MCI & Dementia

Catherine Price, Ph.D.
01-30-2006

Part 1:
A Review of the Basics

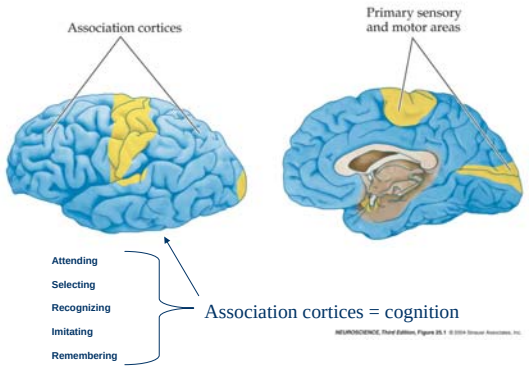
Higher Cortical Function

Denotes complex brain functions such as "reading" or "language"

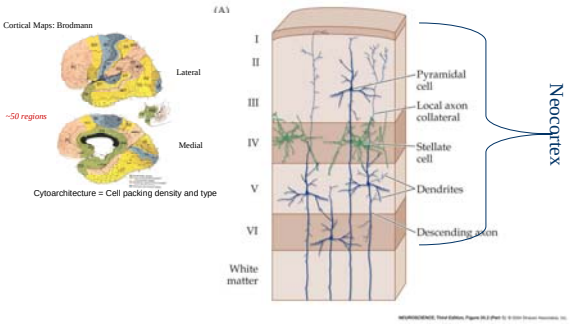
Based on a hierarchical concept - A.R. Luria

Retina → *Primary* → *"Associated" with visual impressions*

Higher Cortical Functions and Association Cortices

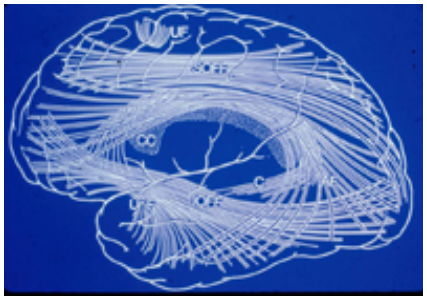


The "Association Cortices" have a distinctive neocortex



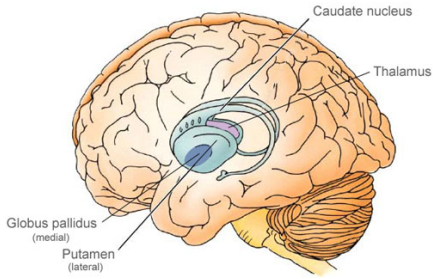
Additional Behavioral Influences

White Matter Connections



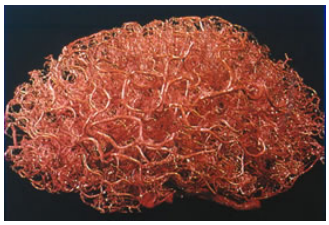
Additional Behavioral Influences

Subcortical Nuclei



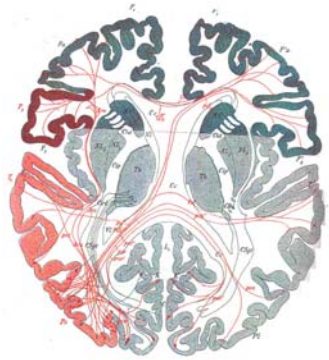
Additional Behavioral Influences

Small and Large Vessel Vascular Supply



Blood vessels in human brain. A plastic emulsion was injected into brain vessels and brain tissue was dissolved. Zlokovic & Apuzzo: Neurosurgery 43(4):877-878, 1998.

