS

Early stages

- Progressive, fluctuating cognitive function impairment
  - Attention, executive, visuospatial functions; memory affected later
- Visual hallucination, disorganized speech, depression

Later stages

- Motor symptoms mimic Parkinson's disease
  - Resting tremor, stiffness, slow movement, reduced facial expressions

Other clinical features

- Rapid eye movement (REM) sleep behavior disorder
  - Sleep disturbance (sleep walking, talking)
- Autonomic nervous system dysfunction
  - Orthostatic hypotension, syncope, urinary incontinence/retention, constipation, impotence
- Repeated falls (parkinsonism), cognitive fluctuation/orthostatic hypotension
- Neuroleptic sensitivity

DIAGNOSIS

- Exclude other dementia causes

DIAGNOSTIC IMAGING

Single-photon emission computerized tomography (SPECT) scanning

- Dopamine transporter ligand ioflupane I-123 (DaTSCAN) shows ↓ transporter perfusion

OTHER DIAGNOSTICS

- Neuropsychological testing
  - Confirms cognitive-impairment diagnosis
- Mental status scale assessment (e.g. MoCA, MMSE)
- Post-autopsy brain biopsy
  - Shows Lewy bodies as eosinophilic intracytoplasmic inclusions in cortical neurons

TREATMENT

- No cure

MEDICATIONS

Alleviate symptoms

- Acetylcholinesterase inhibitors
  - Cognitive symptoms
- Dopamine analogue
  - Motor symptoms
- Atypical neuroleptic agents
  - Persistent disabling hallucinations, psychotic features (used very cautiously)

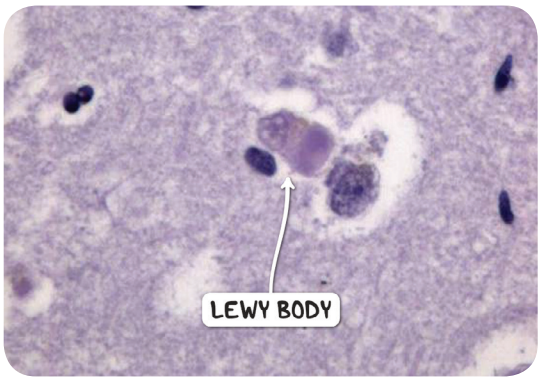

Figure 72.4 A histological section of the brain demonstrating a Lewy body. They are caused by the abnormal deposition of the protein alpha synuclein.

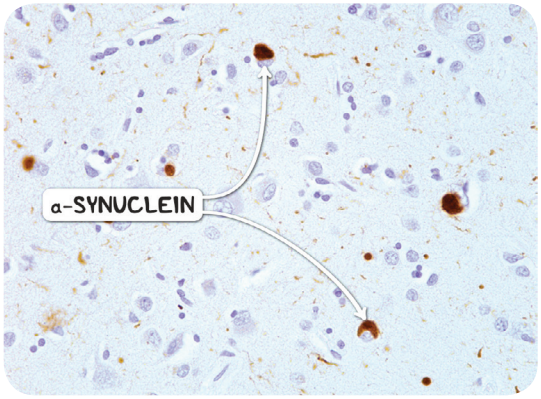

Figure 72.5 Immunohistochemical tain for the protein alpha synuclein highlights the Lewy bodies in the brain tissue of an individual with Lewy body dementia.

FRONTOTEMPORAL DEMENTIA (FTD)

osms.it/frontotemporal-dementia

PATHOLOGY & CAUSES

- Heterogeneous degenerative frontal/temporal lobe disease
  - Presents with personality/behavioral disturbances/aphasia
- Occurs < 65 years old (typically)
  - Memory loss develops later
- Inherited/sporadic
- Associated with specific-protein cellular inclusions
  - Tau proteins (Pick disease)
  - TAR DNA-binding protein 43 (TDP43)
- Protein buildup → stop neuronal signaling, lead neurons to apoptosis
- *Concomitant motor disease:* 15–20% (e.g. parkinsonism, motor neuron disease)

