Memory Loss: What's Normal, What's Not

Alan Zacharias, MD
Associated Neurologists
Boulder Community Health
303-963-9694

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Today's Discussion

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- History of Alzheimer's disease
- Normal aging
- Mild cognitive impairment
- Alzheimer's disease
- Prevention and treatment
- Latest updates

History

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- 1906-Alois Alzheimer reports case of presenile dementia in a 51-year-old woman in Germany.
- He was born in 1864 in Markbreit, Germany.
- Wrote dissertation on wax-producing glands of the ear.
- First worked in mental asylum in Frankfurt where he encountered Frau Auguste D.

History

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- He focused on trying to separate various forms of dementia using detailed pathology.
- Alzheimer wrote in 1898, “Presenile dementia is distinguished from the common senile dementia by the pre-existing feebleness of the intellect and the earlier appearance of senile feeblemindedness, and from paralysis by its long slow course and lack of the characteristic physical symptoms of paralysis.”
- 1910-Emil Kraepelin first applied the eponym to presenile dementia.

History

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- The senium was felt to begin at age 60 until 1887. Sixty-five became the dividing point when old-age insurance was introduced in Germany.
- 1940-McMenemey discourages thinking of Alzheimer's disease only in terms of age because the pathology can be seen at multiple ages.
- Later 20th century-plaques and tangles get better defined and understood as key features of Alzheimer's disease.

Normal Aging

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- Quite variable for physical and cognitive function
- Depends on genetics, environment, and lifestyle
- By age 20, we start to lose brain cells and important chemicals for brain function
- Short-term and remote memories are not usually affected by aging, but recent memory may be (e.g., forgetting the name of someone you recently met)
- Trouble coming up with a word temporarily is common

Normal Aging

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- There should not be a significant impact on your daily function.
- Case example: A 55-year-old business woman has been concerned about her memory for the past 6 months. She is under a great deal of stress at work and has been having difficulties coming up with the names of recent clients. She occasionally misplaces objects at home. Her mother had AD at age 80, and consequently she is concerned that she may be developing symptoms of AD.

Normal Aging

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- Her neurologic exam is normal and neuropsychological testing is normal. Brain MRI and labs are normal.
- This patient represents the “worried well.” She has no significant memory problem and should be reassured and followed clinically. Perhaps modifying her work schedule would help.

Normal Aging

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- Various terms have been applied over the years:
  - Benign senescent forgetfulness
  - Age-associated memory impairment
  - Aging-associated cognitive decline
  - Late-life forgetfulness
- We are often more aware of this than our friends, which is a generally good sign of the benign nature of our concerns.

Mild Cognitive Impairment

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- MCI is meant to refer to an abnormal process, likely the early stages of a dementing condition and, as such, is fundamentally different from the extremes of normal aging.
- 12-18% among nondemented subjects aged over 65 years and somewhat lower when entire population is considered.