Behavior = An Integration of all these Elements



Part 2: Normal Aging and Mild Cognitive Impairment

Question:

Mild Cognitive Impairment:

a) only represents the prodromal stage of Alzheimer's Disease

b) represents the prodromal stage of ANY dementia syndrome

c) only represents the mild stage of Alzheimer's Disease

d) represents the mild stage of ANY dementia syndrome

Question:

Mild Cognitive Impairment:

a) requires neuropsychological assessment for diagnosis

b) can be diagnosed based on informant and patient interview only

c) can be diagnosed based on memory tests only

d) can be diagnosed based on patient complaints only

Question:

Mild Cognitive Impairment:

a) has not been associated to changes in any brain structure

b) has been associated with reduced levels of cerebral spinal fluid

c) has been associated with smaller entorhinal cortices

d) has been associated with larger sylvian fissures

Question:

Mild Cognitive Impairment:

True or False:

Neuropsychiatric symptoms are common in MCI

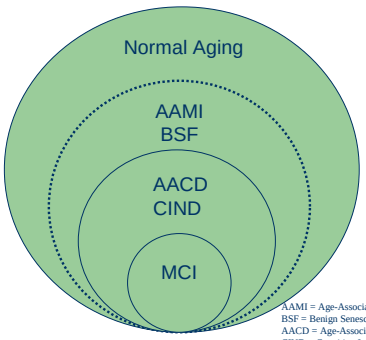
True or False:

Depression and apathy are the most common symptoms in MCI

Controversial Issue #1

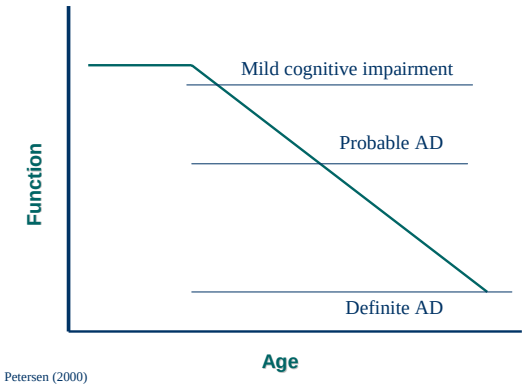
Definition of MCI

Relationship Among Entities



Unverzagt (2004)

AAMI = Age-Associated Memory Impairment
BSF = Benign Senescent Forgetfulness
AACD = Age-Associated Cognitive Decline
CIND = Cognitive Impairment - No Dementia
MCI = Mild Cognitive Impairment



Petersen (2000)

Mild Cognitive Impairment

(Mayo Alzheimer Disease Center and Petersen et al., 1999, 2001)

