° MILD COGNITIVE IMPAIRMENT

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- 9/5/2013
- 70 yo female memory concerns.
- Diagnosis: MCI amnestic variant
- MOCA 24
- Able to work.

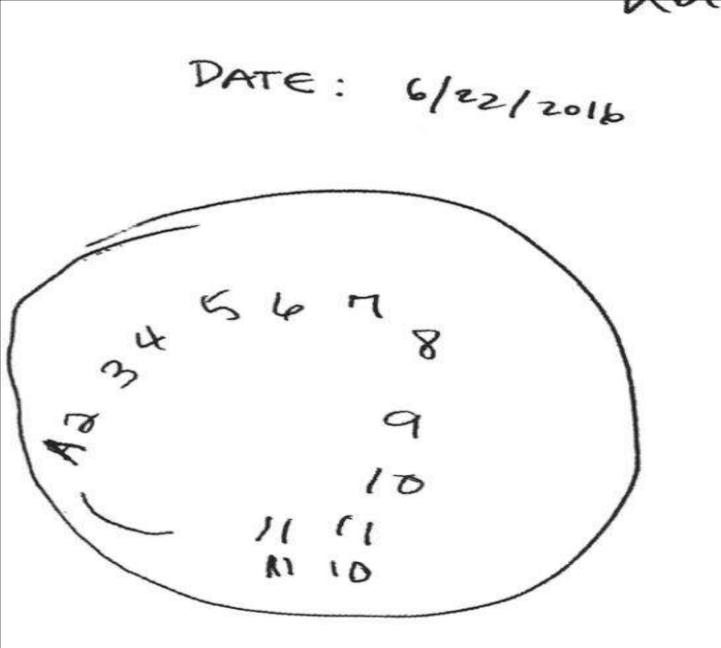
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	Category cuit	X	×				Conserved and		

7/11/2014

Diagnosis: overt arly Alzheimer's isease.

MOCA 17

Less than a year later nable to continue er career.



6/22/16 Less than 2 years later.

Diagnosis: moderate AD MOCA: Unable to complete. Unable to recognize family and friends.



• INTRODUCTION

- EVOLUTION
- EPIDEMIOLOGY
- <u>RISK FACTORS</u>
- <u>TYPES</u>

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- <u>SYMPTOMS</u>
- <u>DIAGNOSIS</u>

• <u>PATHOPHYSIOLOGY</u>

• <u>ASSESSMENT</u>

• OUTCOME

• TREATMENT

• CURRENT STATUS

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• <u>REFERENCES</u>

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introduction

• Mild cognitive impairment (MCI) most simplistically defined as the cognitive changes in the absence of dementia.

• MCI refers to a condition in which there is a decline in one's usual cognitive abilities eg. (Memory, language functions, reasoning) but not to the extent that it is obvious in daily living activities, like banking, driving, managing medication and taking care of usual responsibilities

INTRODUCTION

• In all cases, the term MCI excluded individuals with significant depression, delirium, mental retardation, or other psychiatric disorders likely responsible for the impairment in any Cognitive Domain.

 If the memory loss was severe and accompanied by significant functional impairment, the individual met clinical criteria for dementia, as opposed to MCI

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EVOLUTION

- The concept of MCI has evolved considerably over the years.
- The intent behind the concept of mci was to capture and classify patients who seem to have a cognitive problem that one would hesitate to label as "normal," but that is not severe enough to qualify as dementia.
- In 1962 kral used the term "benign senescent forgetfulness" to describe early memory concerns with aging.

EVOLUTION

- In the 1980s, global clinical staging scales for the study of AD were developed to more rigorously classify the broad spectrum of intellectual performance found in geriatric populations.
- Two of the most commonly used scales, the global deterioration scale (GDS) and the clinical dementia rating (CDR),
- This was followed by a national institute of mental health workgroup in 1986 that proposed the term "age-associated memory impairment" (AAMI) to refer to memory changes that were felt to be a variant of normal aging.

<u>EVOLUTION</u>

• The international psycho geriatric association coined the term "ageassociated cognitive decline" in an effort to bypass many of the shortcomings recognized in AAMI.

- MCI as a term was introduced into the literature in 1988 by Reisberg and colleagues as stage 3 of the GDS
- In 1997 Peterson described this entity as mild cognitive impairment.

EVOLUTION

• The terms like AAMI , AACD were intended to refer extremes of normal aging.

 In contrast, mci is meant to refer to an abnormal process, likely the prodromal stages of a dementing condition and, as such, is fundamentally different from the extremes of normal aging.

