DEMENTIA

Case

A 69-year-old man is brought to his primary care physician by his wife, who complains that his memory has been failing for the past several months. She states that the patient forgets the names of friends and family members and loses his way back home from the grocery store, and that in general he is unable to remember new information he acquires. Previously, he was "meticulous" about remembering his appointments and taking his medication. Now, he has to be reminded each and every time by his wife. The wife also reports that the patient's behavior is much more disorganized—he recently put his cell phone in the freezer and his shoes in the bathtub.

Case

His current medical problems include hypertension, which is well controlled with medication. On mental status examination, the patient is alert but oriented only to person and place. He does not remember his physician's name, although he has seen the same physician for more than 3 years. Some mild aphasia is noted, and the patient can recall only one out of three objects in 5 minutes.

Cognitive disorders

Cognition includes:

- memory
- language
- orientation
- judgement
- conducting interpersonal relationships
- performing actions (praxis)
- problem solving

Cognitive disorders reflect disruption in one or more of these domains and are frequently complicated by behavioral symptoms.

Dementia

- **Dementia** refers to a disease process marked by progressive cognitive impairment in clear consciousness.
- The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) describes dementia, now subsumed under the term **major neurocognitive disorder**, as significant cognitive impairment in one or more of the domains of complex attention, executive function, learning and memory, language, perceptual motor ability, and social cognition.
- These deficits represent a decline from a previous level of functioning, so dementia does not refer to low intellectual functioning or mental retardation that are developmental and static conditions.

DSM-5 Criteria for Major Neurocognitive Disorder

A. Significant cognitive decline from a previous level of functioning in one or more cognitive domains, as evidenced by:

1. Concern from the individual, the clinician or another knowledgeable informant that there has been significant cognitive decline
2. Significant impairment in cognitive performance, ideally seen on standardized neuropsychological testing, or if that is not available, another clinical assessment

B. Cognitive deficits interfere in independence in daily activities

C. The deficits do not occur exclusively during the course of a delirium

D. The deficits cannot be explained by another mental disorder

- In DSM-V, a less severe form of dementia called **mild neurocognitive disorder** is listed.
- Mild neurocognitive disorder requires modest cognitive decline, as well as a lack of interference in activities required for independent living, although greater effort or compensatory mechanisms may be necessary to maintain this independence.

Epidemiology

- 5% in the general population > 65 years of age
- 20-40% > 85 years of age

- 15-20% in outpatients general medical practices
- 50% in chronic care facilities

Etiology

The most common causes of dementia in individuals older than 65 years of age are:

- Alzheimer's disease 50-60%
- Vascular dementia 15-30%
- Mixed vascular and Alzheimer’s dementia 10-15%

Other illnesses that account for approximately 10% include:

- Lewy body dementia
- Frontotemporal dementias
- Normal-pressure hydrocephalus (NPH)
- Alcoholic dementia
- Infectious dementia (e.g. HIV or syphilis)
- Parkinson’s disease

Possible etiologies of dementia

Neurodegenerative

- Alzheimer disease
- Dementia with Lewy bodies
- Frontotemporal dementia
- Parkinson disease
- Huntington disease
- Corticobasal syndrome
- Progressive supranuclear palsy
- Prion disease (Creutzfeldt–Jakob disease, bovine spongiform encephalitis)

Vascular

- Infarction
- Binswanger disease
- Hemodynamic insufficiency

Neurological disease

- Multiple sclerosis
- Normal-pressure hydrocephalus
- Brain tumor (primary or metastatic)

Possible etiologies of dementia

Endocrine

- Hypothyroidism
- Hypercalcemia
- Hypoglycemia

Nutritional

- Vitamin B12 deficiency
- Thiamine deficiency
- Niacin deficiency

Infectious

- Human immunodeficiency disease
- Neurosyphilis
- Cryptococcus

Metabolic

- Hepatic insufficiency
- Renal insufficiency
- Wilson disease
- Metachromatic leukodystrophy
- Neuroacanthosis

Possible etiologies of dementia

Traumatic

- Subdural hematoma
- Chronic traumatic encephalopathy/dementia pugilistica

Exposure

- Alcohol
- Heavy metals
- Irradiation
- Anticholinergic medications
- Carbon monoxide

CLINICAL EVALUATION

- Mental Status Examination
- Physical Examination
- Laboratory Tests
- CT/MRI
- Brain Biopsy
- Neuropsychological Testing

History Taking

The clinician should obtain a detailed information of changes in the patient's daily routine involving such factors as:

- self-care
- job responsibilities and work habits
- meal preparation
- shopping
- interactions with friends
- hobbies and sport
- reading interests
- religious, social and recreational activities
- ability to maintain personal finances

Basic and Instrumental Activities of Daily Living

Basic Activities of Daily Living

- Ambulation
- Dressing
- Grooming
- Bathing
- Feeding
- Toileting
- Laundry

Instrumental Activities of Daily Living

- Transportation
- Using the telephone
- Meal preparation
- Medication management
- Financial management
- Housekeeping

Evaluation of Cognitive Domains

1. Complex attention

- Does the individual have difficulty paying attention?
- Is the individual easily distracted in environments where there are competing stimuli?
- Does the individual have difficulty retaining newly presented information?
- Are routine tasks taking longer than usual?

Evaluation of Cognitive Domains

2. Executive function

- Does the individual have more difficulty with multitasking?
- Is the individual still able to manage their own finances or medications?
- Is more assistance required to plan out activities or instrumental activities of daily living?
- Is more assistance required to make decisions?
- Is the individual having more trouble in large social situations, or finding them less enjoyable?

Evaluation of Cognitive Domains

3. Learning and memory

- Is the individual having difficulty recalling recent events and activities?
- Is the individual repeating himself or herself more often?
- Is the individual needing to rely more on lists or reminders?
- Is the individual misplacing or losing items?
- Does the individual need more reminders to attend to a particular task?

Evaluation of Cognitive Domains

4. Language

- Is there word finding difficulty?
- Is the individual making more grammatical errors in conversation?
- Is the individual forgetting people's names?
- Is the individual making more generalized, vague statements in response to questions?
- Is the individual using more generalized pronouns as substitutes for particular names of items?

Evaluation of Cognitive Domains

5. Perceptual motor

- Is he or she getting lost when travelling or in familiar environments?
- Is he or she having more difficulty using previously familiar tools and appliances?
- Is he or she having difficulty driving a car?

Evaluation of Cognitive Domains

6. Social cognition

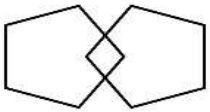
- Has the individual or family members noticed a personality change?
- Does the individual appear to be less empathic or more disinhibited in their speech or behavior?
- Is the individual making sexually, politically, or religiously inappropriate comments?
- Does the individual show a lack of awareness of another's interpersonal space?

MINI MENTAL STATE EXAMINATION (MMSE)

Name:

DOB:

Hospital Number:

One point for each answer	DATE:		
ORIENTATION Year Season Month Date Time	...../ 5	...../ 5	...../ 5
Country Town District Hospital Ward/Floor	...../ 5	...../ 5	...../ 5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	...../ 3	...../ 3	...../ 3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW).	...../ 5	...../ 5	...../ 5
RECALL Ask for the names of the three objects learned earlier.	...../ 3	...../ 3	...../ 3
LANGUAGE Name two objects (e.g. pen, watch).	...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".	...../ 1	...../ 1	...../ 1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").	...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../ 1	...../ 1	...../ 1
COPYING: Ask the patient to copy a pair of intersecting pentagons 	...../ 1	...../ 1	...../ 1
TOTAL:	...../ 30	...../ 30	...../ 30

MMSE scoring
24-30: no cognitive impairment
18-23: mild cognitive impairment
0-17: severe cognitive impairment

Pathology and Laboratory Examination
General Tests

- Complete blood cell count
- Erythrocyte sedimentation rate
- Electrolytes
- Glucose
- Blood urea nitrogen and serum creatinine
- Liver function tests
- Serum calcium and phosphorus
- Thyroid function tests
- Serum protein
- Levels of all drugs
- Urinalysis
- Electrocardiography

Pathology and Laboratory Examination
Ancillary Laboratory Tests

- Blood
  - Blood cultures
  - HIV testing
  - Serum heavy metals
  - Serum copper
  - Ceruloplasmin
  - Serum B12 and folate levels
- Urine
  - Culture
  - Toxicology
  - Heavy metal screen
- Cerebrospinal fluid

Electroencephalography (EEG)

- Electroencephalogram (EEG) may have a role in dementia evaluation if there is a concern about a seizure disorder or delirium.

- In CJD, EEG can show periodic sharp wave complexes. However, EEG is not necessary in the routine evaluation of dementia.

Structural and Molecular Neuroimaging

- Structural neuroimaging studies are obtained to rule out abnormalities in the brain that can cause or contribute to dementia including normal pressure hydrocephalus, subdural hematoma, brain tumor or metastases, or cerebrovascular events.

- Generally a computed tomography (CT) scan is sufficient. However, magnetic resonance imaging (MRI) is preferred if looking for small or deep brain infarcts as this imaging modality is better for visualizing vascular changes.

Structural and Molecular Neuroimaging

- Positron emission tomography (PET) amyloid imaging can be used to identify Aβ accumulation. The absence of amyloid deposits indicates the dementia is not likely to be due to Alzheimer disease.

- Single-photon emission computed tomography (SPECT) can be used to demonstrate blood flow or metabolic rate in various brain regions to try to elucidate the etiology of dementia.

CSF Studies

- These studies may be used to measure amyloid-β (Aβ) protein, tau protein, and phospho-tau, all of which may be altered in Alzheimer disease.