Memory Complaints, preferably corroborated

Objective memory impairment

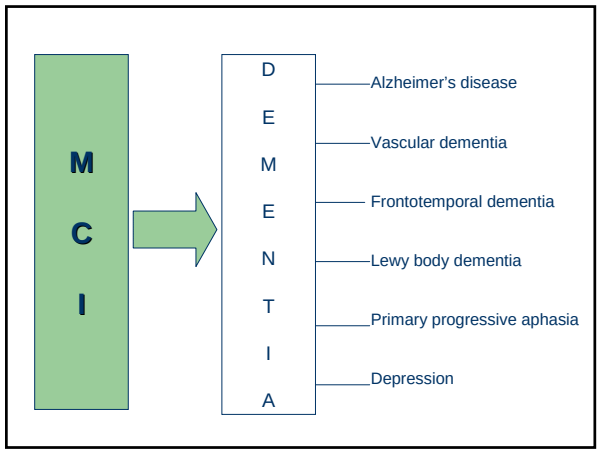
Normal general cognitive function

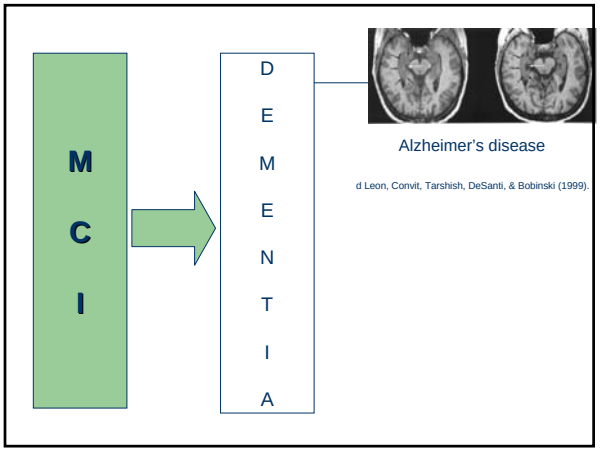
Intact activities of daily living

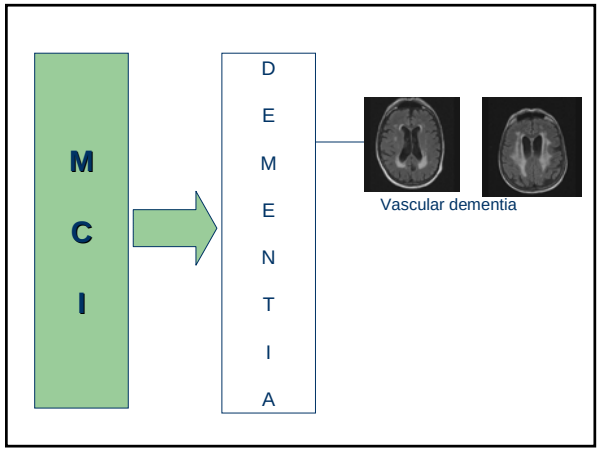
Not demented

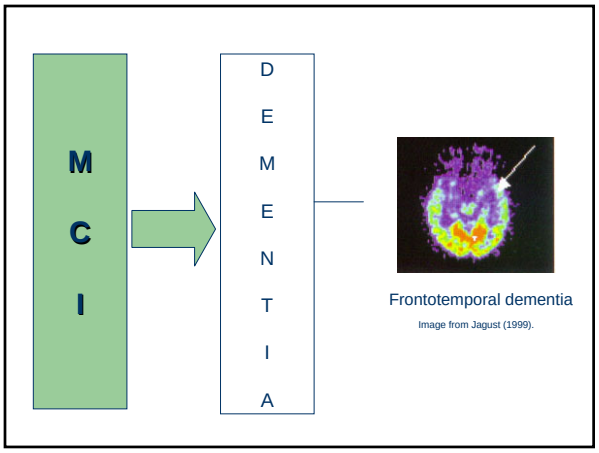
Clinical heterogeneity of MCI

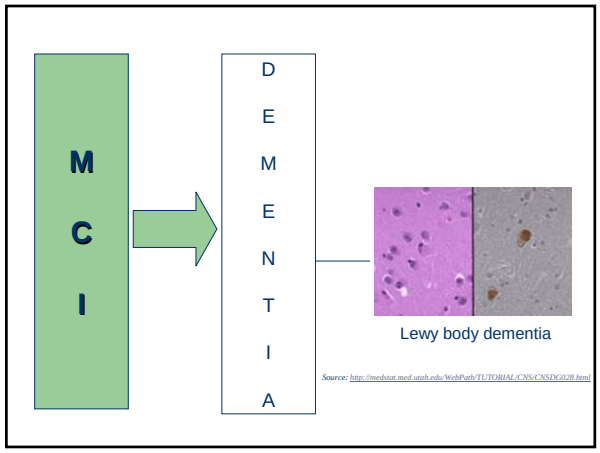
Types of MCI	May Progress To:
Amnestic →	Alzheimer's disease
Multiple domains, Mild impairment →	Alzheimer's disease Vascular dementia Normal aging
Single non-memory domain →	Frontotemporal dementia Lewy body dementia Primary progressive aphasia Vascular dementia