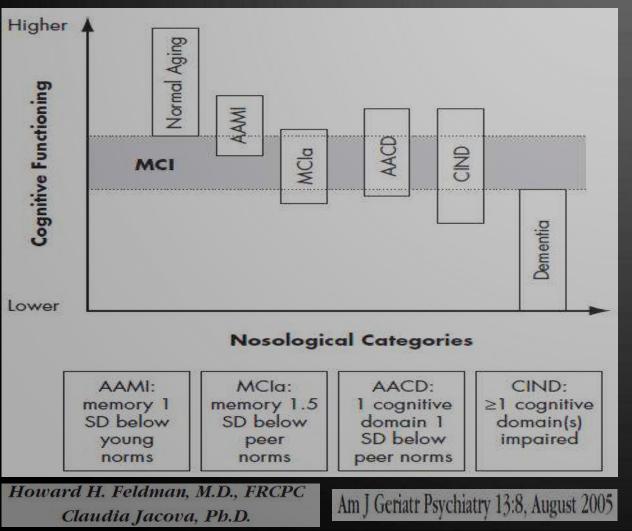
EVOLUTION

Some Of The Terms Closely Related To MCI Are:-

BSF - Benign Senescent Forgetfulness AAMI - Age Associated Memory Impairment AAMD - Age Associated Memory Decline ARCD - Age Related Cognitive Decline MCD - Mild Cognitive Dysfunction MND - Mild Neurocognitive Dysfunction CIND - Cognitive Impairment Not Demented QD - Questionable Dementia LLF – Late Life Forgetfulness

CONCEPTUAL MODEL

Cognitive Continuum From Normal Aging To Dementia



- Slow Processing speed
- Trouble with learning things
- Un-attentive
- Trouble remembering the task

Am I on the TIMELINE Clip slide

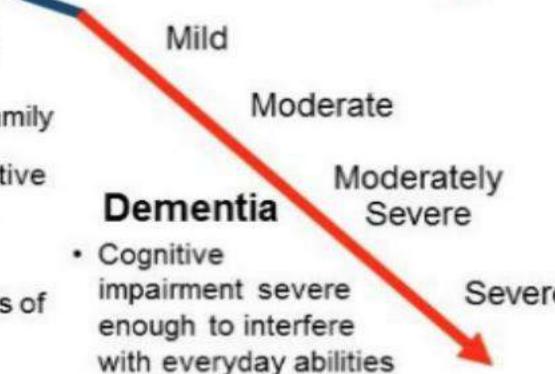
Preclinical

- Silent phase: brain changes without measurable symptoms
- Individual may notice changes, but not detectable on tests
- "A stage where the patient knows, but the doctor doesn't"

 Cognitive changes are of concern to individual and/or family

MCI

- One or more cognitive domains impaired significantly
- Preserved activities of daily living



Time (Years)

EPIDEMIOLOGY

- Prevalence of MCI differs widely according to different criteria's applied and age.
- Ranges from 3 to 17%
- Prevalence increases with age, being 3% at 60 yrs age and 14% to 18% at 75 yrs
- Incidence rates are1-2% per year



 The rate of progression to dementia is reported as 12–15% per year in patients actively seeking care for memory problems in specialized settings like memory disorders clinics.

• The rate is lower in the community at large, when MCI is systematically detected by standardized assessment.

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RISK FACTORS FOR MCI

- Age
- Apo E4
- Low Education
- Diabetes Mellitus
- Hypertension
- Vascular Risk Factors
- Depression
- Anxiety
- Cortical Atrophy

OTHERS

- Depression
- Epilepsy
- Drugs And Toxins
- Alcohol
- Sleep Apnea
- Limbic Encephalitis

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RISK FACTORS FOR MCI

Neuroinfection and inflammation

- Meningitis
- Encephalitis
- Vasculitis
- Neurosyphillis
- Lyme's Disease
- Whipple Disease
- Sarcoidosis

Metabolic conditions

- Hypo And Hyper Thyroidism
- Pituitary Insufficiency
- Hypercalcemia/Hypoglycemia
- Vit. Def (b1,b6,b12,folate)
- Chronic Liver Failure
- Chronic Respiratory Failure
- Chronic Renal Failure
- Wilsons Disease

MILD COGNITIVE IMPAIRMENT

- MCI does not always lead to dementia. In some individuals, MCI reverts to normal cognition or remains stable.
- Mild cognitive impairment is classified into two subtypes:

Based on Cognition

Amnestic mild cognitive impairment.

Non-amnestic mild cognitive impairment.

AMNESTIC MILD COGNITIVE IMPAIRMENT

• Amnestic mild cognitive impairment is clinically significant memory impairment that does not meet the criteria for dementia.

• Typically, patients and their families are aware of the increasing forgetfulness. However, other cognitive capacities, such as executive function, use of language, and visuospatial skills, are relatively preserved, and functional activities are intact except perhaps for some mild inefficiencies

NON-AMNESTIC MILD COGNITIVE IMPAIRMENT

• Nonamnestic MCI is characterized by a subtle decline in functions not related to memory, affecting attention, use of language, or visuospatial skills.

• The nonamnestic type of MCI is probably less common than the amnestic type and may be the forerunner of dementias that are not related to alzheimer's disease, such as frontotemporal lobar degeneration or dementia with lewy bodies.