MCI

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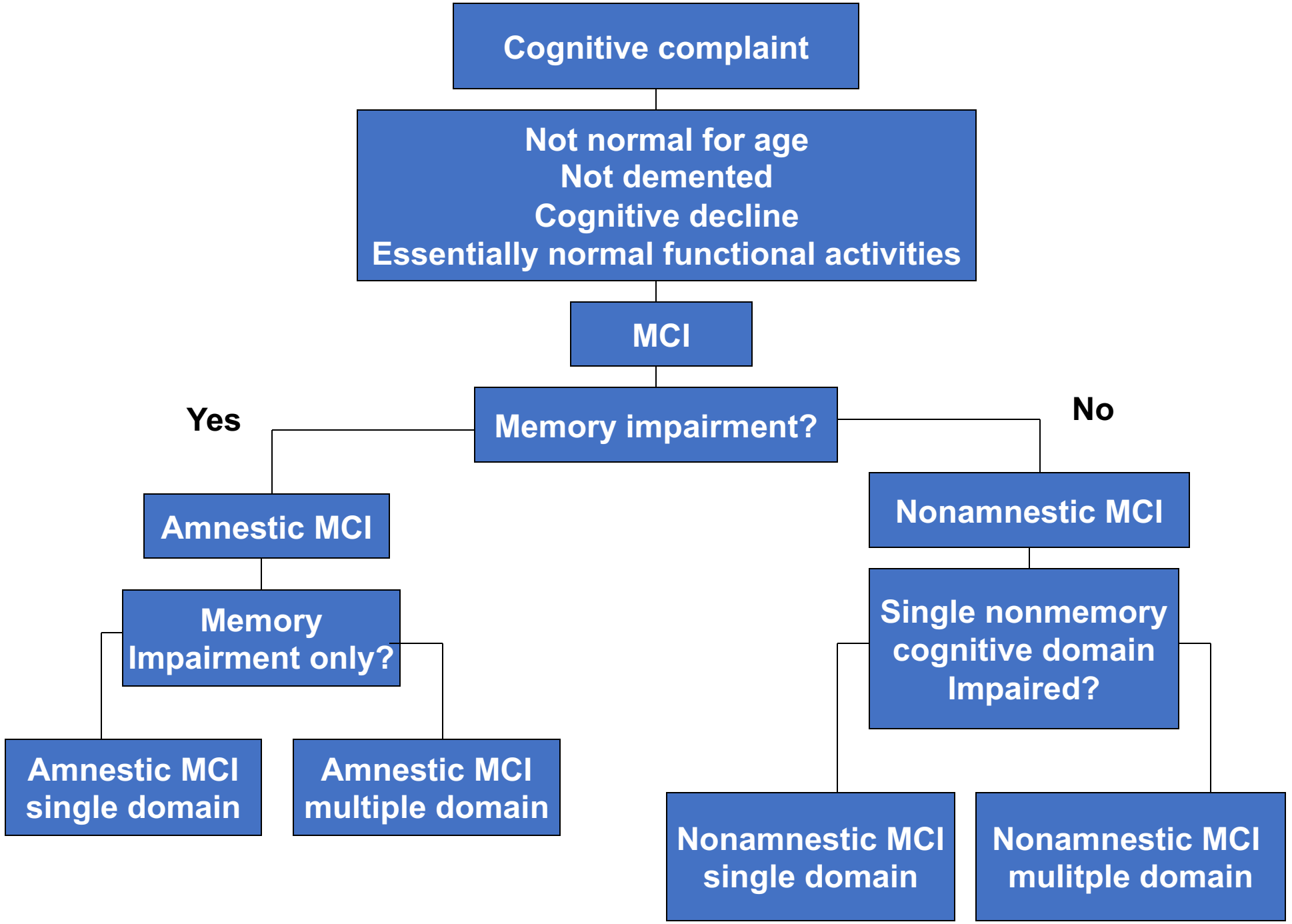
- The incidence is about 1% per year after age 65.
- Originally defined to predict a pre-Alzheimer state, but not all patients with MCI develop AD.
- A consensus conference in 2003 convened in Stokholm to define MCI.


Cognitive complaint
Not normal for age
Not demented
Cognitive decline
Essentially normal functional activities
MCI
Memory impairment?
Yes
No
Amnestic MCI
Memory Impairment only?
Amnestic MCI single domain
Amnestic MCI multiple domain
Nonamnestic MCI
Single nonmemory cognitive domain Impaired?
Nonamnestic MCI single domain
Nonamnestic MCI mulitple domain

MCI

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- There are not absolute rules or tests to prove MCI. It remains a clinical judgment of the physician.
- Case example: A 68-year-old retired teacher has been becoming increasingly forgetful over the past year. Although the demands on this man have been reduced in retirement, he is still having difficulty recalling details of events. He is impaired in trying to recall important information such as doctor appointments, luncheon engagements, and golf tee times with his friends. His family has been noting that he is forgetting information that he formerly would not have forgotten.

MCI

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- Testing in the office reveals missing recall of three words and day of the week. The remainder of the exam is normal. He is not depressed. MRI reveals mild atrophy of the hippocampal formations bilaterally but otherwise normal. Neuropsychological testing was notable only for trouble learning new material and impaired delayed recall.
- This is most likely amnestic-MCI. There is a slowly progressive memory problem with otherwise unremarkable cognitive impairment and he does not have significant functional impairment. Therefore, he does not meet criteria for dementia. This may represent the earliest stages of a degenerative disorder such as AD.

