Dementia

Objectives:

- differentiate delirium from dementia
- differentiate Mild Cognitive Impairment from Dementia
- become familiar with common dementia syndromes, and available treatments

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Resources: 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

Delirium

★ What is Delirium?

- Delirium usually encompasses: "Acute confusional state" and Encephalopathy
- It is not normal to have delirium, while this statement is obvious, patients who have symptoms of delirium are dismissed as being sleepy, tired, or just age related changes
- Old age SHOULD NOT excuse confusion or mental impairment (when you see an elderly person being delirious then look for the history of recent problem as UTI or ingestion of some drugs)
- Cognitive complaints can be an acute presentation with altered level of consciousness > delirium or a non-acute presentation with normal consciousness > non-delirious.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for delirium is as follows:

Disturbance in attention (ie: reduced ability to direct, focus, sustain, and shift attention) and awareness

Change in cognition (eg: memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia

The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.

★ Important clues to recognize delirium:

- Patient will not be able to give you a history
- Rapid development of symptoms (hours or days) while dementia develops within years
- Change in level of consciousness
- When the patient appears awake, assess level of attention
- Poor content of conversation and/or other cognitive deficits (memory loss, disorientation, abnormal language), neuropsychiatric symptoms such as hallucinations (visual, auditory somatosensory…etc) and delusions of harm

✓ The opposite, hypervigilance, may occur in substance withdrawal (eg: alcohol or sedative)

Most of the time with delirium, especially in the hospital, the patient is going to be drowsy and you'll have a hard time waking up the patient and those are called negative symptoms. However when they're agitated and look alert (but actually they're not) it's called positive symptoms.

this is an extra picture.

	Positive Symptoms	Negative Symptoms
Delirium	**Hyperactive delirium** - Hallucinations, delusions - Agitated behavior - Paranoia can occur (but less common)	**Hypoactive delirium** - Withdrawn - Quietly confused - Somnolent

★ Causes of Delirium:

- Metabolic, examples include: dehydration, hyponatremia, hypocalcemia, abnormal thyroid functions, liver and/or renal impairments, hypoglycemia. The older the person is the more likely delirium can occur from a minor disturbance.
- Toxic: ETOH (ethanol) and drugs of abuse or withdrawal effect of alcohol/benzodiazepine
- Infectious (common): UTI, pneumonia, or infections that result in systemic manifestations
- Side effects of drugs or the abrupt discontinuation of certain drugs like benzodiazepines.
- Post surgery (anesthetics, pain)
- Disorders of the central nervous system (large strokes, Post-seizures, infections)

★ Management of Delirium: (it is a medical emergency)

Delirium is Recognized	→	**Exhaustive search for Etiology**	→	**Directly treat the Etiology once found**

1. The choice of the investigations are guided by your history and clinical examination findings
2. There are many causes of delirium, so an initial investigation may include (but not limited to) the following:
    - CBC, electrolytes, urea, creatinine, LFT, ESR, TSH +/- Autoimmune evaluation
    - Arterial blood gases
    - Urinalysis and toxicology screen
    - Chest X-ray It could be an aspiration pneumonia you are not aware of, EKG
    - CT head, EEG, Lumbar Puncture

★ What Can look like delirium?

- Non-convulsive seizures, Their brain is having a seizure but without manifestation and they look confused.
- Sundowning behavior[1]

[1] Sundowning, or sundown syndrome, is a neurological phenomenon associated with increased confusion and restlessness in patients with delirium or some form of dementia this is where people tend to be

- Dementia
- Psychiatric disorders (eg. Someone with schizophrenia)
- Aphasias (doctors think that the aphasia is caused by delirium while it's just a speech disorder in that patient)
- Transient Global Amnesia[2]

Dementia-Major Neurocognitive Disorder

★ What is Dementia?

Evidence of significant cognitive decline (no disturbance in consciousness) from a previous level of performance in one or more cognitive domains**:**

- Learning and memory
- Language
- Executive function[3]
- Complex attention (multitasking)
- Perceptual-motor (how you interact with things around you eg. use tools or devices)
- Social cognition

The cognitive deficits **interfere with independence in everyday activities** (a key finding in defining dementia) if it doesn't interfere with everyday activities it isn't dementia, we may call it Mild Cognitive Impairment).