BASED ON AETIOPATHOLOGY

 Neurodegenerative (Pre Alzheimer, Lewy Body, Frontotemporal Or Focal Atrophy)

• Vascular (Vascular And Mixed)

Dysthymia Or Dysphoria

<u>SYMPTOMS</u>

• The patient with MCI complains of difficulty with memory. Typically, the complaints include trouble remembering the names of people they met recently, trouble remembering the flow of a conversation, and an increased tendency to misplace things, or similar problems.

 In many cases, the individual will be quite aware of these difficulties and will compensate with increased reliance on notes and calendars.

<u>DIAGNOSIS</u>

- Different studies use different criteria's and different cut offs which leads to different rates of MCI.
- Because of this confusion it has further complicated the factors like conversion rates to dementia, subtypes, pathophysiology and other factors.
- Most importantly, the diagnosis of MCI relies on the fact that the individual is able to perform all their usual activities successfully, without more assistance from others than they previously needed.

Table 1. Original 1999 Mild Cognitive Impairment Criteria^a

Criterion

Memory complaint, preferably corroborated by an informant Memory impairment documented according to appropriate reference values Essentially normal performance in nonmemory cognitive domains

Generally preserved activities of daily living

Not demented

Table 1

General Criteria for Mild Cognitive Impairment

- Subjective complaint of memory loss
- Objective impairment of memory
- Other cognitive abilities generally preserved
- Preserved basic, day-to-day functioning
- No other obvious medical, neurologic or psychiatric explanation for the memory problems
- Criteria for dementia not met

Adapted from references 8 and 45.

PETERSON'S ORIGINAL CRITERIA

- Memory Impairment
- Objective Memory Disorder
- Absence Of Other Cognitive Disorders Or Repercussions On Daily Life
- Normal General Cognitive Function
- Absence Of Dementia

PETERSON'S ORIGINAL CRITERIA

- MEMORY IMPAIRMENT
- OBJECTIVE MEMORY DISORDER
- ABSENCE OF OTHER COGNITIVE DISORDERS OR REPERCUSSIONS ON DAILY LIFE
- NORMAL GENERAL COGNITIVE FUNCTION
- ABSENCE OF DEMENTIA
- 0.5 STAGE OF CDR SCALE

Subject Initials

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA	•	0 5	2	2
RATING (CDR):	U	0.5	2	3

9	Impairment							
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3			
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain			
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only			
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems			
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independe Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home			
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home			
Personal Care	Fully capable	e of self-care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence			

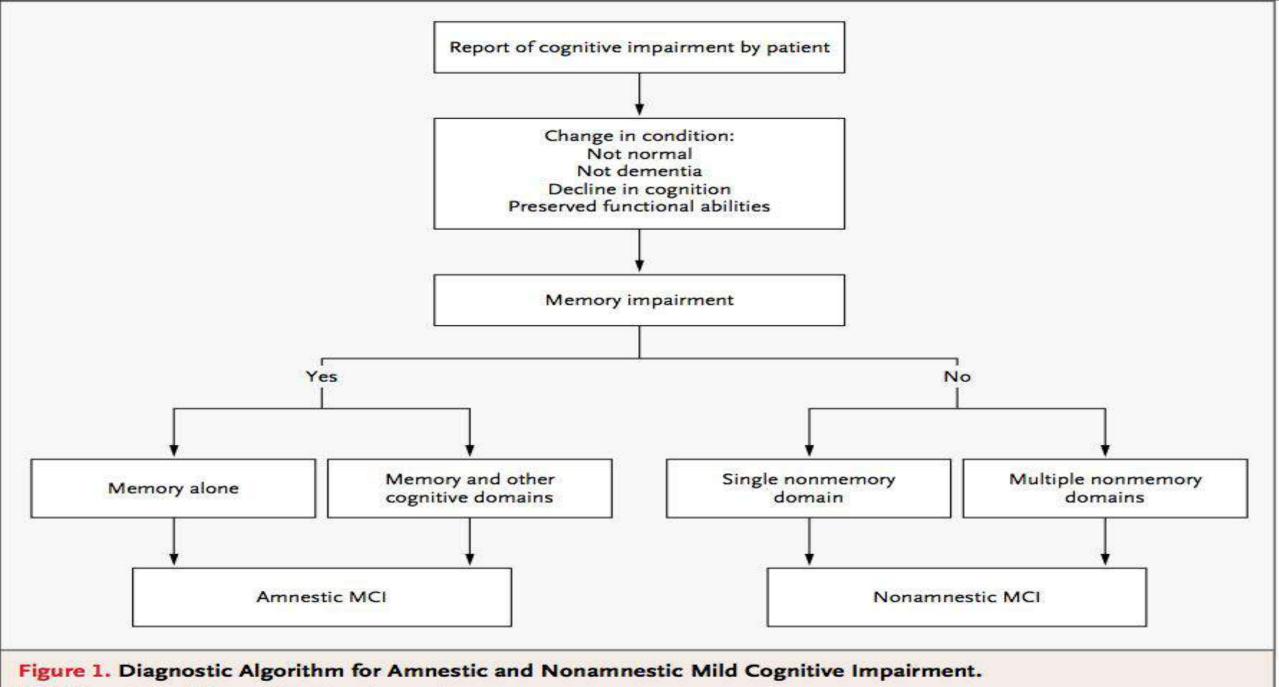
Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

EADC WORKING GROUP CRITERIA

- Cognitive complaint emanating from patient and/or his family.
- The subject and /or informant report a decline in cognitive function relative to previous abilities during past year
- Cognitive disorders evidenced by clinical evaluation: impairment in memory and/or another cognitive domain
- Cognitive domain does not have major repercussions on life , however subject may report difficulty concerning complex day to day life activities
- No dementia.