MCI

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- Determining the cause of MCI
  - Degenerative
    - Gradual onset, insidious progression
  - Vascular
    - Abrupt onset, hypertension, increased cholesterol, diabetes, smoking, history of TIA or strokes
  - Psychiatric
    - History of depression, depressed mood, or anxiety
  - Medical
    - Congestive heart failure, systemic cancer, kidney failure, diabetes

MCI

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- Amnestic MCI of a degenerative cause progresses to dementia, usually AD, at a rate of 10% to 15% per year. If there is AD pathology then up to 35%/year.
- This compares to population incidence figures for AD of 1% to 2% per year.
- A small percentage will improve and some will remain stable for many years.

MCI

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- Predictors of progression
  - Clinical severity
  - MRI hippocampal volumes
  - APOE4 carrier status
  - {18 F} fluorodeoxyglucose (FDG)-PET
  - CSF biomarkers (tau and beta-amyloid)
  - Amyloid imaging in PET scans
  - Tau imaging in PET scans

MCI

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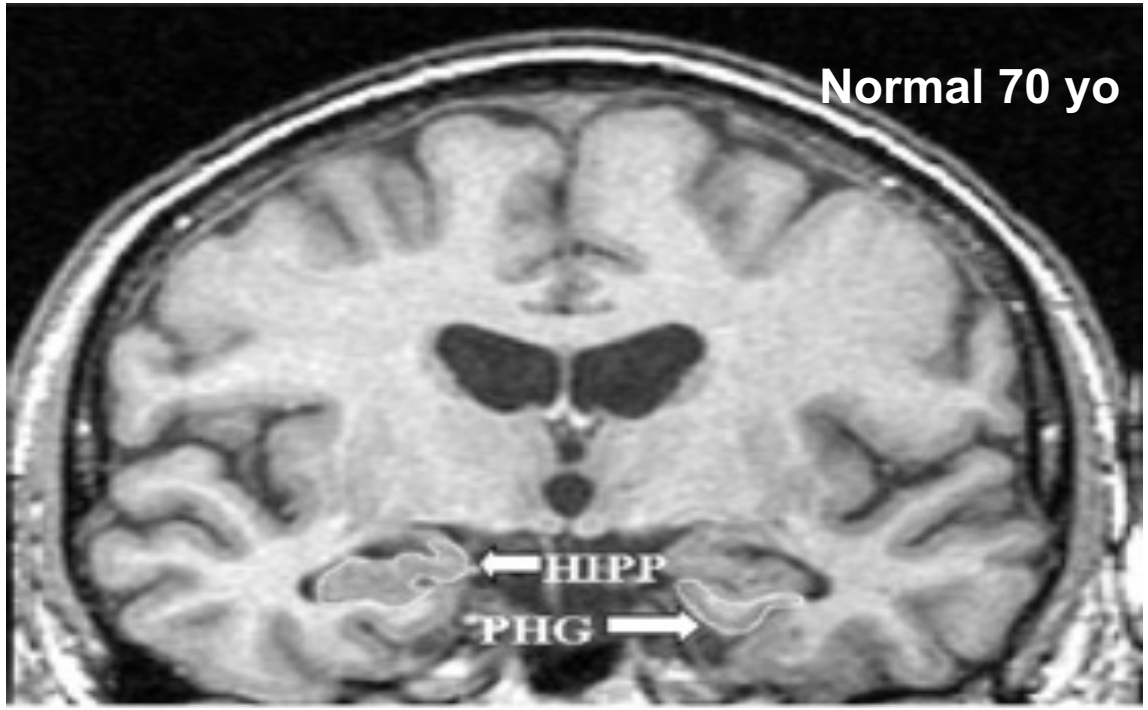
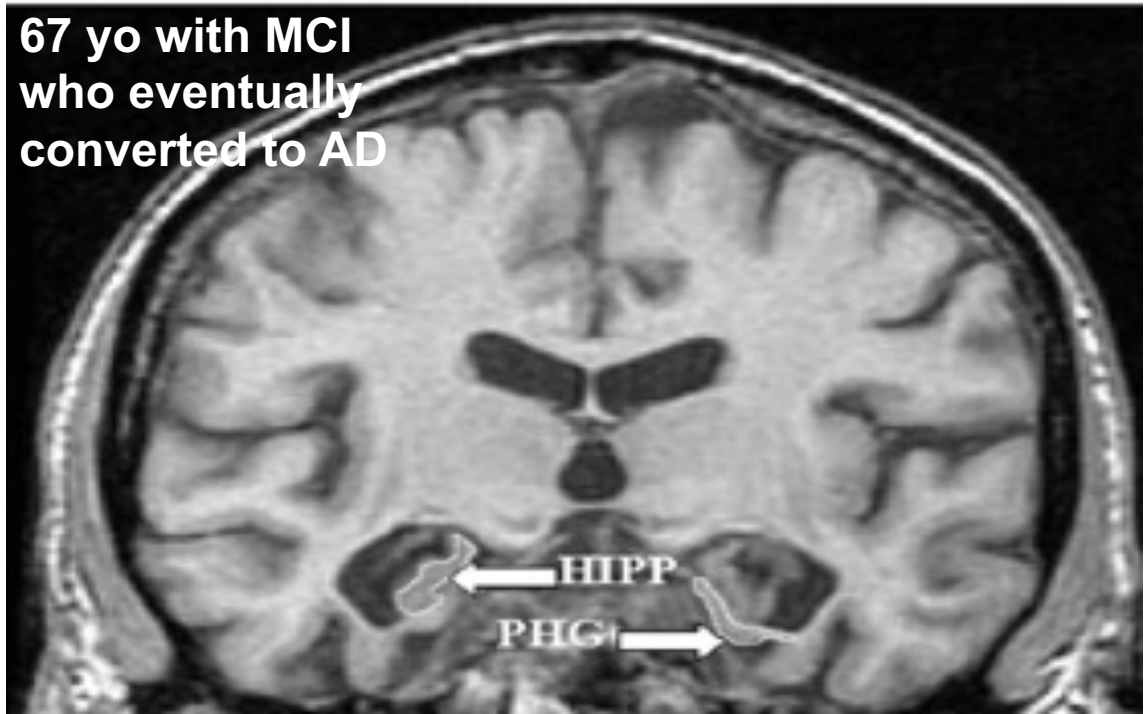
- Patients with more severe memory loss and multiple domain MCI tend to progress faster than those with amnestic MCI and less severe memory loss.
- Atrophy (loss of cells and mass) in the hippocampus increases the likelihood of progression. Subjective and quantified assessments are valid.