The cognitive deficits do not occur exclusively in the context of a delirium (eg. someone with UTI developed delirium then when he is cured of UTI the cognitive impairment is gone away. Then it's not dementia)

The cognitive deficits are not better explained by another mental disorder eg, major depressive disorder, schizophrenia… they may have some cognitive problems but when they are treated of these psychiatric disorders the deficit will go away)

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awake during the night and sleepy during daytime, you try to wake them up but they're so sleepy they go back to sleep again.

[2] a person comes in with memory impairment within 24hr then he comes back to normal, يجيبونه عائلته للمستشفى وهو عنده مشكلة بالذاكرة يقول انا وش جابني هنا ؟ وبعد خمس دقائق يرجع يسأل with NO history of trauma… he is ok in language and everything but the problem is with lapses in memory

[3] It's like going on a business trip to Jeddah, you book your own ticket, drop your luggage, get on the plain and receive your luggage from the airport then you order a cab to your hotel, this is all considered executive function.

★ Delirium Vs. Dementia:

Delirium	Dementia
• Acute presentation symptoms develop with in hours to days • Altered level of consciousnesses • Early loss of attention • Cognitive domain deficit happens all in one go (e.g. memory, orientation, language are all affected at once)	• Non-acute presentation symptoms develop within years • Normal consciousness • Late loss of attention • Cognitive domain deficit happens one by one (ex. memory might be lost first, then orientation, then language)

★ Major Dementias:

Neurodegenerative	Other
• Alzheimer's Disease • Lewy Body Dementia • Parkinson's Disease Dementia • Frontotemporal Dementia • Huntington's Disease	• Vascular Dementia • Normal Pressure Hydrocephalus • Creutzfeldt-Jakob Disease • Wernicke-Korsakoff Syndrome • Secondary to infection or systemic illness

Alzheimer's Disease

★ Clinical Features:

- Uncommon under the age of 60
- Decreased memory and new learning is the hallmark of the condition
- Language impairment: Word finding difficulties with circumlocution[4] and anomia[5]
- Executive dysfunction
- Apraxia[6] (praxia= practice), Unawareness of illness
- Visual-spatial impairments
- Passivity, apathy > agitation
- Delusions

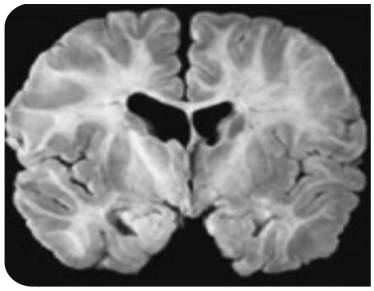
[4]The unnecessary use of more words
[5]A form of aphasia where a person cannot recall the name of objects like knowing what a pen can do but forgetting its name
[6]Apraxia is a motor disorder caused by damage to the brain (specifically the posterior parietal cortex). In which the individual has difficulty with the motor planning to perform tasks or movements when asked, provided that the request or command is understood and he/she is willing to perform the task

- Depression
- Circadian rhythm disturbances (sundowning)
- Weight loss

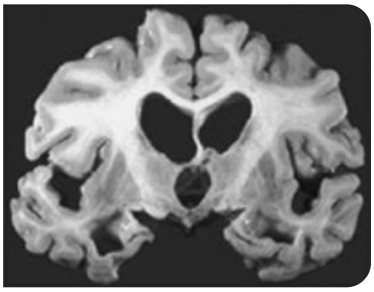
★ Major Risk Factors:

- **Increasing age** (most important)
- (APOE ε4) The E4 allele for Apolipoprotein E on chromosome 19, we do not test for it, because many people will have it and not develop the disease. But if someone has it, it will increase the risk of having the disease
- Down Syndrome (almost all of them start developing Alzheimer's by the age of 40)
- specific inherited types, some inherited type which lead to very early onset in the 30s or 40s.
- Mid-life vascular risk factors (DM, HTN, Hyperlipidemia, Lack of exercise)
- Brain trauma (as concussion and punch drunk syndrome)

Normal



Atrophic



Cortical and hippocampal atrophy which are typical to alzheimer's disease. There is atrophy through out, but the bulk of it is in intermedio-temporal lobe.