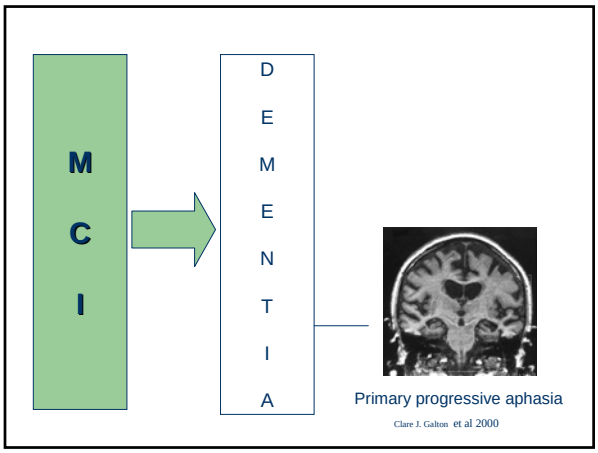


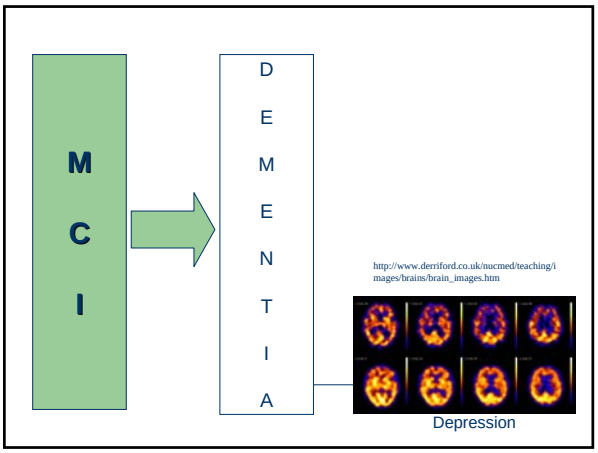


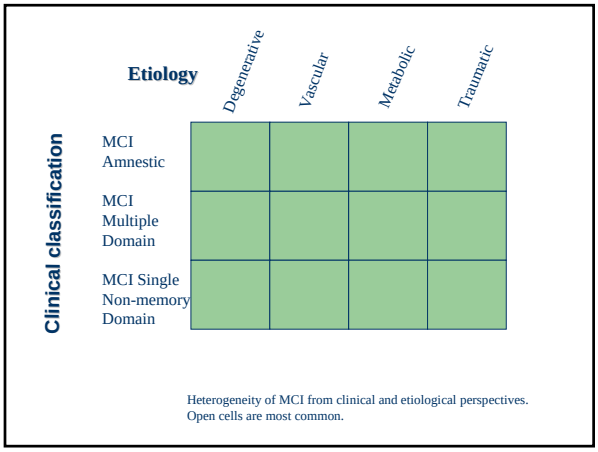


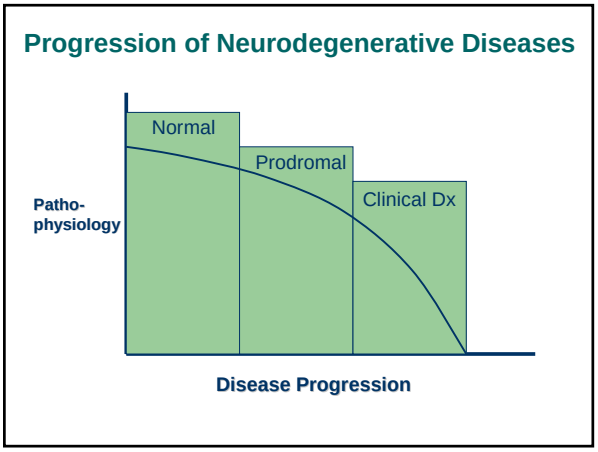


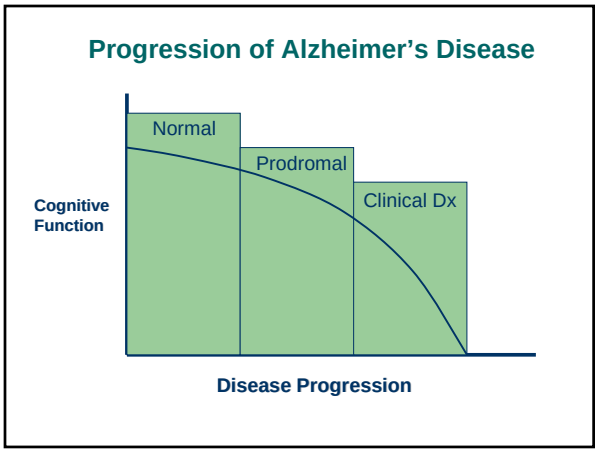


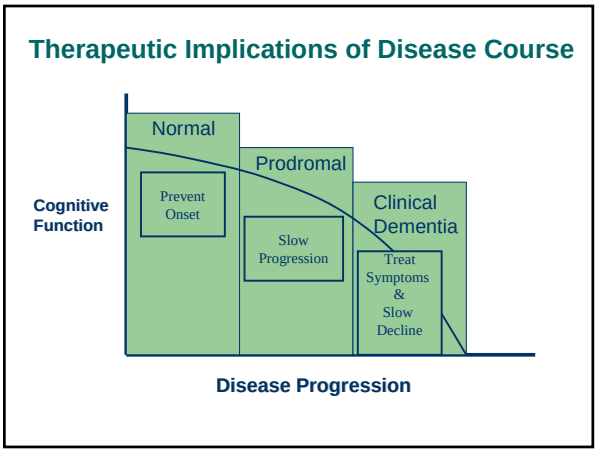

MCI
DEMENTIA
Primary progressive aphasia
Clare J. Galton et al 2000


MCI
DEMENTIA
http://www.derriford.co.uk/nucmed/teaching/images/brains/brain_images.htm
Depression


Etiology
Degenerative
Vascular
Metabolic
Traumatic
Clinical classification
MCI Amnestic
MCI Multiple Domain
MCI Single Non-memory Domain
Heterogeneity of MCI from clinical and etiological perspectives.
Open cells are most common.


Progression of Neurodegenerative Diseases
Normal
Prodromal
Clinical Dx
Patho-physiology
Disease Progression


Progression of Alzheimer's Disease
Normal
Prodromal
Clinical Dx
Cognitive Function
Disease Progression


Therapeutic Implications of Disease Course
Normal
Prodromal
Clinical Dementia
Prevent Onset
Slow Progression
Treat Symptoms & Slow Decline
Cognitive Function
Disease Progression