AMERICAN ACADEMY OF NEUROLOGY

- Memory complaints preferably corroborated by an informant.
- Objective memory impairment
- Normal general cognitive function
- Intact activities of daily living
- Not demented



MCI denotes mild cognitive impairment.

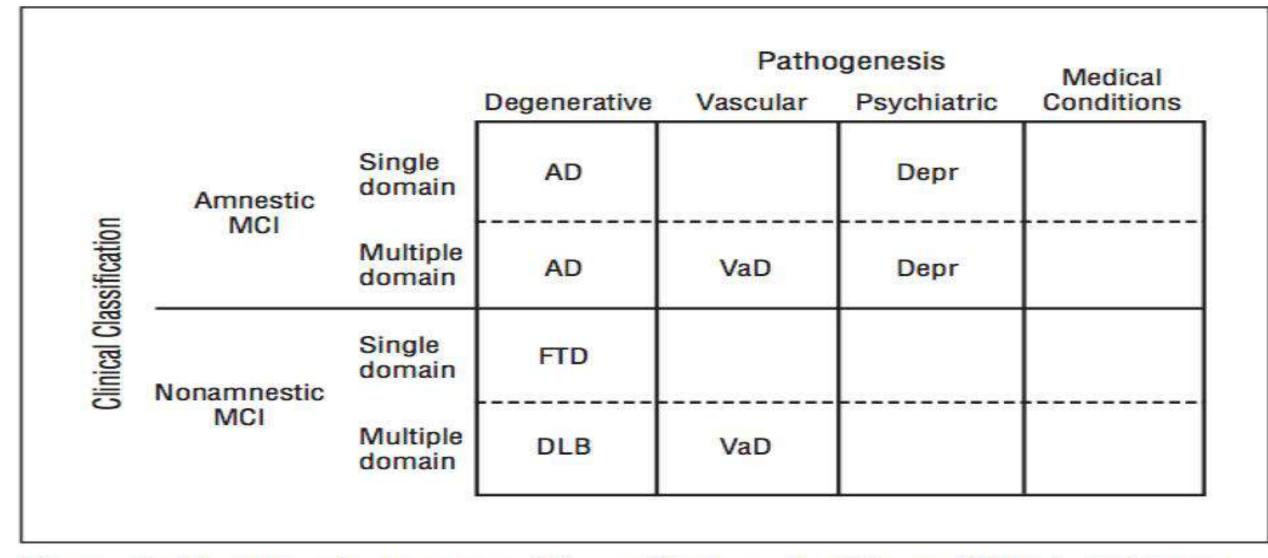


Figure 3. Presumed outcome of the subtypes of mild cognitive impairment (MCI) when combined with the presumed pathogenesis. Adapted from Petersen.⁴ Reprinted with permission from Oxford University Press, Inc. AD indicates Alzheimer disease; Depr, depression; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; and VaD, vascular dementia.

PATHOPHYSIOLOGY

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- GROSS PATHOLOGICAL CHANGES
- MICROSCOPIC CHANGES
- BIOLOGICAL MARKERS
- GENETIC MARKERS

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NEUROIMAGING

GROSS PATHOLOGICAL CHANGES

Neurofibrillary tangles

Neuritic plaques

Amyloid deposition

- These changes are observed in patients those who progress to alzheimers
 Disease
- Plaques and tangles appear before amyloid

MICROSCOPIC CHANGES

- Neuronal loss decrease in neuronal number and volume mainly seen in cortex and hippocampus.
- Beta amyloid deposition intermediate between normal and Alzheimer.
- Neurofibrillary tangles Phosphorylated tau proteins in the tangles
- Down regulation of TRKA RNA decrease in trka containing neurons 46% in MCI and 56% for Alzheimer's
- Up regulation of choline acetyl transferase in hippocampus and superior frontal cortex.

BIOLOGICAL MARKERS

- CSF Alpha-beta 42, total tau, phosphorylated tau
- Isoprostane (related to lipid peroxidation) is elevated in CSF, urine, blood of AD patients and has promising value in conversion of MCI to AD
- Other protein bio marker complex which may include transthyretine , pgl-h2 d-isomerase protien.
- Significant rise in monocytes producing cytokines (il1b,il6,il12,tnf-alfa)
- Inflammatory markers such as c-reactive protein (CRP) and cytokines in the blood and CSF of AD patients

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- APOE4
- ACE GENE POLYMORPHISM
- COMT GENE POLYMORPHISM
- BDNF GENE POLYMORPHISM
- Mutations in the *APP, PSEN1* and *PSEN2* genes directly associated with the amyloid cascade account for AD in much less than 5% of affected patients.