Pathophysiology

- Defects in the mechanisms for clearing amyloid beta results in its accumulation and forming senile plaques
- Abnormal accumulation of hyperphosphorylated Tau protein results in accumulation and the formation of neurofibrillary tangles
- Tangles and plaques are pathological hallmarks in Alzheimer's disease
- The resultant loss of neurons and synapses is responsible for the clinical profile (synapses will degenerate first, then the neurons will begin to die).
- We are born with a number of neurons and we start losing them day by day… we never make new neurons and in Alzheimer losing neurons is much faster, but we can make new synapses by learning new things...and maybe that is why educated people tend to have Alzheimer at older ages

- The neuronal loss in the basal forebrain region is responsible for a cholinergic deficit (no Ach? then the treatment is to increase Ach in the body by Cholinesterase Inhibitors)
- Why is Ach important? Because it is important for neuron function and memory
- amyloid accumulation occurs very early before anything else, then synaptic dysfunction will begin to follow later on, then tau begins to accumulate, so much happens before any symptoms appear.
- MCI patient will have a small hippocampi, it increases the risk to develop alzheimer.
- MCI patients still can perform well in daily activities and don't depend on others but they start forgetting so they try to compensate by taking notes
- The graph on the left shows a group of patients followed for five years. We notice that patients with MCI start developing Alzheimer but not all will turn into Alzheimer disease and that is an important thing to tell MCI patients because they don't need medication, they only need reassurance and some coping strategies
- The picture on the right shows that some changes are already happening since 30s or 40s when people still don't realize any symptoms.

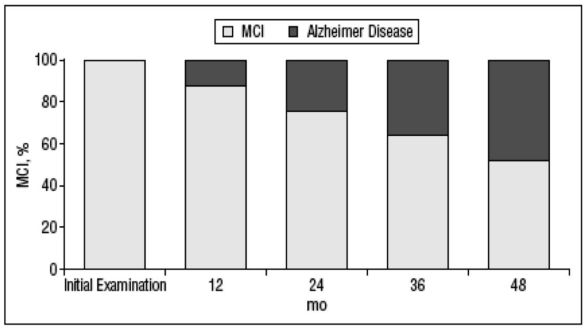
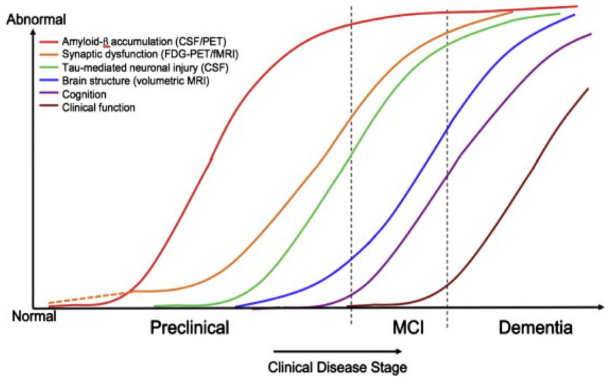


Figure 2. *Annual rates of conversion from mild cognitive impairment (MCI) to dementia over 48 months.*



★Diagnosis:

- Diagnosis is clinical
- Rely on history and cognitive/neuropsychological assessments that demonstrates a slowly progressing cognitive disorder which causes functional impairments in daily life eg. If they start to depend on others or if they start losing their hobbies then it might be dementia (if there was cognitive disorder with no Functional impairment in the clinical assessment it is called: cognitive impairment non-dementia)
- Brain structure on MRI may demonstrate medial temporal atrophy bilaterally
- PET scans can demonstrate decreased metabolism in temporal and parietal regions which later on spreads to the whole brain

- Cerebrospinal fluid might show low Amyloid beta, and elevated Tau (not specific)
- Do investigations to rule out other causes (CBC) and brain imaging

Lewy Body Dementia (Pick Disease)