HIPP=Hippocampus

PHG=Parahippocampal gyrus





MCI

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- APOE4 carrier status is a well-known predictor of AD
  - Also predictor of conversion from MCI to AD
  - A carrier of cholesterol and lipids in the blood and in the brain and spinal fluid. It also transports beta-amyloid.
  - Types are e2 (rare), e3 (most common), e4 (15%-20% of population)

MCI

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- The 1-2% of individuals who are homozygous for e4 have 50% risk of developing AD in their mid-to-late 70s.
- Because of lack of specific therapy and ability to predict which individuals will convert to AD, the American Academy of Neurology does not currently recommend routine testing for APOE4 status.

MCI

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- Imaging techniques
  - MRI is mainly used to exclude other causes of cognitive impairment or dementia
  - PET scanning looks at the metabolism or substances in the brain with various markers
    - Generally valid and helpful in studies
    - Glucose, Amyloid, Tau, Synapse markers
    - Not considered mandatory or necessary for diagnosis of MCI or AD yet
    - Expensive and still not widely available
    - Other labeling techniques are being studied and intriguing and just starting to be used outside research studies

MCI

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- The pathology of amnestic MCI is generally the same as that of AD
  - There are neuritic plaques and neurofibrillary tangles in both conditions.
  - The volume is less in MCI than AD.
  - Some argue that this is AD because the vast majority of patients develop the clinical features eventually. However, there are some cases of other dementias such as dementia with Lewy bodies, frontotemporal dementia, progressive supranuclear palsy and vascular dementia that start with amnestic MCI.