NEUROIMAGING STUDIES

- MRI Reductions in the medial temporal cortex particularly the entorrhinal and hippocampal volumes are well-established risk factors in AD. However, in MCI, their predictive value is yet to be evidenced.
- 2. Magnetic resonance spectroscopy (MRS) effect of cognitive changes on the metabolite ratios is the principle of assessment of the MRS.
- 3. Diffusion tensor imaging (DTI) higher diffusivity in the left centrum semiovale, left and right temporal regions and left hippocampal region is seed in cognitively affected subjects

NEUROIMAGING STUDIES

4. Diffusion weighted imaging (DWI) - Higher diffusion have been found in hippocampus, temporal lobe gray matter, amygdale, posterior cingulated and corpus callosum

- 5. Functional MRI (fMRI) Lower hippocampal activation during retrieval was the most significant correlate of clinical severity of memory loss in mild cognitive impairment.
- 6. Positron emission tomography (PET) -reduced glucose metabolism.7. SPECT reduced blood flow.

The NEW ENGLAND JOURNAL of MEDICINE

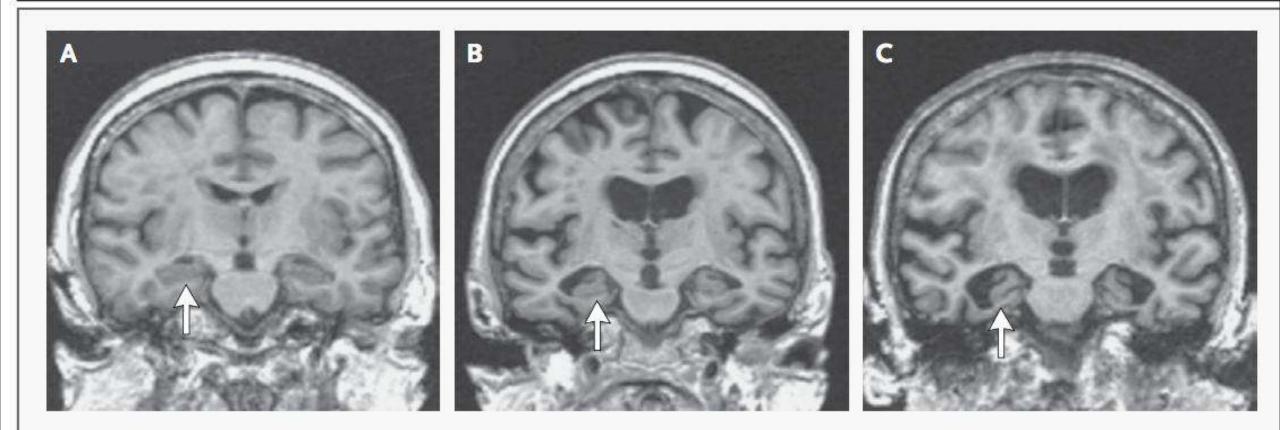


Figure 2. Coronal MRI Scans from Patients with Normal Cognition, Mild Cognitive Impairment, and Alzheimer's Disease.

The arrows depict the hippocampal formations and the progressive atrophy characterizing the progression from normal cognition (Panel A) to mild cognitive impairment (Panel B) to Alzheimer's disease (Panel C).