- In sporadic CJD, there may be elevations in 14-3-3, total tau, or neurospecific enolase.

Neuropathology

- In individuals whose dementia does not arise from a previously characterized familial autosomal dominant mutation, a definitive diagnosis of dementia type can only be made with neuropathological investigation of the brain through either brain biopsy or autopsy.
  - Brain biopsy is conducted stereotactically and indicated when no other investigative techniques such as MRI or lumbar puncture have been sufficient to make a diagnosis. The procedure is not without risk. Seizures may occur if scar tissue forms at the biopsy site.
- There is usually not a clinical indication for brain biopsy so postmortem evaluation of the brain is the only way to provide a definitive diagnosis of dementia type.

Neuropsychological Testing

- Neuropsychological testing may be useful in elucidating the pattern of cognitive deficits in cases where the presentation is not typical of any one type of dementia.

- In Alzheimer disease, there is a pattern of early short-term memory and language impairment followed by the development of executive dysfunction and then visuospatial dysfunction.

Neuropsychological Testing

- In FTD, memory is relatively spared, while either language impairments or executive dysfunction predominate.

- In vascular dementia, there is a pattern of patchy deficits depending on where vascular lesions have occurred in the brain.

- Neuropsychological testing may also be helpful in identifying when cognitive impairment is due to depression or a factitious disorder.

DIFFERENTIAL DIAGNOSIS

- **Delirium**
- **Mild Neurocognitive Disorder**
- **Medical Conditions**
- **Medications**
- **Schizophrenia Spectrum and Other Psychotic Disorders**
- **Depressive Disorder**
- **Alcohol Use Disorder**
- **Factitious Disorder**

Delirium versus Dementia– differential diagnosis

Delirium

- Onset: sudden
- Course: dynamic
- Duration: days, weeks
- Cognitive impairment: fluctuations
- Consciousness: episodes of decreased consciousness
- Thinking: dezorganised
- Halucinations: mostly visual, often scenic
- Propulsion: changing
- Prognosis: often reversible

Dementia

- Onset: insidious
- Course: chronic
- Duration: months, years
- Cognitive impairment: more stable over time
- Consciousness: alert
- Thinking: straitened
- Halucinations: less often, mainly in the evenings
- Propulsion: proper
- Prognosis: usuallly irreversible

Mild Neurocognitive Disorder

- Mild neurocognitive disorder, more commonly known as MCI, is impaired cognition in one or more domains, but to a lesser degree than in dementia.

- There may be mild impairments in the more complex aspects of daily functioning, or an individual may need to rely on more compensatory strategies; however, there is no significant impairment on activities of daily living.

Mild Neurocognitive Disorder

- Because the pathophysiological process of neurodegenerative dementias begins years before there is evidence of cognitive or functional impairment, MCI may represent a prodromal state of these disorders.

- However, not all individuals with MCI will go on to develop dementia.

Medical Conditions

- General medical conditions that can cause or exacerbate cognitive impairment must be ruled out.
- Treatable factors that can cause or contribute to dementia include:
  - hypothyroidism,
  - hypercalcemia,
  - hypoglycemia,
  - vitamin B12, thiamine or niacin deficiency,
  - renal or hepatic impairment,
  - autoimmune disease (i.e., lupus erythematosus, vasculitis, neurosarcoidosis, Hashimoto encephalopathy).

Medications

- Many medications, alone or in combination, can cause cognitive impairment that may mimic dementia.

- Medications with anticholinergic properties are major culprits.

Schizophrenia Spectrum and Other Psychotic Disorders

- Schizophrenia is associated with multiple cognitive deficits.
- These cognitive deficits may emerge prior to the onset of the psychotic syndrome in young adulthood, and often progress during the early years of subsequent illness, but are relatively constant thereafter.
- Some individuals with schizophrenia will develop a progressive deterioration of cognitive functions beginning in late life, which may represent a superimposed neurodegenerative process.

Depressive Disorder

- Cognitive impairment frequently co-occurs with depressive episodes in late-life. The impairment is substantial (though less so than in dementia) and is present in about 50 percent of depressed elderly, which is more frequent than in younger patients.

- Cognitive impairment in the context of depression was formerly termed “pseudodementia.” In the past, it was widely believed that cognitive impairment mimicked the symptoms of dementia, but reversed upon resolution of the depressive episode.

Depressive Disorder

- Numerous studies have now shown that when cognitive impairment co-occurs with depression in late life, it generally persists into depression remission, particularly in the memory and executive function domains.

- Moreover, depression seems to increase the risk for future dementia (both Alzheimer disease and vascular dementia), although it is not known whether depressed mood represents prodromal dementia or is etiologically related to future progressive decline.

Alcohol Use Disorder

- Substance use disorders, particularly alcohol abuse and dependence, can cause dementia.

- Cognitive impairment is usually worse when patients are still actively using alcohol or other substances, and there may be some improvement with abstinence.

Factitious Disorder

- Malingering or factitious disorder may present with dementia-type symptoms.
- The cognitive deficits are inconsistent over time and generally uncharacteristic of the pattern and course seen in dementia.
- There is some secondary gain from appearing cognitively impaired.

COURSE AND PROGNOSIS

- The course and prognosis of dementia is variable depending on the etiology.
- Generally, onset is insidious, although abrupt onset due to a cerebrovascular or traumatic event is possible.
- Duration is generally years although it may vary from 6 months in the case of CJD to 15 years with Alzheimer disease.
- Dementia eventually leads to death unless another disease process supersedes.

COURSE AND PROGNOSIS

- Identifying the correctable causes of cognitive impairment such as vitamin B12 deficiency, hypothyroidism, or normal-pressure hydrocephalus can result in some improvement in symptoms.
- Also, modifying vascular risk factors can ameliorate the course of dementia, even of nonvascular etiologies.
- Gradual functional decline renders patients increasingly more dependent over the course of the illness.
- They slowly lose the ability to function independently.

COURSE AND PROGNOSIS

- They lose the ability to perform instrumental activities of daily living such as shopping, meal preparation, managing finances, and managing medications.
- Then they have difficulty bathing and maintaining hygiene and dressing and feeding themselves.
- They require more and more prompting and then assistance with these tasks as the disease progresses, and they will eventually require total care.

COURSE AND PROGNOSIS

- Dementia increases the risk for complications from intercurrent medical illness including delirium.

- Any medical illness can precipitate rapid decline in cognition and functioning and markedly increase the level of care required.

- Dementia is also associated with an increased risk of falls and adverse reactions to medications.

DEMENTIA SUBTYPES

- Alzheimer Disease
- Frontotemporal Dementia
- Dementia with Lewy Bodies
- Dementia in Parkinson Disease
- Dementia in Huntington Disease
- Prion Diseases

Alzheimer Disease

- According to the DSM-5 a diagnosis of probable Major Neurocognitive Disorder due to Alzheimer Disease is made when the criteria for major neurocognitive disorder is met, and there is either evidence of a causative genetic mutation or the individual shows impairment in memory and learning, in addition to one other cognitive domain.
- There must also be a steadily progressive decline, and there is no evidence of another etiology of the cognitive impairment.
- Diagnosis is further classified into subtypes as with or without behavioral disturbance.

Alzheimer Disease

Epidemiology

- The incidence of Alzheimer disease increases with age from about
  - 0.5 percent per year at ages 65 to 69
  - 1 percent per year from age 70 to 74
  - 2 percent per year from age 75 to 79
  - 3 percent per year from age 80 to 84
  - 8 percent per year after age 85

Alzheimer Disease

Etiology

- The etiology of Alzheimer disease is multifactorial.
- Mutations or copy number variations within several genes that result in the cleavage of amyloid precursor protein (APP) into Aβ invariably lead to early-onset Alzheimer disease within affected families.
- In contrast, late-onset Alzheimer disease is a complex disorder, in which risk is influenced by multiple genes, by environmental factors, and by their interactions.

Alzheimer Disease
Genetics

Early-Onset Alzheimer Disease

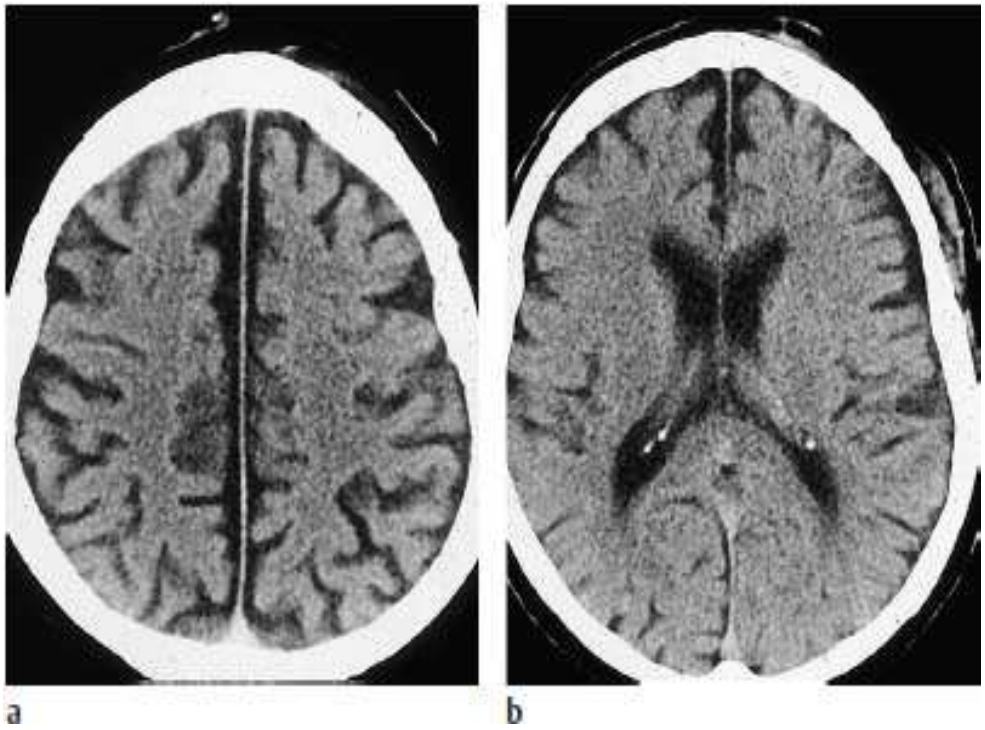
- Mutations at three genetic loci associated with early-onset Alzheimer disease have been identified. The first identified Alzheimer disease gene was the **APP** gene located on chromosome 21.
- A second Alzheimer disease locus was found on chromosome 14, presenilin-1 (**PS1**).
- A third Alzheimer disease gene has been localized to chromosome 1 and termed presenilin-2 (**PS2**).