SIGNS & SYMPTOMS

- Frontal lobe involvement → behavior/emotional changes
- Disinhibition, emotional blunting, apathy/empathy-loss, hyperorality, compulsive behavior, family/friend dissociation (argumentative/hostile behavior)
- Temporal lobe involvement → language impairment, emotional disturbance
- Difficulty finding correct word, progressive aphasia, impaired word comprehension, emotional impairment (anxiety/irrational fear), sarcasm-recognition difficulty
- Later stages → cognitive decline
- Worsening memory, inability to learn new things, concentration loss

TYPES

Pick disease

- Specific pathological FTD subtype characterized by presence of Pick bodies (tangles of abnormal Tau proteins—3R tau isoforms)
  - 3R tau isoforms (particular amino-acid sequence repeated three times) are hyperphosphorylated, stop supporting microtubules, tangle into round silver-staining inclusion bodies (Pick bodies)

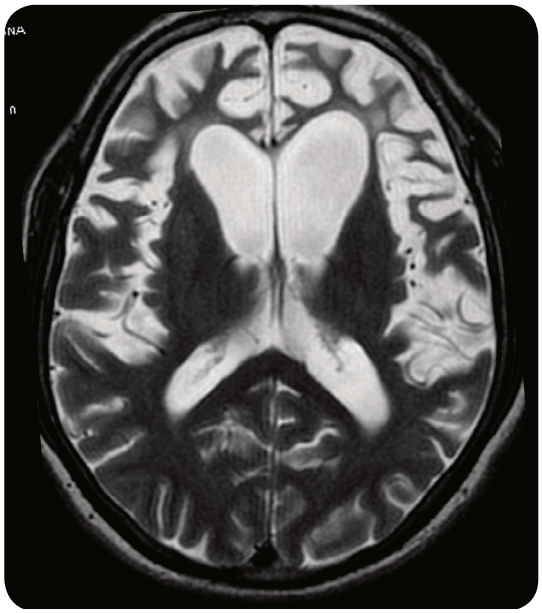

Figure 72.6 An MRI scan of the head in the axial plane demonstrating frontotemporal volume loss.

DIAGNOSIS

- Exclude other dementia causes
  - Laboratory, imaging tests

DIAGNOSTIC IMAGING

MRI

- Structural imaging
- Unilateral frontal/temporal atrophy, may → both hemispheres, ventricle enlargement

SPECT/perfusion-MRI/PET

- Functional imaging
- Affected-lobe hypometabolism, hypoperfusion

LAB RESULTS

Genetic testing

- Familial FTDs

Pick disease-specific biopsy findings

- Pick bodies
  - Round/oval, Tau-positive, neuronal cytoplasmic inclusions
- Pick cells
  - Swollen (ballooned) neurons

OTHER DIAGNOSTICS

- Neuropsychological tests
  - Normal in early stages
- Mental status scale assessment (e.g. MoCA, MMSE)
- Post-autopsy brain biopsy shows characteristic microscopic findings
  - Microvacuolation, neuronal loss, swollen neurons, myelin loss, astrocytic gliosis, abnormal protein inclusions

TREATMENT

- No cure

MEDICATIONS

Symptom alleviation

- Antidepressants
  - Severe behavioral symptoms
- Atypical antipsychotic drugs have significant side effects
- Cholinesterase inhibitors
  - No convincing evidence of benefit

OTHER INTERVENTIONS

- Physical exercise; physical, occupational, speech therapy; ↑ supervision

MNEMONIC: PICK

Features of Pick disease

Progressive degeneration of neurons
Intracytoplasmic Pick bodies
Cortical atrophy
Knife edge gyri

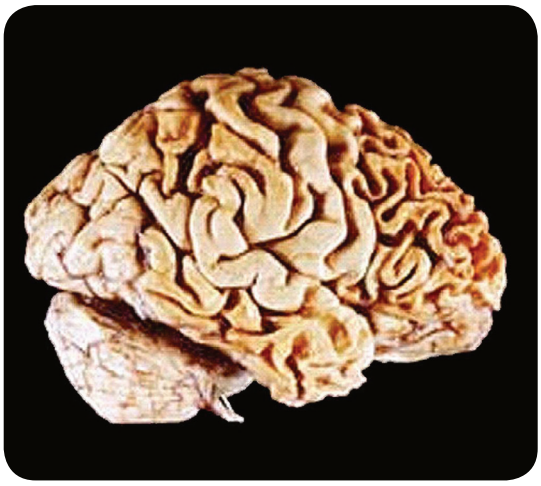

Figure 72.7 A brain at post mortem with frontotemporal degeneration.