Controversial Issue #2:

How do you diagnose MCI?

St. Louis Method

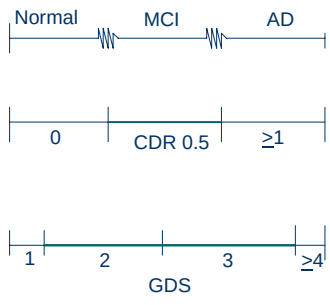
- *Clinical Dementia Rating*
- Developed by John C . Morris, M.D.
  - Morris, Ernesto, Schafer, et al. (1997)
- Informant corroborated interview

What is the CDR?

- 5 point scale to characterize 6 domains of cognitive and functional performance to AD and related dementias:
  - Memory, Orientation, Judgment & Problem solving, Community Affairs, Home & Hobbies, and Personal Care

CDR Scale

0 = Normal
0.5 = Very Mild Dementia
1 = Mild Dementia
2 = Moderate Dementia
3 = Severe Dementia



Petersen (2000)

Mayo Criteria

Memory Complaints, preferably corroborated

Objective memory impairment

Normal general cognitive function

Intact activities of daily living

Not demented

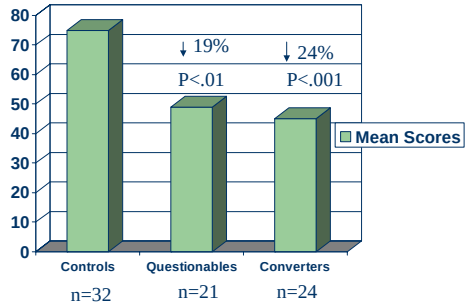
Defined with Neuropsychology

- Memory complaint/ corroborated by Informant
- Not demented
  - Preserved general cognitive function
  - Normal activities of daily living
- Memory impaired for age and education (tends to be ↓ 1.5 S.D.