Alzheimer Disease
Genetics

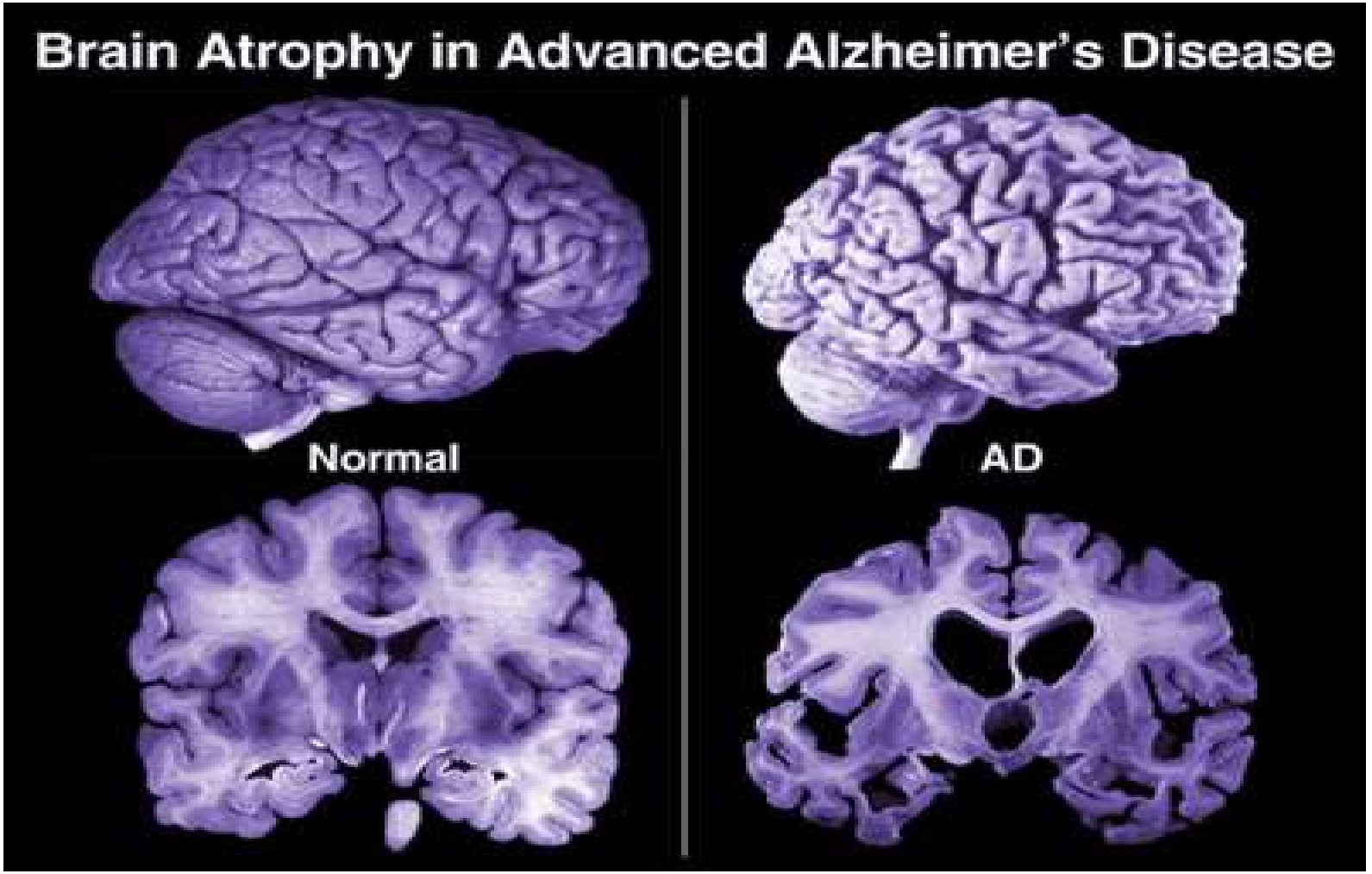
Late-Onset Alzheimer Disease

- The first gene to have an established relationship to late onset Alzheimer disease was apolipoprotein E, with increased risk of Alzheimer disease found in individuals carrying the epsilon 4 allele (**APOE4**) in both familial and sporadic cases.
- The risk of Alzheimer disease increases, and the mean age of onset of Alzheimer disease is earlier, as the number of epsilon 4 alleles an individual carries increases from 0 to 2.
- A single copy of the APOE4 allele confers an approximate two- to fourfold increased risk while two APOE4 alleles increase the risk by approximately four- to eightfold.
- It is generally estimated that APOE4 accounts for up to 50 percent of the genetic contribution to late onset Alzheimer disease.
- Genome wide association studies have recently identified 20 additional genes/loci associated with late onset Alzheimer disease; these include CR1, BIN1, CLU, PICALM, MS4AA/MS4A6E, CD2AP, CD33, EPHA1, ABCA7, HLA-DRB5–DRB1, SORL1, PTK2B, SLC24A4/RIN3, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2, and CASS4.

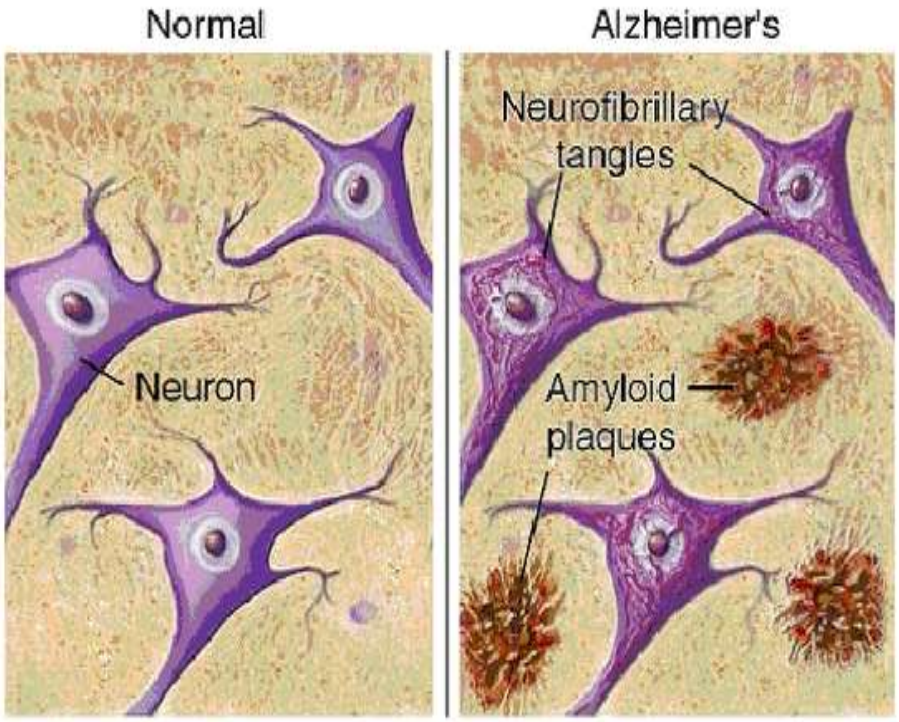
Alzheimer Disease Pathology



The classic gross neuroanatomical observation of a brain from a patient with Alzheimer's disease is diffuse atrophy with flattened cortical sulci and enlarged cerebral ventricles.


Brain Atrophy in Advanced Alzheimer's Disease
Normal
AD

Alzheimer Disease Pathology



The classic and pathognomonic microscopic findings are:

- Senile plaques (also referred to as amyloid plaques, more strongly indicate Alzheimer's disease, although they are also seen in Down syndrome and, to some extent, in normal aging, the number and the density of senile plaques present in postmortem brains have been correlated with the severity of the disease that affected the persons)
- Neurofibrillary tangles
- Neuronal loss (particularly in the cortex and the hippocampus)
- Synapsis loss
- Granulovascular degeneration of the neurons

Alzheimer Disease Pathology

As the pathological cascade in Alzheimer disease progresses, other brain changes may become evident. For example, numerous neurochemical abnormalities have been demonstrated on autopsy and with functional neuroimaging in Alzheimer disease in later disease stages. These include deficits in:

- acetylcholine (ACh),
- norepinephrine,
- serotonin,
- dopamine,
- γ-aminobutyric acid (GABA),
- glutamate,
- corticotrophin-releasing hormone,
- somatostatin.

The most robustly described neurochemical deficits are in the **cholinergic system**. This finding has led to the successful development of efficacious therapies directed at the enhancement of cholinergic function.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Age

- Age is the greatest risk factor for developing Alzheimer disease.