★ Clinical Features:

- Second most common cause of "**degenerative**" dementia
- Primary degenerative (not vascular related)
- Lewy body dementia is very distinctive from Alzheimer's, since in lewy dementia the memory isn't the prominent deficit, rather the following are more prominent.
- Core clinical features includes visual hallucinations (seeing things that are not really there), parkinsonism (feature of parkinson disease mainly rigidity and bradykinesia, tremors, gait abnormalities), and fluctuations in cognitive ability and level of consciousness.
- visual hallucinations, parkinsonism, and fluctuations are the important criteria of lewy body.
- Other symptoms include Visual spatial impairment (examples, unable to draw a clock or cubes, they can get confused between right and left, can't read a map or put on their clothes upside down) followed by short term memory, sensitivity to neuroleptics (they get severe parkinsonism, and if you do see a patient react to neuroleptics like that, then we have to think of lewy body), REM sleep behavior disorder (they kick or scream while sleeping) and autonomic dysfunction (orthostatic hypotension, ED)
- Pathologically there are "Lewy Bodies" present in neurons, which are the result of abnormal synuclein protein accumulation.

✓ Parkinson's Disease Dementia is similar to LBD. The difference is that a clear history of PD with NO cognitive impairment precedes the development of dementia by at least a year.

★ Diagnosis:

- Diagnosis is primarily clinical
- PET scan may show decreased occipital lobe metabolism
- Myocardial scintigraphy may be abnormal due to abnormal cardiac sympathetic innervation

Vascular Dementia

★ Clinical Features:

- Frequently coexists with Alzheimer's disease (bc alzheimer is common, and has the same risk factors)
- Occurs secondary to
  - A single stroke in a region important to cognition such as hippocampus or thalamus, or a large stroke that affects multiple lobes

  - Recurrent strokes that accumulate over time, there is a step-wise development of cognitive deficits
  - Slowly progressing cognitive deficits due to subclinical progressing of small vessel disease
- Associated with vascular risk factors
  - Hypertension and hyperlipidemia
  - Diabetes Mellitus
  - Smoking

Frontotemporal Dementia

★ Clinical Features:

- Mean age of onset is 58 (earlier than the other forms of dementia
- Affects social cognition before memory or anything
- Preferentially involves the frontal and temporal lobes, symptoms depend on the region (lobe) involved, therefore there are variants:
  - Behavioral Variant (disinhibited behaviour is common as touching the other sex or unusual sexual relationships) or apathy towards others (seeing someone crying in pain and not caring about it)
  - Primary Progressive Aphasia (as a slowly progressive form of broca's aphasia)
  - Semantic Dementia (semantic = meaning, e.g. if you show them a pen they don't know what it is anymore)
- Common pathological inclusions include hyperphosphorylated Tau protein, TDP-43 protein, or FUS protein

★ Behavioural Variant:

- Associated with personality changes
- Inappropriate social behaviors (disinhibited)
- Lack of insight
- Binging on certain foods
- Emotional blunting
- Rigid and cannot adopt to new situations along with decreased attention modulation
- MRI shows atrophy in the frontal lobes (may be asymmetric)

★ Progressive non-fluent aphasia:

- Patients present first with a non-fluent type of aphasia (similar to a broca's lesion)
- MRI may show focal left frontal atrophy

★ Temporal Variant of FTD: also known as **(Semantic Dementia)**

- Usually have intact fluency, but comprehension is impaired and decreased naming ability
- MRI may show focal left temporal atrophy.

Normal Pressure Hydrocephalus

★ Clinical Features:

- A rare disorder
- It classically presents with the triad of:
  a. **Gait impairment (ataxia)**: the typical unique gait has been described as "magnetic", the patient may shuffle their feet on the ground with a normal or wide base, some may have some features of parkinsonism
  b. **Dementia:** is of a subcortical type, where there is executive dysfunction, and psychomotor slowing first. Other features of cognitive impairment develop later on
  c. Urinary incontinence

✓ However these features above are not unique to NPH

- It usually results from impaired CSF absorption at the level of the arachnoid villi
- In secondary NPH, there is usually a history of a previous meningitis, inflammatory disorder, or subarachnoid hemorrhage. Idiopathic NPH is when there is no preceding explanation for the condition
- Patients who present with gait impairment > cognitive impairments have better prognosis if identified early
- Some patients will improve after a lumbar puncture that removes 30-50 cc of CSF. If this test is positive, then a CSF shunting procedure is performed
- MRI of the brain may also show dilated ventricles (however CSF pressure is normal) hence the name normal pressure hydrocephalus.