California Verbal Learning Test

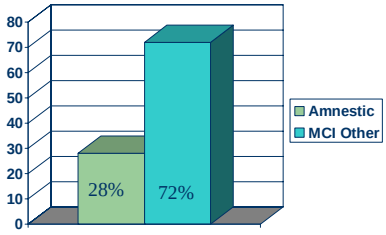
Total Learning Score at Baseline

Marilyn S. Albert, Ph.D.



Prevalence Rates

Cardiovascular Health Study (CHS)



General elderly population=653, Overall MCI prevalence = 19%
Wash U, Johns Hopkins

Prevalence Rates

Unverzagt (2004)

-Nature of criteria affect prevalence
  -3 to 28% for MCI
  -9-27% for CIND and AACD

-Study design affects prevalence:
  -Adherence to criteria
  -Age range of sample

Reversion Rates

Larrieu et al (2002), *Neurology*

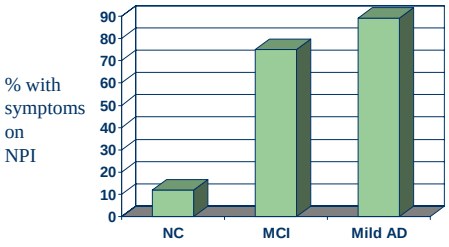
Community based cohort
Followed for 5 years
At baseline, there were 58 prevalent cases of MCI (2.8% of the sample).
At 5-year follow-up - 40 incident cases of MCI occurred in 1,265 subjects.

MCI was a good predictor of AD with an annual conversion rate of 8.3%, but it was very unstable over time:
Within 2 to 3 years, only 6% of the subjects continued to have MCI, whereas >40% reverted to normal.

Other Issues:

Non-Cognitive Features of MCI

Non-Cognitive Features of MCI



Hwang, et al., ADAD, 2004

Non-Cognitive Features

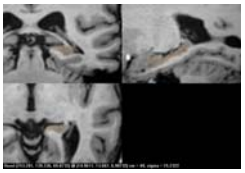
- UCLA Sample
  - Mood, apathy distinguished MCI from Normal Adults
  - Symptoms, when present, were of moderate severity
- Cardiovascular Health Study
  - Depression is common in MCI (40%)
  - Depression equally common in amnestic type and multiple cognitive deficit type MCI
  - Depression may signal the presence of MCI

Other Issues:

Neuroanatomy

Hippocampal Volume

Jack, C (2004)



Risk of Converting to AD

- 9% - Hippocampal Volume $\geq$ 50th percentile
- 26% - Hippocampal Volume between 1st and 50th %ile
- 50% - Hippocampal Volume $\leq$ 1st percentile

Non-Cognitive Features of MCI

Nestor et al., (2003)

Limbic structural changes in MCI on MRI

Limbic functional changes in MCI on PET
- -Hippocampus
- -Thalamus
- -Posterior cingulate

Neuropsychiatric features may reflect limbic dysfunction

Case RW

Case RW – 83 year-old right-handed Caucasian male

•Referred by neurologist who initially treated him for an episode where he observed a series of dark wavy lines moving across his left visual field. This was later found to be benign. MRI normal.

•Neurologist's general examination revealed mild memory difficulties and she recommended that he begin a course of Aricept (inhibitor of the enzyme acetylcholinesterase). Death of recent wife that same year.