- Whereas approximately 3 percent of people older than 65 years of age have Alzheimer disease, about one third of people older than 85 years of age have Alzheimer disease.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Education

- Epidemiological studies have suggested that people with less education are at increased risk of developing Alzheimer disease.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Estrogen

- A number of observational studies have suggested that estrogen replacement after menopause reduced the risk of Alzheimer disease.
- However, prospective studies of estrogen treatment in patients with Alzheimer disease have yielded little evidence of cognitive enhancement or reduced cognitive decline.
- Current recommendations are that hormone therapy not be used in the prevention of dementia.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Head Trauma

- Traumatic brain injury can increase the rate of cognitive decline in the elderly, and is associated with an increased risk of developing dementia, and in particular Alzheimer disease.
- There is evidence that head trauma can lead to overexpression of APP, increase inflammatory mediators, and cause Aβ deposition in the brain.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Inflammation

- Several lines of evidence suggest a role of the immune system in Alzheimer disease.
- Neuropathological studies demonstrate that the brains of patients with Alzheimer disease have increased concentrations of acute phase reactants, cytokines, and complement protein, when compared to aged-matched controls.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Nicotine

- The literature on nicotine is unclear.
- Initial case-control studies suggested a reduced likelihood of Alzheimer disease in smokers. In contrast, cohort studies evaluating Alzheimer disease incidence have found the opposite relationship, with smoking associated with an increased risk of developing Alzheimer disease dementia.

Alzheimer Disease
RISK AND PROTECTIVE FACTORS

Oxidative Stress

- Oxidative stress has been postulated to contribute to Alzheimer disease.
- For example, Aβ can damage and kill neurons by inducing oxidative stress, as can the microglial inflammatory reaction surrounding plaques.
- Increased markers of oxidative stress have been found in the brains of subjects with MCI, suggesting that these processes may be altered relatively early in the disease course.

Alzheimer Disease
TREATMENT

Cholinesterase Inhibitors

- The first class of medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer disease was the cholinesterase inhibitors:
  - donepezil (Aricept)
  - rivastigmine (Exelon)
  - galantamine (Reminyl)
- These agents are reversible inhibitors of the enzyme acetylcholinesterase, which degrades ACh in the synaptic cleft, thereby increasing the availability of intrasynaptic ACh.

Alzheimer Disease
TREATMENT

- These agents have all been shown in multiple randomized, double-blind, placebo-controlled trials to slow cognitive decline in mild to moderate Alzheimer disease. There are limited trials in severe Alzheimer disease. Donepezil is the only cholinesterase inhibitor FDA approved for the treatment of severe Alzheimer disease.
- All of these agents show similar efficacy, and there is insufficient evidence comparing these agents to each other.
- Common side effects are related to cholinergic excess and include:
  - nausea and vomiting
  - decreased appetite and weight
  - increased gastric acid secretion
  - muscle cramps
  - bradycardia with syncope
  - sleep disturbances

Alzheimer Disease
TREATMENT

Memantine (Ebixa)

- It is a noncompetitive NMDA receptor antagonist.
- It is FDA approved for use only in moderate to severe Alzheimer disease and has demonstrated efficacy for both cognitive and functional improvement over placebo.
- Infrequent adverse events include:
  - confusion
  - dizziness
  - headache
  - sedation
  - agitation
  - falls
  - constipation

Frontotemporal Dementia (FTD)

- FTD (**Pick disease**) is characterized by progressive circumscribed atrophy of frontal and temporal lobe cortices, identified as frontotemporal lobar degeneration.
- FTD includes two broadly accepted subgroups:
  - behavioral-variant FTD (bv-FTD);
  - language predominant FTD (including progressive nonfluent aphasia and semantic dementia).

Frontotemporal Dementia (FTD)

Behavioral-variant FTD

Behavioral disinhibition can be characterized as:

- socially inappropriate behavior
- loss of manners or decorum
- impulsive, rash or careless actions
- loss of sympathy or empathy
- diminished social interest
- perseverative, stereotyped, compulsive or ritualistic behaviors (e.g. collecting specific objects, or hoarding)
- stereotypy of speech
- mental rigidity
- hyperorality or dietary changes (including altered food preference, such as eating foods that are just one color, or binge eating)

Frontotemporal Dementia (FTD)

- Core features of the **semantic variant**, also known as semantic dementia, include impaired confrontation naming and impaired single word comprehension.
- Other diagnostic features include impaired object knowledge and surface dyslexia (difficulty with recognition of irregular sounding words, like yacht) or dysgraphia. Individuals may substitute categories for words (“food” for “apple”), and eventually may refer to all nouns as “things.”
- As the disease progresses speech becomes empty of content.
- Repetition and speech production are usually spared.

Frontotemporal Dementia (FTD)

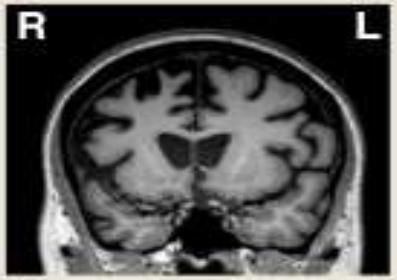
- The **nonfluent/agrammatic variant**, also known as progressive nonfluent aphasia, requires one of the two core features for a diagnosis: agrammatism in language production or apraxia of speech.

- Speech is often described as slow, labored, effortful or halting. Speech sound errors are made and there is abnormal prosody. There may also be impaired comprehension of syntactically complex sentences. Single-word comprehension and object knowledge are spared.

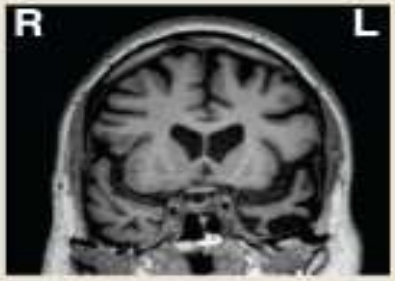
Frontotemporal Dementia

Primary Progressive Aphasia
Progressive disorder of language

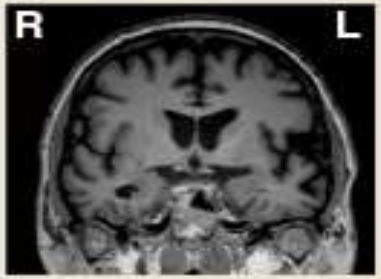
Behavioural-variant frontotemporal dementia (bvFTD)
- Changes in social conduct and behaviour
- Loss of empathy
- Apathy
- Disinhibition
- Lack of insight



Semantic dementia (SD)
- Loss of semantic knowledge, impaired word comprehension and object naming
- Fluent speech with spared repetition



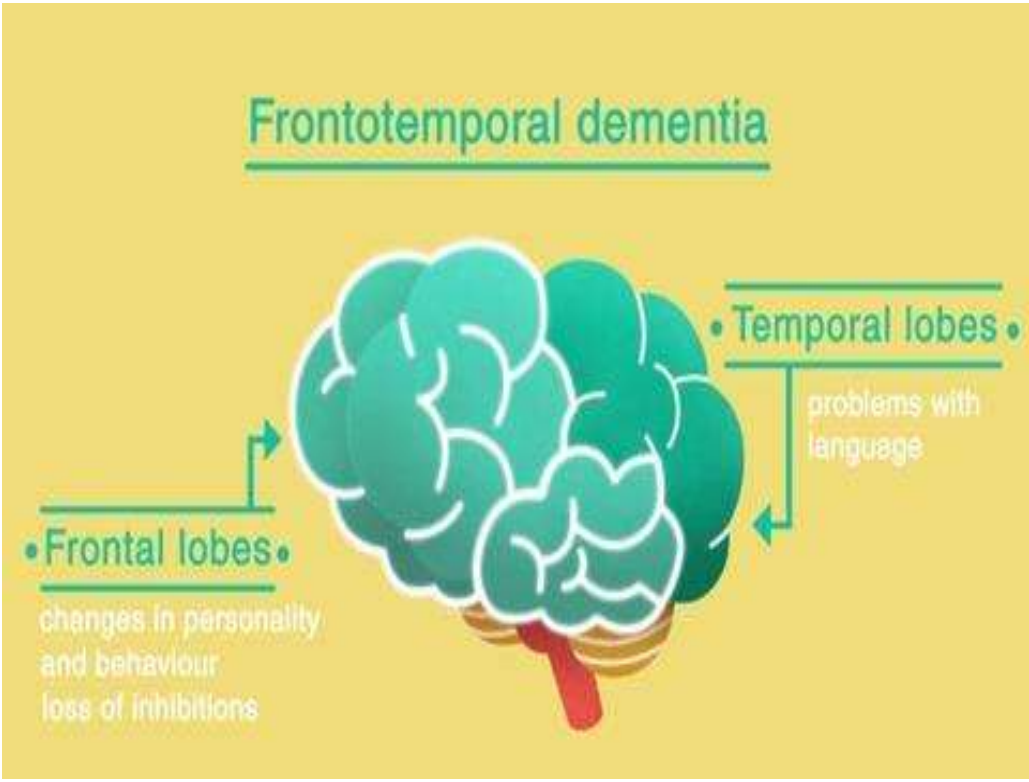
Progressive nonfluent aphasia (PNFA)
- Apraxia and effortful speech
- Spared object knowledge and word comprehension