Alzheimer's Disease

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- Most common form of dementia
- 4.5 million individuals
- Incidence doubles every 5 years after age of 60
- Estimated prevalence of 14 million by 2050 in the US and 100 million worldwide
- Most common cause of nursing home placement
- Cost of about $140 billion dollars
- If we could just delay onset or functional deterioration by 1-2 years cost savings would be tremendous

AD

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- The atrophy begins in the hippocampus and spreads to affect all other areas of cortex except the occipital lobe.
- Microscopically there is neuronal loss, amyloid plaques (diffuse and compact), deposits of amyloid in blood vessels, neurofibrillary tangles (abnormal tau proteins)—these are the principle features described 100 years ago by Alzheimer.

AD

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- A cascade of events is theorized to lead to AD, starting with inflammation and free radical formation.
- The neurotransmitter, acetylcholine, decreases significantly with others declining later in the disease (glutamate, noradrenaline, serotonin).
- Synapses are reduced.
- The volume and distribution of plaques and tangles define the disease pathologically, but some normal elderly individuals have the pathology without symptoms of the disease.

AD

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- The major risk factor is age
  - Prevalence 1-2% age 65, 15% at 75, 40% at 85
- Family history
  - 20% of patients have one or more siblings or parents affected
  - Some mutations in genes cause familial forms but only about 1% of all cases
- More common in Women
  - Estrogen replacement may actually increase risk

AD

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- Increased education and exercise are associated with lower risk.
- More religious and spiritual individuals seem to have a lower risk.
- Anti-inflammatory medicines (Advil) once thought to be protective probably are not.
- Diabetes, high cholesterol, hypertension, obesity increase risk.

AD

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- The diagnosis is based on impaired memory and other cognitive impairment that is gradual and progressive and impairs function with no other identifiable causes. It cannot be diagnosed in the setting of an acute confusional state (delirium).
- Pathologic criteria usually confirm the diagnosis at autopsy but not always.

AD

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- An appropriate history is the most important clue for the disease. The patient is often unreliable, but family or friends can usually provide the key information.
- Key information
  - Insidious onset of short-term memory loss
  - Repetitive conversations
  - Language difficulties
  - Getting lost while driving or in a parking lot
  - Trouble with the checkbook or finances
  - Trouble following a recipe or planning a trip

AD

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- Behavioral disturbances
  - Common as the illness progresses
  - Apathy is common early
  - 30% with depression in the early stages
  - Anxiety, especially when alone or forced to interact in large groups
  - As the disease progresses paranoia and delusions are common
  - 75% with agitation as disease progresses
    - Verbally and physically aggressive with family or caregivers
  - Disinhibition in the form of jokes or sexual behavior

AD

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- The physical and neurological exams help primarily to exclude other conditions that may mimic AD.
- Laboratory tests and imaging primarily exclude other potential causes (maybe 10-20% of cases), but are also now starting to allow diagnosis to be more certain. This includes blood and spinal fluid tests as well as amyloid PET scans.
- Formal neuropsychological testing very helpful as well.

Prevention and Treatment

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- Mild cognitive impairment
  - No FDA approved treatments. But now aducanumab may be appropriate to consider with proper markers to suggest high-risk of AD developing.
  - Most attention has been for amnestic MCI
  - Trials with Vitamin E, donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne), and rofecoxib (Vioxx) were all negative except Aricept delayed conversion to AD for the first 12-24 months but not different at 36 months.

Prevention and Treatment

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- So what does the doctor say to a patient with MCI?
  - It depends on all of the factors present and one's acceptance of risk.
  - It is an important time to plan for the future, including financial issues, retirement, living arrangements, etc.
  - Be physically and intellectually engaged, eat healthy, keep your eyes open for new therapies.

Prevention and Treatment

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- Alzheimer's disease
  - All current therapies are primarily symptomatic, focused on cognitive or behavioral symptoms.
  - None had been proven to delay biological progression of disease until the recently approved aducanumab, which reduces amyloid volume.
  - Most of the beneficial effects of current therapies are mild at best, but still appropriate to consider in all patients with AD and perhaps for MCI and mild AD cases consider aducanumab.