Creutzfeldt-Jakob Disease

★ Clinical Features:

- Rare, 1 in a million
- This dementia is rapidly progressive, sometimes they confuse it with delirium because it develops rapidly (within 6 months someone can turn from normal to severe dementia)
- It is a prion disorder and can be transmitted (transmissible spongiform encephalopathy transmitted from person to person but not infectious, usually comes sporadically (not by transmission)
- Prions are abnormally formed proteins that induce pathological transformations in other proteins.

- It has been transmitted after the use of surgical equipment or growth hormones
- CJD presents as a rapidly progressing dementia, disease duration usually 6 months. Myoclonic jerks may occur
- Any picture of cognitive impairment may occur, as may other neurological symptoms like parkinsonism, ataxia, field defects, spasticity, hyper-reflexia, and + Babinski
- MRI may show abnormal signal intensity in the basal ganglia and cortical ribbon
- EEG shows characteristic periodic sharp wave complexes
- No treatment, patients die within a year
- The bovine variant CJD has been linked to consumption of beef (UK outbreak in the 90s)

Other Causes of Dementia

- HIV Associated neurocognitive disorder
- Syphilis
- Vitamin B12 deficiency (if you see someone has megaloblastic anemia then check for dementia)
- Autoimmune disorders (eg: SLE)
- Alcohol leading to wernicke-Korsakoff's syndrome, characterized by confabulations to compensate for amnesia

★ Treatment of Cognitive impairment:

- **Cholinesterase Inhibitors:** Drugs such as Donepezil, rivastigmine and galantamine which increase the presence of central nervous system acetylcholine help with cognitive and behavioral symptoms in Alzheimer's dementia.
- Does not stop disease progression, but may provide transient clinical stability (it slows down the decline but usually we don't expect improvement)
- NMDA receptor antagonist, memantine, is helpful in moderate to advanced alzheimer's disease
- No pharmacological treatment available for MCI
- Not a treatment, but education and physical activity protect from cognitive decline (exercising and eating fruits and vegetables might benefit them)

Summary

	Delirium	Dementia
Definition	Disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day	Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains develop within years
Presentation	• Reduced ability to direct, focus, sustain, and shift attention. • Memory deficit, disorientation, language disturbance, perceptual disturbance • Change in level of consciousness	• Learning and memory • Language • Executive function • Complex attention • Perceptual-motor • Social cognition • Normal consciousness
Causes	• Metabolic • Drugs & toxin • Infection • Post-surgery • CNS disorders	• **Neurodegenerative:** ○ Alzheimer's Disease ○ Lewy Body Dementia ○ Parkinson's Disease ○ Dementia ○ Frontotemporal Dementia ○ Huntington's Disease • **Other:** ○ Vascular Dementia ○ Normal Pressure Hydrocephalus ○ Creutzfeldt-Jakob Disease ○ Alcohol leading to Wernicke-Korsakoff Syndrome ○ Secondary to infection or systemic illness ○ HIV Associated neurocognitive disorder ○ Syphilis ○ Vitamin B12 deficiency ○ Autoimmune disorders (eg: SLE)
Management	**(it is a medical emergency)** • **ABCDE** • CBC & routine tests, arterial blood gases • Urinalysis and toxicology screen • Chest X-ray, EKG • CT head, EEG, Lumbar Puncture	Depends on the cause but remember it **does not** stop disease progression, but may provide transient clinical stability