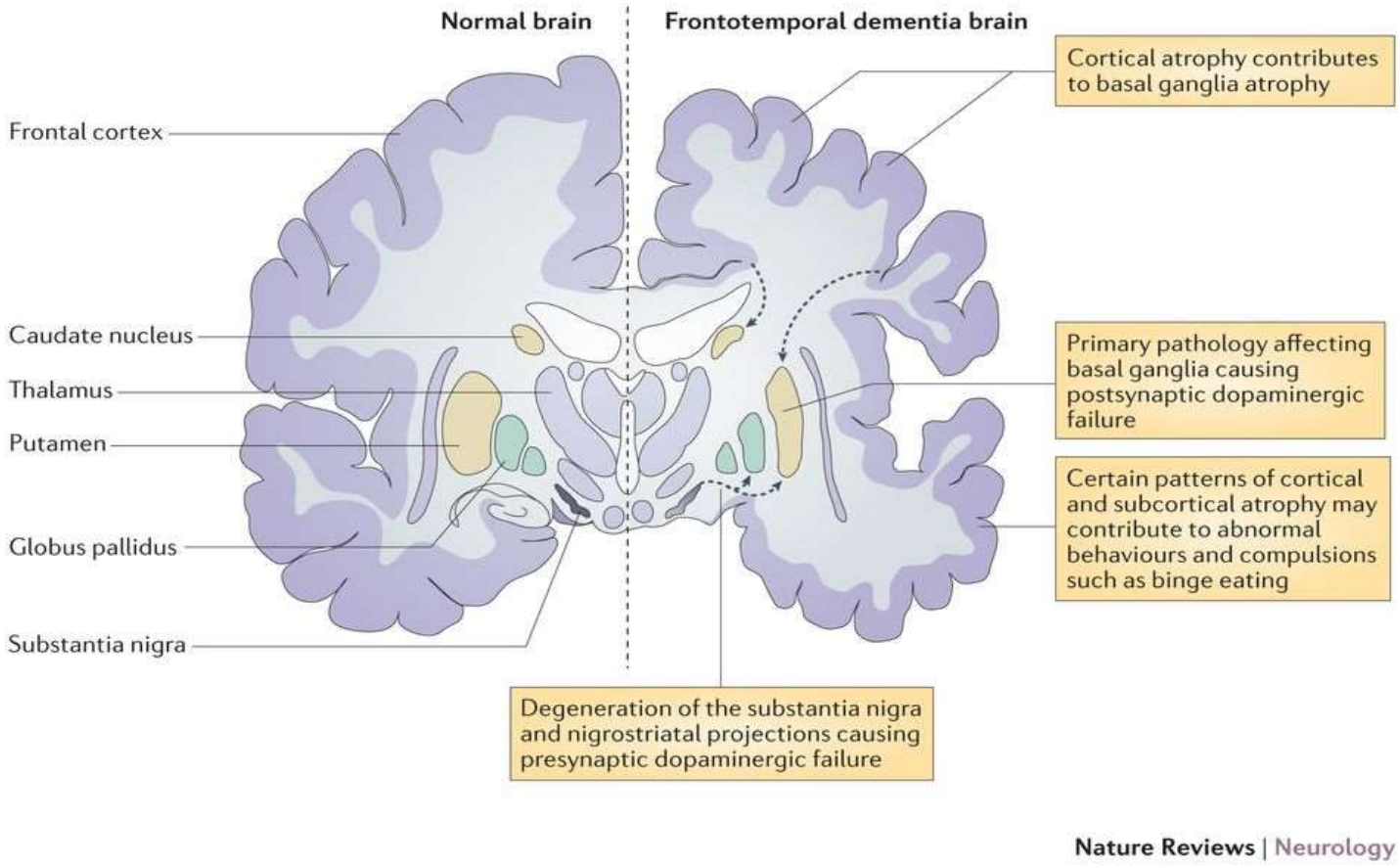
Current Opinion in Behavioral Sciences

Frontotemporal Dementia (FTD) Pathology

Macroscopically, FTD is characterized by focal atrophy of the frontal cortex, the temporal cortex, or both. Atrophy is usually symmetric, though asymmetry is sometimes present.



Frontotemporal Dementia (FTD) Pathology



Frontotemporal Dementia (FTD) Treatment

- Currently there are no treatments for the cognitive deficits associated with FTD, and no treatments to prevent progression of the underlying pathologies.
- Insufficient data exists to recommend cholinesterase inhibitors, and a recent randomized double-blind placebo controlled study showed no benefit of memantine in the treatment of frontotemporal lobar degeneration.
- Symptomatic use of trazodone, second-generation antipsychotics, SSRIs, and anticonvulsants may help agitation, disinhibited, and aggressive behavior.

Dementia with Lewy Bodies (DLB)

Clinical Criteria for DLB

The patient must have sufficient cognitive decline to interfere with social or occupational functioning. Of note early in the illness, memory symptoms may not be as prominent as attention, frontosubcortical skills, and visuospatial ability.

Probable DLB requires two or more core symptoms. Possible DLB requires only one core symptom.

Core features

- Fluctuating levels of attention and alertness
- Recurrent visual hallucinations (which are typically well formed and detailed)
- Parkinsonian features (cogwheeling, bradykinesia, and motor tremor)

Supporting features

- Repeated falls
- Syncope
- Sensitivity to neuroleptics
- Systematized delusions
- Hallucinations in other modalities (e.g., auditory, tactile)

Dementia with Lewy Bodies (DLB)

Etiology

- Lewy bodies are comprised of abnormal fibrillar deposits of α-synuclein.
- Normally, α-synuclein is a protein located in presynaptic axon terminals, and presumed to have a role in synaptic function.
- Mutations and copy number variations in the gene encoding α-synuclein, SNCA, result in disorders with Lewy body pathology, including DLB and Parkinson disease.

Dementia with Lewy Bodies (DLB)

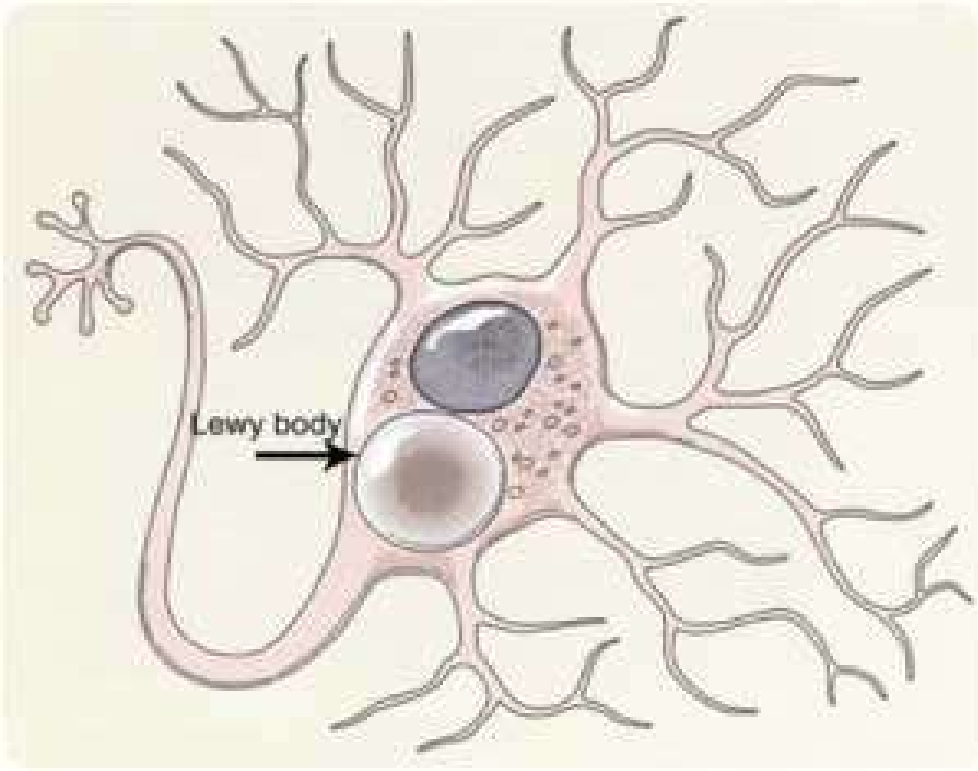
- If dementia onset **precedes** or is **concurrent** with the onset of parkinsonian symptoms, a diagnosis of DLB is warranted.
- The most common extrapyramidal symptoms noted in DLB are rigidity and bradykinesia, followed by hypophonic speech, masked facies, stooped posture, and a slow and shuffling gait.
- Postural instability is also common.
- The parkinsonism seen in DLB tends to include greater postural instability, gait impairment, and facial immobility compared to those patients with Parkinson disease without dementia.
- Resting tremor may occur, but is less common in DLB than in Parkinson disease.