•Approximately 6 weeks ago RW requested that he be weaned off of the medication in order to facilitate his admission into a lifetime care community: Oak Hammock.

•One requirement for the community is a medical history that contains no diagnosis of, or treatment for, any form of dementia.

•The current evaluation was directed toward determining whether RW shows signs of early-stage dementia of the Alzheimer's type or if they are typical of normal age-related memory functioning.

Case RW – 83 year-old right-handed Caucasian male

•Other Points:
- •Wife died a few months before neurologist prescribed Aricept
- •RW reports that he has had problems all of his life with his memory.
- •Education – Bachelor's degree in electrical engineering
- •Occupation – engineer and supervisor for a large company.
- •Current activities – no changes in activities of daily living, very socially active.

Case RW – 83 year-old right-handed Caucasian male

Intellectual Estimate

BARONA=119.93

WAIS-III

VIQ = 115 (84%ile), PIQ = 119 (90%ile), FSIQ = 118, WMI = 99, PSI = 106

Verbal Subtest		**Performance Subtest**	
Information	13	Picture Completion	15
Digit Span	7	Picture Arrangement	11
Vocabulary	14	Block Design	12
Arithmetic	15	Matrix Reasoning	15
Comprehension	14	Digit Symbol	11
Similarities	12	Symbol Search	11

Attention/ Executive

Trail Making Test Part A	10
Trail Making Test Part B	10
Wisconsin Card Sort	1 category out of 6, ss=5

Language

Boston Naming	55/60, Normal Score (85%ile)
CFL	40, ss=11
Animal Naming	13, ss= 7

Case RW – 83 year-old right-handed Caucasian male

Memory

WMS-III

	Index Score	Percentile
Auditory Memory		
Immediate Recall	120	91
Delayed Recall	120	66
Delayed Recog.	105	63
Visual Memory		
Immediate Recall	106	66
Delayed Recall	100	50
Immediate Memory	116	86
General Memory	111	77

CVLT-II 16 words

Trial 1	3 words	z= -.87, ss=7
Trial 2	7 words	
Trial 3	10 words	
Trial 4	10 words	
Trial 5	10 words	z= .35, ss=10
Total words	40 words	z= .21, ss=10
Long Delay	10 words	z = 1.0, ss=12
Recognition	16 total, no false positives	

RW – Does he fit MCI criteria?

Memory Complaints, preferably corroborated

Normal general cognitive function

Intact activities of daily living

Not demented

Objective memory impairment

RW – Is he aging normally?

Is there any other area of impairment?

MCI – Take home thoughts

- MCI – Is the dx useful for research purposes?
- MCI – Is the dx useful for clinical purposes?
- MCI – Should the criteria be improved?

Part 3: Dementia

Review: Dementia

- Progressive Cognitive ↓
- Can begin in any cognitive domain but usually spreads to include other domains.
- Unrelated to alertness, mobility
- NOT secondary to stress, mood, acutely acquired, static conditions
  - EX: single stroke, encephalitis, head injury

Dementia in DSM-IV

- DSM-IV Definition requires presence of a memory dysfunction
  - Do not rely only on this definition
  - many types of dementia have relative preservation of learning and memory

Differential Dementia Dx

- Mostly aided by clinical cognitive examination
- Diagnosis typically supported by:
  - History of a persistent decline
  - Scores falling >2SD from age norms
  - Change in scores >1SD in 6 to 12 month period
- Formal diagnosis made by histopathology postmortem

How do you differentially diagnose?