VASCULAR DEMENTIA

osms.it/vascular-dementia

PATHOLOGY & CAUSES

- Heterogenous dementia
  - Results from multiple cerebrovascular events/chronic ischemia
- Second most common dementia cause in elderly
- High Alzheimer disease comorbidity
- Multiple, bilateral, cortical, subcortical infarcts/chronic ischemia → ↓ brain blood supply → stepwise cognitive function decline, gait abnormality, focal neurological deficits
  - Prominent executive function deficit
  - Late-onset memory impairment
- Binswanger's disease
  - Large subcortical white matter areas involved

CAUSES

- Cerebral artery atherosclerosis
- Carotid artery/heart embolization
- Chronic hypertension → cerebral arterioles sclerosis
- Vasculitis

RISK FACTORS

- Smoking, hypertension, diabetes, insulin resistance, hyperlipidemia, hyperhomocysteinemia

SIGNS & SYMPTOMS

- Progressive, stepwise cognitive function impairment (affected cortical area-dependent)
  - *Frontal:* executive dysfunction (frontal)
  - *Left parietal:* aphasia, apraxia, agnosia
  - *Right parietal:* hemineglect, confusion, agitation, visuospatial, constructional difficulty
  - *Temporal:* anterograde amnesia
- Deficits due to subcortical infarcts
  - Focal motor signs
  - Gait disturbance
  - Urinary frequency/urgency
  - Personality, mood change
  - Relatively mild memory deficit
  - Improvements may occur between cerebrovascular events

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI/CT scan

- Show multiple cortical, subcortical infarcts
- Microinfarcts identified
  - Initiate evaluation to define etiology
  - *Carotid Doppler ultrasound:* reveal carotid plaques
  - *Echocardiogram:* reveal cardiogenic emboli

OTHER DIAGNOSTICS

- Neuropsychological testing
  - Detects cognitive impairment, domains involved
  - Similar language, construction, memory registration deficits with AD, but more impaired executive functioning
- Microinfarcts identified
  - Initiate evaluation to define etiology
  - Holter monitor (detect arrhythmias)
  - Risk factor screening

TREATMENT

- No cure

MEDICATIONS

- Vascular risk factor control
  - Antihypertensive drugs, antidiabetic agents, statins, antiplatelet agents
- Acetylcholinesterase inhibitors/memantine

OTHER INTERVENTIONS

- Vascular risk factor control
  - Lifestyle changes

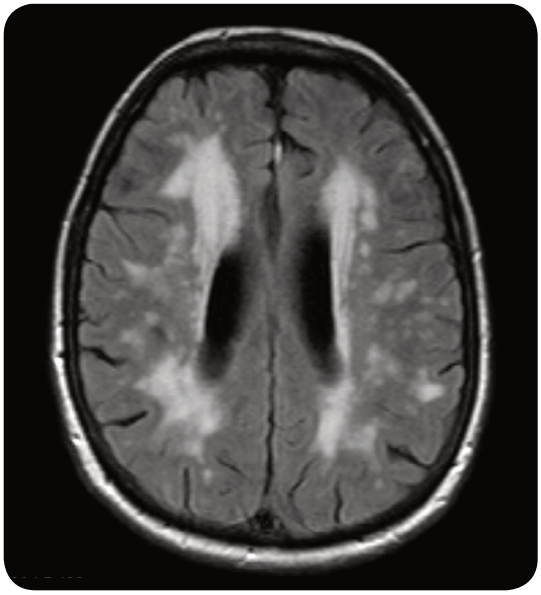

Figure 72.8 An MRI scan in the axial plane of the head of an individual with cognitive impairment. There are multiple small white matter infarcts and an absence of cortical atrophy.