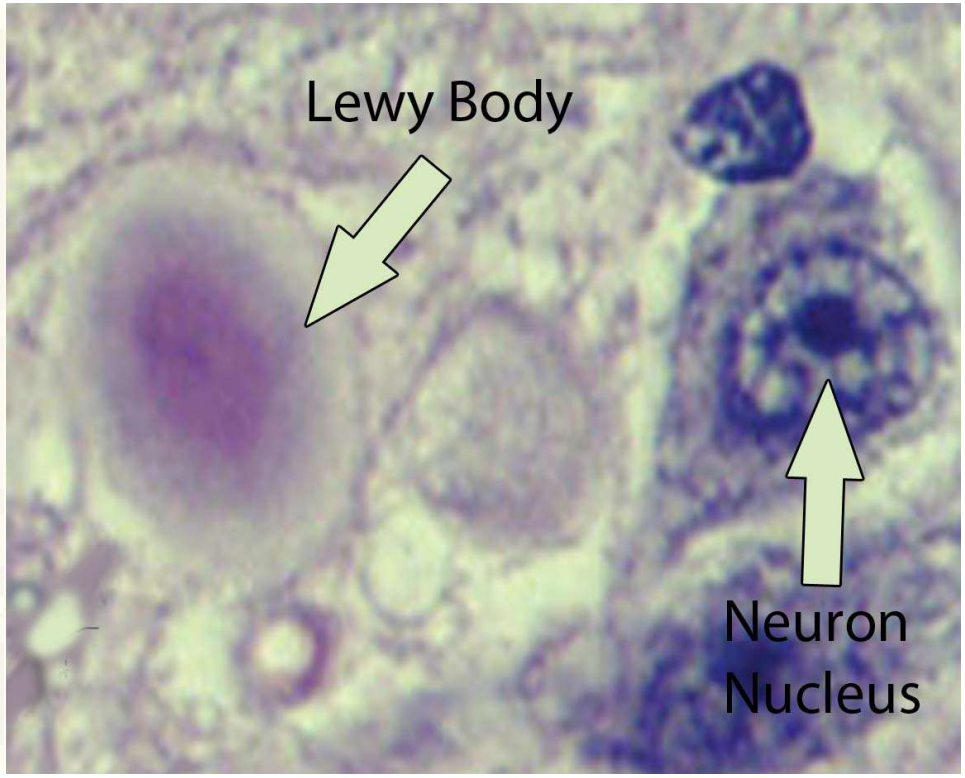
Dementia with Lewy Bodies (DLB)

Pathology

- Lewy bodies are the only essential finding in the pathological diagnosis of DLB:
  - spherical intracytoplasmic eosinophilic neuronal inclusion bodies
  - typically seen in the brain stem nuclei, substantia nigra, and locus coeruleus
  - composed predominantly of fibrillar deposits of α-synuclein
- The number of cortical Lewy bodies correlates significantly with cognitive impairment in DLB.
- There are also other pathological changes that may be seen in DLB but that are not required for diagnosis.

Dementia with Lewy Bodies (DLB)





Dementia with Lewy Bodies (DLB) Treatment

Cholinesterase Inhibitors

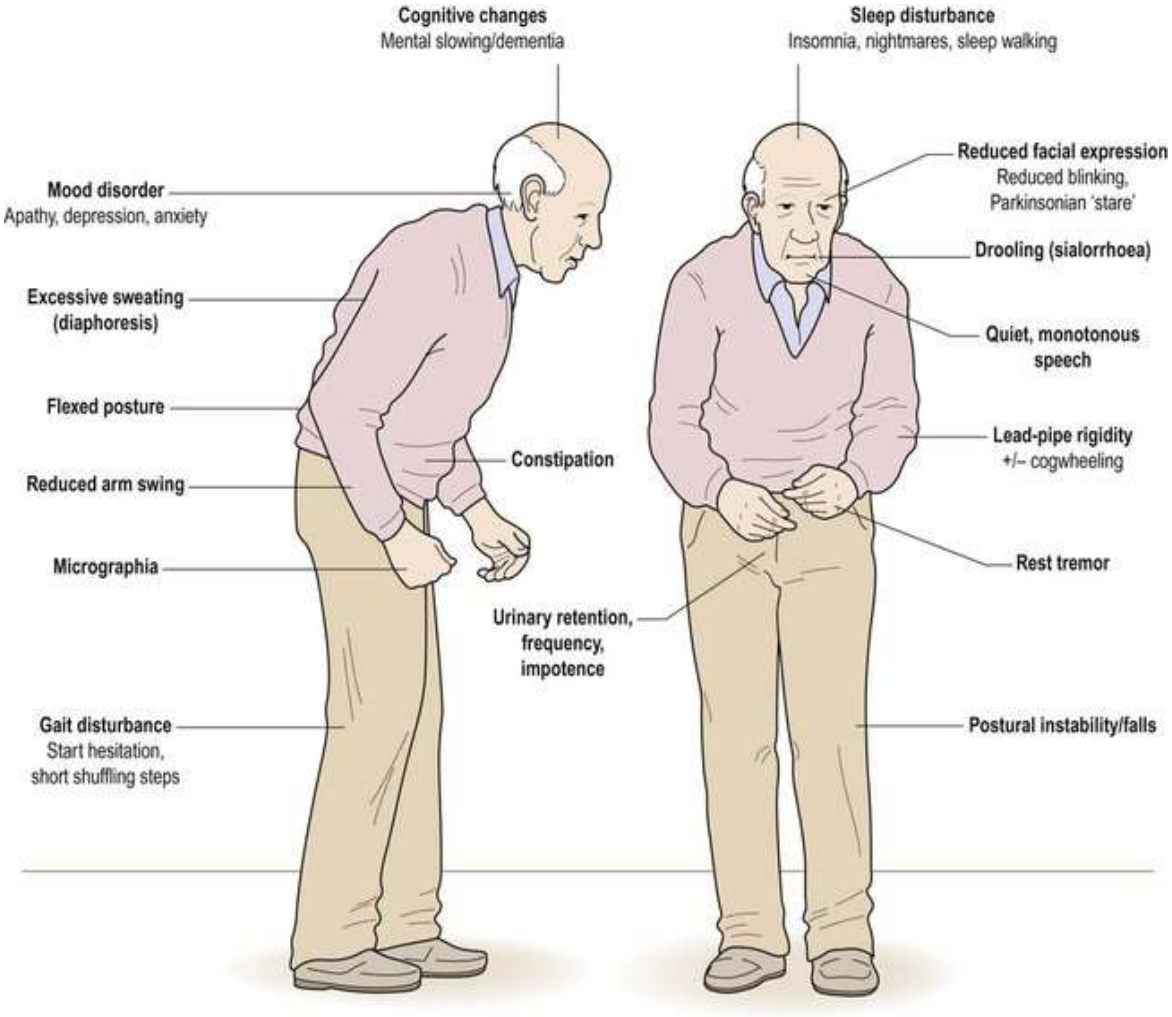
- The cholinesterase inhibitors are the mainstay of treatment for the cognitive impairment of DLB.

Antipsychotics

- Severe neuroleptic sensitivity is present in about half of patients with DLB.
- They will demonstrate acute onset or exacerbation of parkinsonism and impaired consciousness with even a low dose of a first- or second generation antipsychotic agent.

Dementia in Parkinson Disease

In the DSM-5, for a diagnosis of major neurocognitive disorder due to Parkinson disease, the criteria for major neurocognitive disorder must be met, the impairment occurs in the setting of well-established Parkinson disease, there is insidious onset and gradual progression, and the impairment cannot be attributable to another medical condition or mental disorder.



Dementia in Parkinson Disease

Diagnosis and Clinical Features

- As this clinical entity occurs within Parkinson disease, the cognitive impairment should occur **at least 1 year after** symptoms of Parkinson disease were first noted.
- On neuropsychiatric examination, impairments in attention, executive function, visuospatial function, language, and memory may be seen.
- Impaired mental speed may be evident.
- On memory testing, recognition is better than free recall.
- Regarding language impairment, word finding difficulties, and impaired comprehension of complex sentences may be seen.

Dementia in Parkinson Disease

Associated **neuropsychiatric symptoms** that may be present include:

- apathy
- depression
- anxiety
- hallucinations (in 45 to 65% of individuals with PDD)
- delusions (in 25 to 30% of individuals with PDD)
- personality changes

Dementia in Parkinson Disease

Pathology

- Parkinson disease is associated with neuronal loss in the substantia nigra.
- Lewy bodies, made up of α-synuclein, are present in the cell bodies of the surviving neurons.
- α-synuclein pathology is more extensive in Parkinson disease dementia compared to Parkinson disease without dementia, with more global cortical and limbic involvement.
- Individuals may also have β-amyloid plaque burden as well as the presence of tau neurofibrillary tangles.

Dementia in Parkinson Disease

Treatment

- Evidence suggests that **acetylcholinesterase inhibitors** can improve cognition, attention, executive function, and global status, and may have beneficial effects on overall activities of daily living.
- **Antipsychotic medication** should be used very cautiously. Clozapine is the only antipsychotic medication that has been deemed clinically useful for the treatment of psychosis in Parkinson disease.

Dementia in Huntington Disease

- Huntington disease is a rare disorder that is characterized by motor, cognitive, and psychiatric symptoms.
- The motor symptoms include chorea, or involuntary dance-like movements, and ataxia; the disease inevitably leads to dementia.
- For an individual to be diagnosed with the DSM-5 diagnosis of major neurocognitive disorder due to Huntington disease, there must be clinically established Huntington disease, or risk of this based on family history or genetic testing, in addition to meeting the criteria for major neurocognitive disorder, and there being a gradual and insidious onset.

Dementia in Huntington Disease

Etiology

- Huntington disease is an autosomal-dominant inherited disease transmitted through a triplet CAG repeat mutation located on chromosome 4 in the HTT gene.
- This mutation results in a polyglutamate expansion in the Huntington protein.
- Expression of the abnormal protein ultimately results in neuronal cell death, primarily in the caudate nucleus and frontal lobes.

Dementia in Huntington Disease

Diagnosis and Clinical Features

- In addition to the chorea and ataxia individuals may also develop personality changes, depression, blunting of affect, irritability, psychosis, and aggressive–compulsive behavior.
- Cognitive changes include visuospatial deficits, psychomotor slowing, impairments in executive functioning and attention, and memory deficits.
- Dysarthria and dysphagia are present in more severe stages.

Dementia in Huntington Disease

Pathology

- Atrophy of the caudate is evident on structural imaging, and striatal atrophy may be seen on imaging before a clinical diagnosis of Huntington disease is made.
- A family history is important in the diagnosis of this disease, and it can be confirmed by genetic testing.