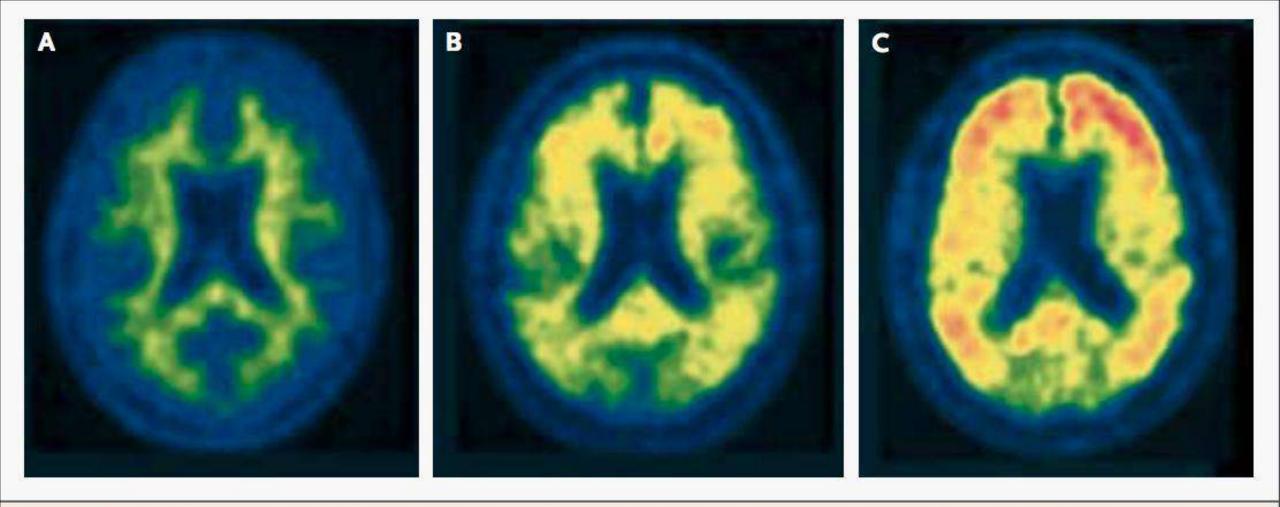


Figure 3. Axial Scans of the Brain Obtained with Positron-Emission Tomography and the Use of Amyloid-Binding Carbon 11–Labeled Pittsburgh Compound B.

The yellow and red areas indicate retention of the amyloid-binding tracer, reflecting amyloid deposits. The patient with normal cognition (Panel A) has no tracer retention, whereas the patient with amnestic mild cognitive impairment has an intermediate amount of tracer retention (Panel B) and the patient with Alzheimer's disease has prominent tracer retention (Panel C).

ASSESSMENT

• Memory testing would be the single most important test in assessing MCI

 However a comprehensive set of tests is required to accurately diagnose MCI as studies have shown that people diagnosed with one test were unstable most of them revert to normal while those diagnosed with multiple tests were relatively stable over period.

MINIMENTAL STATUS EXAMINATION

- MMSE had very limited value in making a diagnosis of MCI against healthy controls and modest rule-out accuracy.
- It had similarly limited ability to help identify cases of alzheimer's disease against MCI.
- SCORES OF 25-30 OUT OF 30 ARE CONSIDERED NORMAL;
 - 21-24 AS MILD,
 - 10-20 AS MODERATE
 - 10 AS SEVERE IMPAIRMENT

ASSESSMENT TOOLS

• CLINICAL DEMENTIA RATING SCORE (CDR) -

The score of 0.5 on this scale is of diagnostic importance in petersons modified criteria. But it has been largely debated and american academy of neurology doesn't accept this criteria.

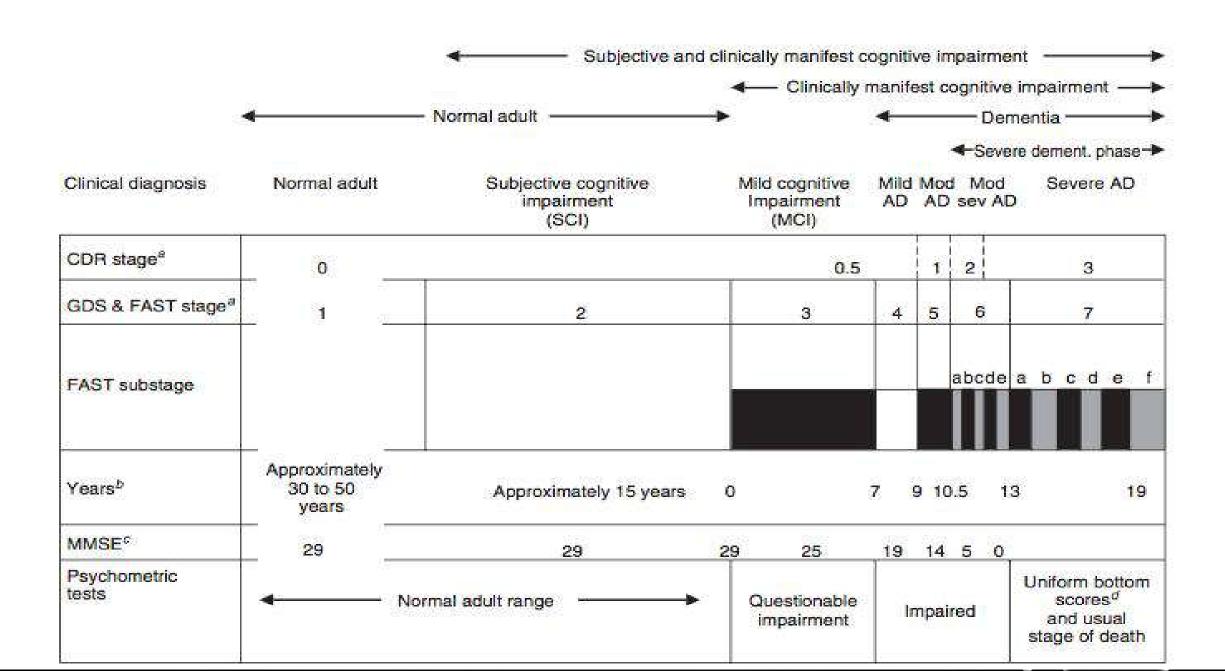
• GLOBAL DETERIORATION SCALE (GDS) -Score of 3 is considered indicative of MCI