Prevention and Treatment

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- AD
  - The FDA approved drugs are Aricept, Razadyne, Exelon, and Namenda.
  - Aricept, Razadyne, and Exelon all increase the levels of acetylcholine by blocking its breakdown (cholinesterase inhibitors).
  - Namenda is an NMDA receptor antagonist that protects neurons from toxic effects of calcium and glutamate.

Prevention and Treatment

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- The cholinesterase inhibitors have the potential to mildly improve cognition, function in activities of daily living, and behavior in patients with mild to moderate AD for periods of between 6 and 18 months. Aricept has also recently been shown to be effective for treating moderate to severe stages of dementia.

Prevention and Treatment

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- Namenda mildly improves cognitive deficits, function in ADLs, and behavior in patients with moderate to severe disease. It may be used alone or added to Aricept.
- Vitamin E was originally shown to delay functional deterioration in moderate to severe disease, but no benefit was seen in MCI. There is also theoretical risk of clotting causing enthusiasm to wane for its use.

Prevention and Treatment

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- Ongoing trials will focus on trying to prevent amyloid and other abnormal protein deposition (e.g. antibodies directed against amyloid).
- Several amyloid antibody studies have failed until now with aducanumab.
- Amyloid vaccination - a phase 2 study was stopped when some patients developed encephalitis.
- Treatment of behavioral symptoms eventually becomes the major focus of family, health care facility and physicians.

Prevention and Treatment

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- Behavioral symptoms
  - No specific FDA approved drugs for treating behavioral symptoms associated with dementia.
  - A consistent environment is helpful.
  - Atypical antipsychotic medications may help agitation, delusions, hallucinations, mood swings. There are reports of increased risk of stroke and deaths with these drugs.

Prevention and Treatment

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- Depression can be treated with drugs that increase serotonin such as Prozac.
- Anxiety and obsessive behaviors may respond to mild tranquilizers like Ativan or antidepressants or antipsychotics.
- Insomnia can be treated with mild tranquilizers or some of the newer sleep aids such as Ambien.

When is the Beginning of AD?

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- From the Religious Orders Study (1994) and Rush Memory and Aging Project (1997)
  - 2000 individuals originally free of dementia
    - Initially similar declines in those who ultimately develop AD and those who don't.
    - 65 months before AD diagnosed the rates of decline are 15 times faster.
    - Combining MCI data suggests that there may be a 10 year decline before AD is diagnosed.

New Alzheimer's Criteria

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- Three stages
  - Preclinical AD
    - No outward symptoms but only biomarkers as in spinal fluid or abnormal PET scans
  - Mild cognitive impairment due to AD
    - Changes in memory and thinking but not yet compromising everyday activities and function
  - Dementia
    - Functional impairment

Implications of New Criteria

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- The disease really has a continuum of preclinical, early and full blown stages.
- We still need more work to determine who with MCI will go on to develop AD but biomarkers are here and can be helpful.
- Changing research approaches
  - Better biomarkers (amyloid, Tau, synapses)
  - Earlier treatment now a consideration
- More attention to prevention - early education of our children.

iDEAS Study

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- Imaging dementia-Evidence For Amyloid Scanning (PET scans)
- Results influence decisions about care
- May influence patient decisions on life plans
- Creating evidence to pay for the scans
- Building a database of patients for study
- Likely to lead to more understanding

Summary

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- Forgetfulness is common in normal individuals with age.
- When there is impaired short-term memory, alone or with mildly impaired other areas of cognition, that does not cause significant functional impairment then MCI should be considered.
- AD is diagnosed when functional impairment is present in the setting of memory loss and other cognitive impairment.

Summary

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- We must always try to find reversible or treatable causes of dementia with careful examination and testing.
- There are no good treatments for MCI to consider until now.
- There are approved therapies for AD with only mild effects in most cases, including aducanumab
- We need much better prevention and treatment for the diseases that take away what make us human.

Questions?

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