Dementia in Huntington Disease

Treatment

- Antidepressants and sedatives can be used for associated mood disorders.
- Dopamine depleting agents may be used for the treatment of chorea.
- Antipsychotic medications may be used for the treatment of agitation and psychosis.
- Cholinesterase inhibitors have not been shown to have benefit in the treatment of the cognitive impairment.

Prion Diseases

The DSM-5 criteria for major neurocognitive disorder due to prion disease include an insidious onset with rapid progression of impairment, and motor features of prion disease or biomarker evidence must be present, and the presentation cannot be attributable to another medical or mental disorder.

Prion Diseases

Etiology

- The prion diseases can be sporadic, inherited, and also horizontally transmissible.
- The gene for the prion protein is found on chromosome 20.
- Underlying these diseases is a misfolding of the prion protein, which occurs via a spontaneous or genetically induced mutation.
- Iatrogenic CJD has been associated with medical or surgical equipment contaminated with the pathological prion protein.

Prion Diseases

Diagnosis and Clinical Features

- Sporadic and familial CJD initially present with memory impairment and confusion, which quickly progress to a cortical dementia like picture, as well as ataxia and myoclonus.
- Iatrogenic forms of CJD typically show more cerebellar ataxia at symptom onset.

Prion Diseases

Pathology

- The hallmark clinical feature of sporadic and familial CJD is spongiform degeneration of the cortical gray matter; reactive gliosis is often evident as well.
- Pathology is usually focused in the neocortex, subiculum of the hippocampus, caudate, putamen, and the thalamus.

Prion Diseases

Course and Prognosis

- Sporadic CJD is most commonly diagnosed in the seventh or eighth decade.
- Course is rapidly progressive, with the prognosis somewhere between 4 and 6 months.
- The familial form of the disease has a more extended course, typically of 1 to 5 years.

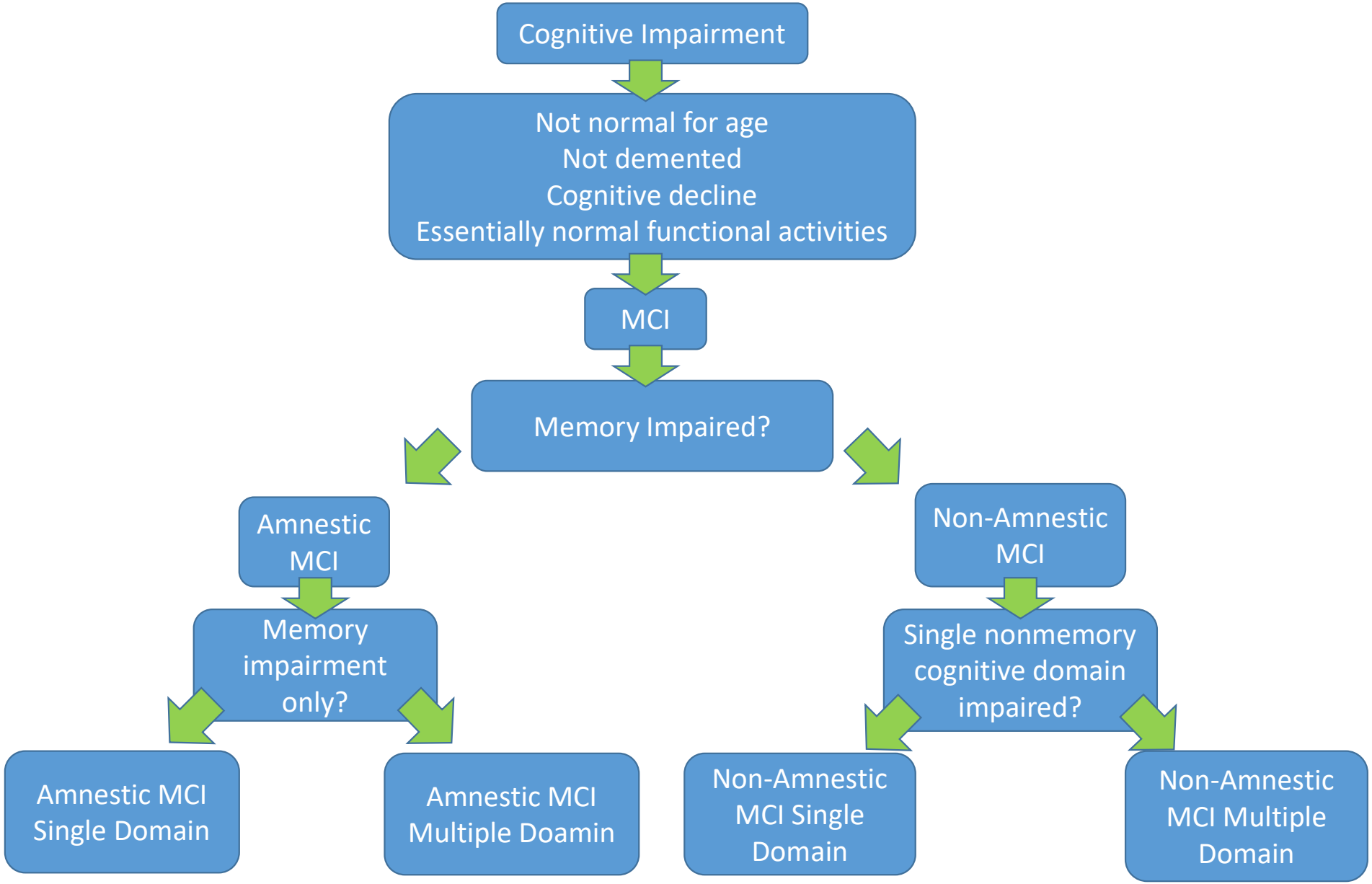
Prion Diseases

Treatment

- At this time, treatment is limited to symptomatic therapies, including antiepileptic medications for seizure control, clonazepam for myoclonus, and small doses of antipsychotic medications for distressing psychiatric symptoms including hallucinations and delusions.

Mild Cognitive Impairment (MCI)

- Although the term Mild Cognitive Impairment (MCI) has been in use since 1982 as a descriptor of stage 3 on the Global Deterioration Scale, more recently it was developed by the Mayo Clinic Group as a diagnostic category designed to fill the gap between cognitive changes associated with aging and cognitive impairment suggestive of dementia.
- The criteria proposed by the Mayo Clinic Alzheimer's Disease Research Center (MCADRC criteria) are:
  (1) memory complaint, preferably confirmed by an informant
  (2) objective memory impairment for age and education
  (3) preserved general cognitive function
  (4) intact activities of daily living
  (5) not demented


Cognitive Impairment
Not normal for age
Not demented
Cognitive decline
Essentially normal functional activities
MCI
Memory Impaired?
Amnestic MCI
Memory impairment only?
Amnestic MCI Single Domain
Amnestic MCI Multiple Doamin
Non-Amnestic MCI
Single nonmemory cognitive domain impaired?
Non-Amnestic MCI Single Domain
Non-Amnestic MCI Multiple Domain

Mild Cognitive Impairment (MCI)

The concept of MCI is currently defined in DSM-5 as mild neurocognitive disorder.

DSM-5 Diagnostic Criteria for Mild Neurocognitive Disorder

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and

2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with the capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medication are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Mild Cognitive Impairment (MCI)

Etiology

- The clinical expression of MCI can be viewed as a result of the interaction between several risk factors and several protective factors.
- The most significant risk factors are related to the different types of neurodegeneration witnessed in dementias.
- These are clinically expressed in different subtypes of MCI (e.g., amnestic MCI [a-MCI], single domain, is considered to be related to underlying AD pathology; a-MCI, multiple domains, is considered to be related to either AD or vascular dementia type of pathology; while nonamnestic MCI [na-MCI] has been related more closely to DLB or frontotemporal neurodegeneration).

Mild Cognitive Impairment (MCI)

Etiology

- Other risk factors include the apolipoprotein E 4 (APOE4) allele status and cerebrovascular events in the form of either cerebrovascular accident or lacunar disease.
- The role of chronic exposure to high levels of cortisol, as seen in late life depression, is also hypothesized to increase the risk of cognitive impairment through hippocampal volume reduction.
- The notion of “brain reserve” suggests that effects of brain size and neuron density may be protective against dementia despite the presence of neurodegeneration (a larger number of neurons and a bigger brain volume would protect against clinical manifestations of AD despite the presence of neurodegeneration).

Mild Cognitive Impairment (MCI)

Neuropsychological Assessment

- Most experts agree that earlier deficits are noted in episodic (vs. semantic) memory.
- There is no consensus among experts with regard to which memory tests and which cutoffs to use.
- Brief mental status instruments (like **Mini-Mental State Examination**) are relatively insensitive for the detection of memory problems in MCI.
- **The Montreal Cognitive Assessment (MoCA)** has been used in recent years as a more adequate way to screen patients with MCI.
  - It has been validated multiple times, in different pathologies, populations, and languages. It includes more adequate testing for frontal lobe dysfunction when compared to the MMSE and is readily available.

Mild Cognitive Impairment (MCI)

Biomarkers

- Several markers of progression from MCI to AD have been studied in the past decade. The most well-established biomarkers have been divided into two categories, those that measure amyloid deposition and those that relate to neurodegeneration.
- Low levels of Aβ42 (the 42 amino acid form of β-amyloid) and increased uptake of amyloid PET tracers are associated with fibrillar Aβ deposits.
- Increased levels of cerebrospinal fluid (CSF) total tau (t-tau) and phosphorylated tau (p-tau), hypometabolism on PET, and atrophy on magnetic resonance imaging (MRI) are measures of neurodegeneration.