ASSESSMENT TOOLS

Neuropsychiatric inventory (NPI) and short form (NPI-Q) -Presence of psychiatric symptoms and caregivers distress can be assessed

- Informant questionnaire on cognitive decline in elderly (iq-code) Objective reporting by caretaker on day to day behavior of the patient Requires very well informed caregiver
- Tests which can be used to detect progression of problem:-Clock drawing test Test for verbal fluency and verbal memory Digits forward and digits backward

DIAGNOSIS AND ASSESSMENT

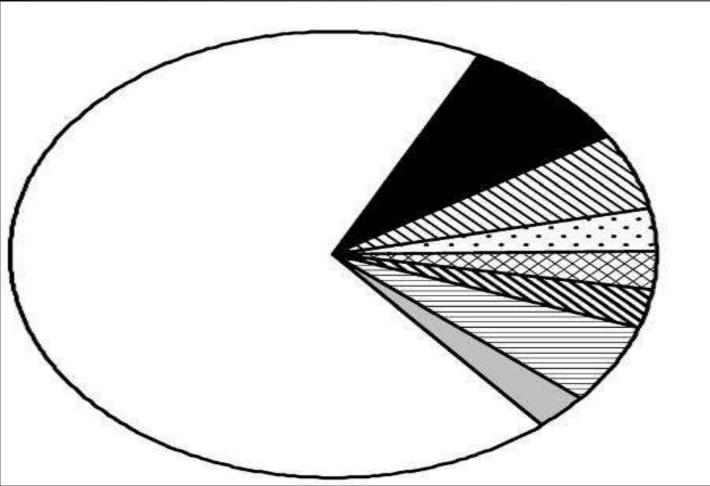


OUTCOME

 The cumulative proportion that progressed to dementia rarely exceeded 50% even in long-term studies.

- This suggests that many, perhaps most people with mci do not deteriorate to dementia in the medium term.
- A significant proportion improve and others do not survive long enough to allow dementia to develop.





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- DLB
- Hippocampal sclerosis
- 🖸 FTD

- Nonspecific tauopathy
- 🔲 Vascular

Table 4. Factors Influencing Rates of Progression

Predictor of Progression

Clinical severity ApoE £4 carrier status Atrophy on MRI ¹⁸FDG PET pattern of Alzheimer disease CSF markers compatible with Alzheimer disease Positive amyloid imaging scan



Table 3. Rates of Progression

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Source	Study Location	No. of Participants	Participant Age, y	Reported Rate of Progression	Annual Crude Progression Rate, % ^a
Solfrizzi et al,30 2004	Italy	1524	≥65	3.8/100 person-years	3.8
Busse et al, ¹² 2006	Leipzig, Germany	863	≥75	44% per 4.3 y	10.2
Tschanz et al, ³¹ 2006	Cache County, Utah	3266	≥65	46% per 3 y	15.3
Fischer et al, ²⁴ 2007	Vienna, Austria	476	75-76	33.9% per 30 mo	13.6
Ravaglia et al,32 2008	Italy	937	≥65	14% per 1 yr	14.0
Farias et al. ²⁸ 2009	California	111	>60	3% per 1 y ^b	3.0 ^b
Petersen et al, unpublished data, 2009	Rochester, MN	1969	70-89	7.5% per 1 y	7.5

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Progression rate for clinic cohort reported as 13% per 1 year

- Till date no drug is approved for use in MCI. However lot of research is going on as many patients with MCI Progress to dementia.
- The following drugs has been studied in mild cognitive impairment.
- Acetylchoine esterase inhibitors :- donepezil ,galantamine ,rivastigmine.
 Relative risk of progression to dementia in choline esterase treated group was 0.75 noted in Studies.
- Donepezil delays the progression to AD in MCI patients with depression without affecting their depressive symptoms, and some evidence suggests that cognitive interventions may have a positive effect.

- Memantine :- Memantine has not been reported to benefit patients with MCI
- Cox-2 inhibitors :- like rofecoxib have met with little benefit.
- Anti-amyloid therapies:- secretase inhibitors, fibrillogenesis inhibitors
- Neurotonics: like piracetam no evidence has been found

Table 2

Preventing Progression to AD: Drugs Under Investigation

- Cholinesterase inhibitors
- Anti-inflammatories
- Estrogen
- Statins
- Cholesterol-lowering drugs
- Anti-amyloid drugs (beta-secretase inhibitors, gamma-secretase inhibitors, glycosaminoglycan [GAG] mimetics, amyloid immunotherapy)
- Various antioxidants, including vitamin E
- Ampakines
- Nootropics and psychic stimulants (e.g., piracetam)

DRUGS ON TRIAL FOR MCI :-

- Vip
- Metabotropic glutamate receptor antagonist (C-105)
- I-type calcium channel blocker (MEM-1003)
- Phosphodiesterase inhibitor (MEM-1414)
- GABA antagonist (SGS-742)
- Selective serotonin receptor (5HT6) antagonist (SGS-518).