	=> Directly treat the Etiology once found	

Disease	Clinical features	Pathophysiology	Risk factors	Management & Treatment
Alzheimer's Disease **(hallmarks)**	• **Decreased memory** and new learning • Language impairment • Apraxia • Unawareness of illness • Visual-spatial impairments • Delusions • Depression & weight loss	• Accumulation of amyloid beta and forming senile **plaques** • Formation of neurofibrillary **tangles**	• **Increasing age** • APOE ε4 • Down Syndrome • DM, HTN, Hyperlipidemia, Lack of exercise • Brain trauma	• Diagnosis is clinical • MRI: medial temporal atrophy bilaterally • PET scans: decreased metabolism in temporal and parietal regions • Cholinesterase Inhibitors & NMDA receptor antagonist
LBD	• Visual hallucinations • Parkinsonism • Fluctuations in cognitive ability and level of consciousness. • REM sleep behavior disorder	"Lewy Bodies" present in neurons, which are the result of abnormal synuclein protein accumulation		• Diagnosis is primarily clinical • PET scan: decreased occipital lobe metabolism • Abnormal myocardial scintigraphy
Vascular Dementia	• Frequently coexists with Alzheimer's disease	Recurrent strokes in cognitive area	• Hypertension • Hyperlipidemia • Diabetes Mellitus • Smoking	
Frontotemporal Dementia	• Behavioral Variant • Primary Progressive Aphasia • Semantic Dementia	Inclusions of hyperphosphorylated Tau protein, TDP-43 protein, or FUS protein		MRI: focal left frontal atrophy
Normal Pressure Hydrocephalus	Classically triad of: • **Gait impairment (ataxia)** • **Dementia** • **Urinary incontinence**	Impaired CSF absorption at the level of the arachnoid villi		• MRI: dilated ventricles (CSF pressure is normal) • Improvement after removal 30-50 cc of CSF

Creutzfeldt-Jakob Disease	• Cognitive impairment • Neurological symptoms like parkinsonism, ataxia, field defects, spasticity, hyper-reflexia, and + Babinski	Prions are abnormally formed proteins that induce pathological transformations in other proteins		• MRI: abnormal signal intensity in the basal ganglia and cortical ribbon • EEG:characteristic periodic sharp wave complexes • No treatment, patients die within a year

Questions

1. **73 year old male retired judge presents with 1 year history of cognitive concerns**
   Trouble recalling names. He can completely forget a discussion, forgets the location of previously placed tools, only recalls fragments of a previous doctor visit 2 weeks earlier.
   Does not follow the dates as accurately as he used to and indicates that this is because he is retired. Sometimes he is repetitive with questions. Confusion about how to do things especially when tired. His ability to use household appliances is also affected. Tried putting on his shirt while still on the hanger. What do you think most likely his problem is? (This case is from doctor's slides)
   A. Alzheimer's
   B. Lewy body dementia
   C. Frontotemporal dementia
   D. Creutzfeldt-Jakob Disease

   Note: here there are multiple cognitive deficit but the most prominent cognitive deficit is memory. Age of 73 + memory deficit then we most likely think of Alzheimer's

2. **Which brain lobes are most commonly affected in Alzheimer's disease?**
   A. Occipital and temporal
   B. Frontal and temporal
   C. Parietal and temporal
   D. Occipital and parietal

3. **Which brain lobes are mostly affected in Lewy Body dementia?**

A. Occipital and temporal
B. Frontal and temporal
C. Parietal and temporal
D. Occipital and parietal

4. Which brain lobes are mostly affected in frontotemporal Dementia?

A. Occipital and temporal
B. Frontal and temporal
C. Parietal and temporal
D. Occipital and parietal

5- Which of the following are commonly seen in brain imaging of patients with Alzheimer disease?

A. Enlarged cerebral ventricles and atrophic brain tissue
B. Normal cerebral ventricles and atrophic brain tissue
C. Enlarged cerebral ventricles and no atrophy of brain tissue
D. Normal cerebral ventricles and normal brain tissue, acetylcholine deficiency

Answers:

1. A, 2.C 3. D, 4. B, 5. A, because Alzheimer disease typically has enlarged cerebral ventricles and brain atrophy, whereas normal pressure hydrocephalus has enlarged brain ventricles without brain atrophy.