Mild Cognitive Impairment (MCI)

Genetics

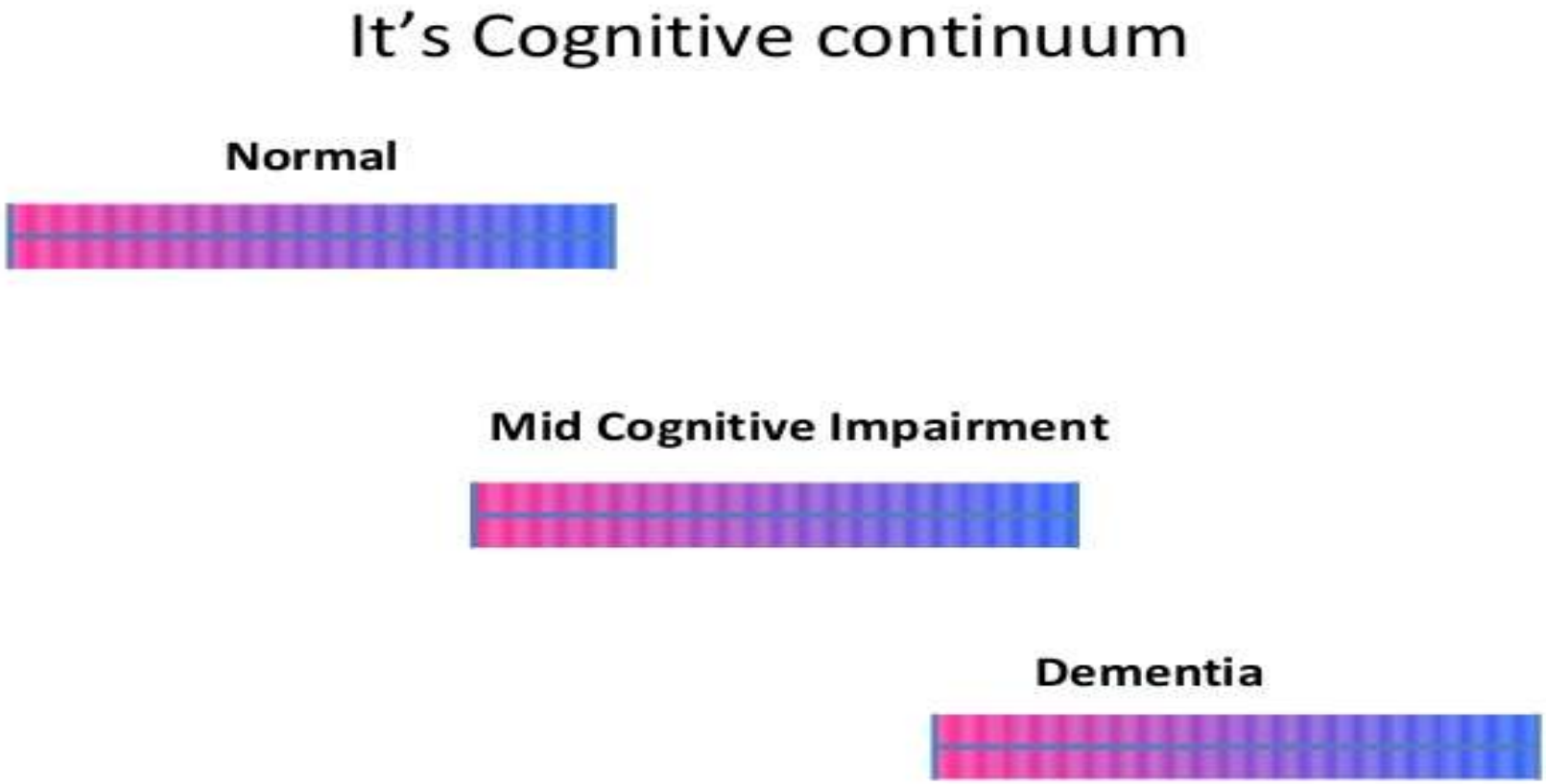
- As MCI is regarded as the prodromal stage for several disorders (AD, frontotemporal, Lewy body disease or vascular dementia), different genes are probably related to MCI.
- Three genes involved in rare autosomal dominant forms of AD have been identified:
  - the amyloid precursor protein (APP) gene
  - presenilin-1 (PSEN1)
  - presenilin-2 (PSEN2)
- Screening for each of these mutations will have very limited value for the diagnosis of MCI in the general population unless a clear family history is present.
- Multiple other genes have been associated with sporadic AD. Among those APOE has the greatest effect in subjects with MCI.
- As the etiology of MCI is heterogeneous, it is likely that a very large number of different genes underlie the pathology of MCI.

Mild Cognitive Impairment (MCI)

Neuroimaging

- Advances in neuroimaging studies aim to develop measures allowing the differentiation between MCI and healthy aging as well as within MCI between subjects who will convert to AD or will remain stable over time.
- Structural volumetric studies of subjects with MCI showed early changes in the medial temporal structures, reflecting neuronal atrophy, decreased synaptic density, and overall neuronal loss seen in postmortem studies. Atrophy of the hippocampal volume and entorhinal cortex has been described in MCI.

Mild Cognitive Impairment (MCI)



Mild Cognitive Impairment (MCI)

Course and Prognosis

- The typical rate at which patients with MCI progress to AD is 10 to 15 percent per year and is associated with progressive loss of function.

- The clinical manifestations and rate of decline in MCI are likely not only dependent on the underlying neuropathology, but also on a host of factors that can either exacerbate or ameliorate the biological impact of the underlying disease.

Mild Cognitive Impairment (MCI)

Course and Prognosis

- Some of these factors include but are not limited to the expression of specific genes, the age of disease onset, baseline brain and cognitive reserve, comorbid medical and psychiatric illness, cerebrovascular burden, and lifestyle characteristics (e.g., diet, physical and cognitive activity).

- The manipulation of some of these factors has been considered as a potential way to decrease the likelihood of progression from MCI to dementia.

Mild Cognitive Impairment (MCI)

Treatment

- There are no FDA approved treatments of MCI at this time.
- MCI treatment involves adequate screening and diagnosis.
- Ideally, MCI treatment would also include improvement in memory loss, together with prevention of further cognitive decline to dementia.
- Cognitive training programs have been reported as mildly beneficial for compensating memory difficulties in MCI.
- Controlling for vascular risk factors (high blood pressure, hypercholesterolemia, diabetes mellitus) may be a preventive method for those MCI cases underlying vascular pathology.

Mild Cognitive Impairment (MCI)

Treatment

- Currently, sensitive tools (imaging techniques or biomarkers) are not available for MCI screening in the general population.
- In primary care setting, clinicians should maintain a high suspicion for subjective cognitive complaints and should corroborate these complaints with collateral information whenever possible.
- Also, identifying reversible causes of cognitive impairment (hypothyroidism, vitamin B12 deficiency, medication-induced cognitive impairment, depression) can further benefit some of the prodromal dementia MCI cases.
- Currently, there is no evidence for long-term efficacy of pharmacotherapies in reversing MCI.

Mild Cognitive Impairment (MCI)

FUTURE DIRECTIONS

- Advances in MCI detection will be paramount for early detection and treatment of AD, as experts agree that disease-modifying treatments of AD will focus on cognitively intact individuals at increased risk.

- The field of identifying sensitive and specific biomarkers (biological and neuroimaging markers) will probably witness an exponential development in the coming years.

Questions

1. A 75-year-old man is brought in by his daughter to a psychiatrist for an evaluation. He has become increasingly forgetful over the past year, missing engagements with his children and grandchildren. He is also unable to remember directions, resulting in his becoming lost when driving alone. He has no psychiatric history, although his wife died 14 months ago. His medical history is significant for poorly controlled hypertension. Which of the following additional features is necessary in order to accurately diagnose dementia?

A. Agitation
B. Fluctuation in consciousness
C. Radiographic findings
D. Hallucinations
E. Another cognitive deficit

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2. For the past 10 years, the memory of a 74-year-old woman has progressively declined. Lately, she has caused several small kitchen fires by forgetting to turn off the stove, she cannot remember how to cook her favorite recipes, and she becomes disoriented and confused at night. She identifies an increasing number of objects as “that thing” because she cannot recall the correct name. Her muscle strength and balance are intact. Which of the following is the most likely diagnosis?

A. Huntington disease
B. Multi-infarct dementia
C. Creutzfeldt-Jakob disease
D. Alzheimer disease
E. Wilson disease

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3. A 70-year-old man with a dementing disorder dies in a car accident. During the previous 5 years, his personality had dramatically changed and he had caused much embarrassment to his family because of his intrusive and inappropriate behavior. Pathological examination of his brain shows frontotemporal atrophy, gliosis of the frontal lobes' white matter, characteristic intracellular inclusions, and swollen neurons. Amyloid plaques and neurofibrillary tangles are absent. Which of the following is the most likely diagnosis?

A. Alzheimer disease
B. Pick disease
C. Creutzfeldt-Jakob disease
D. Vitamin B12 deficiency dementia
E. HIV dementia

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B. Pick disease
C. Creutzfeldt-Jakob disease
D. Vitamin B12 deficiency dementia
E. HIV dementia

Questions

4. A 72-year-old retired English professor with a long history of hypertension has been having difficulties with tasks he used to find easy and enjoyable, such as crossword puzzles and letter writing, because he cannot remember the correct words and his handwriting has deteriorated. He has also been having difficulty remembering the events of previous days and he moves and thinks at a slower pace. These symptoms have been progressing slowly in a stepwise fashion over time. Subsequently, he develops slurred speech. Which of the following is the most likely diagnosis?

A. Vascular dementia
B. German-Strausser syndrome
C. Rett disorder
D. Wernicke-Korsakoff syndrome
E. Alzheimer disease

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Thank you for your attention.