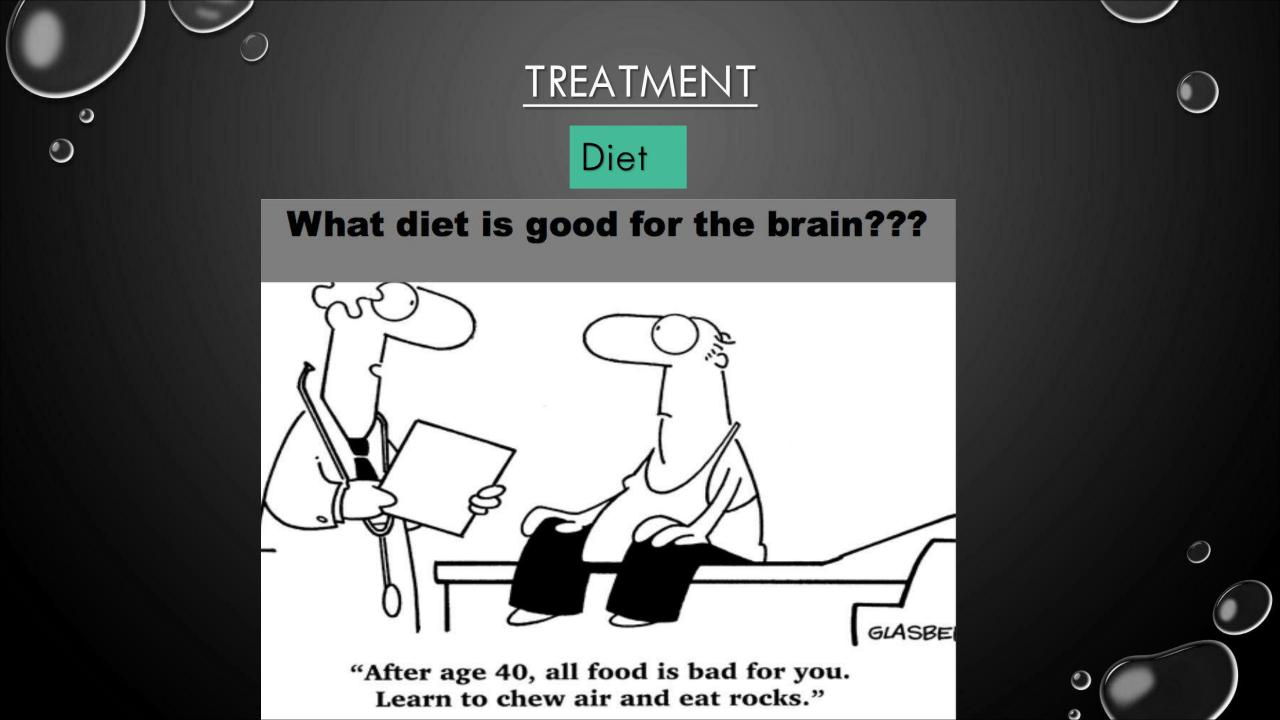
• These measures will assume more importance in future. These can be :-

- Treatment of associated co-morbidities like sleep, depression, etc.
- Treatment of vascular risk factors: like hypertension, weight gain, smoking, hyperlipidaemia, diabetes, etc.
- Social networking: isolation exacerbates cognitive decline. Patients with MCI should be encouraged to socialize.

TREATMENT Exercise

- The mental activity and exercise (MAX) RCT of 126 inactive, older adults with memory complaints demonstrated that a 12-week program of combined physical plus mental activity was associated with small, significant improvements in GCF regardless of the types of physical activity (aerobic vs. Stretching/toning) and mental activity (intensive vs. Educational videos)
- Slows decline on testing and on functional MRI.
- Slows conversion to AD

ED FISCHER 0008 1. EXercise resides, res-now, seriously do what can we do what can we reve 2. EXercise 3. Exercise 4. Exercise health? 5. EXercise 6 Exercise 7. exercise setc.







Diet

• NUTS, COMPLEX GRAINS, OLIVE OIL

- FRUITS AND VEGETABLES
- COFFEE AND TEA
- OMEGA-3 FATS.
 - SALMON, TUNA, TROUT, SARDINES, SEAFOODS.
- AVOID REFINED SUGARS, RED MEAT AND PROCESSED FOODS
 - SUGARY DESSERTS, BAKED GOODS
 - RED MEAT, FAST FOOD, "DIET" FOOD

- Cognitive activities and training: Activities like crossword puzzles, novels, Sudoku, etc. all help against cognitive decline.
- Patients should be encouraged to participate in leisure activities, voluntary work, etc.
- Physical exercise: does improve cognitive ability, or definitely slows down decline.



- Mild cognitive impairment is the grey zone between normal people and dementia.
- In future dementia cases are going to increase largely. According to delphi census the cases are going to increase by 100% in developed countries and by 300% in india, south east asia, and other developing countries.



- MCI is considered as potential condition at which the progression can be halted to dementia.
- Currently there is no standard criteria. Also no drug is approved. In future these things may be fulfilled.



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