- YOUR  to diagnosis:
  - A very thorough history
  - What was/were the patient and caregivers 1st symptom?
    - Symptoms will change with the disease process
    - This technique has been validated with autopsy

Review: Causes of Dementia

Infectious Organisms:
HIV, Syphilis, Herpes simplex, Lyme disease

Nutritional-Metabolic-Toxic:
Wernicke-Korsakoff disease, Chronic alcoholism, B12 deficiency, Organic Solvent exposure, Heavy metal intoxication, Hepatic encephalopathy

Immune Inflammatory
Systemic lupus

Vascular Disease
Multiple infarcts, Binswanger's Disease

Review: Causes of Dementia

Prion Diseases:
Creutzfeld-Jacob Disease

Primary (Neurodegenerative) Neuronal Diseases:
Alzheimer's Disease
Focal atrophies (Frontotemporal dementia)
Pick's Disease
Cortical Lewy body disease
Parkinson's disease
Progressive supranuclear palsy
Cortico-basalganglionic degeneration
Huntington's disease, etc…

Today - Our Progression Through the Syndromes:

Subcortical, Cortical, Mixed

Syndromes for Today's Discussion

- Parkinson's Disease
- Parkinson's Disease with Dementia
- Parkinson's Disease Plus Syndromes
  - Progressive Supranuclear Palsy (PSP)
  - Multiple System Atrophy
  - Diffuse Lewy Body Disease
  - Cortical Basal Degeneration
- Small Vessel Vascular Dementia vs. Multi-Infarct Dementia
- Alzheimer's Disease
- Frontotemporal Dementia
  - Pick's Disease
  - Progressive Non-Fluent Aphasia
  - Semantic Dementia
  - Dysexecutive Syndrome
- Creutzfeld Jacob Disease (CJD)

Key Terms to Know

- Tremor Types
  - Essential, Active, Passive
- Cogwheel Rigidity
- Masked Facies
- Bradyphrenia/ Bradykinesia
- Dysarthria
- Dyskinesia
- Dystonia
- Apathy
- Retropulsion
- Rigidity
- Festination
- Hypophonia
- Amyotrophy
- ophthalmoplegia
- Anterograde Amnesia
- Retrograde Amnesia
- Agrammatism
- Apraxia
- Anasognosia

•Which of these symptoms are most likely subcortical in nature?

•Which denote involvement of association cortices?

Dementia Syndromes

- Parkinson's Disease
- Parkinson's Disease with Dementia
- Parkinson's Disease Plus Syndromes
  - Progressive Supranuclear Palsy (PSP)
  - Multiple System Atrophy
  - Diffuse Lewy Body Disease
  - Cortical Basal Degeneration
- Small Vessel Vascular Dementia
- Alzheimer's Disease
- Frontotemporal Dementia
  - Pick's Disease
  - Progressive Non-Fluent Aphasia
  - Semantic Dementia
  - Dysexecutive Syndrome
- Creutzfeld Jacob Disease (CJD)

Question:

Dementia is NOT a primary characteristic of:

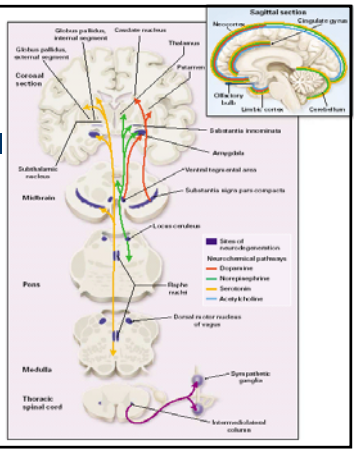
1. Parkinson's Disease
2. Alzheimer's Disease
3. Diffuse Lewy Body Disease
4. Small Vessel Vascular Disease

Parkinson's Disease:

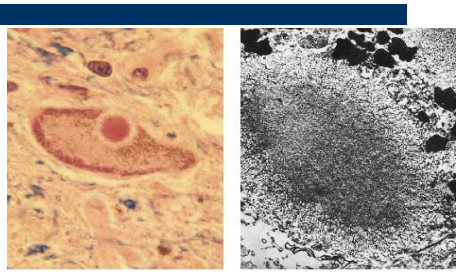
- Cardinal Features
  - Resting tremor
  - Rigidity
  - Bradykinesia
  - Postural instability
  - Positive and long-lasting response to levodopa

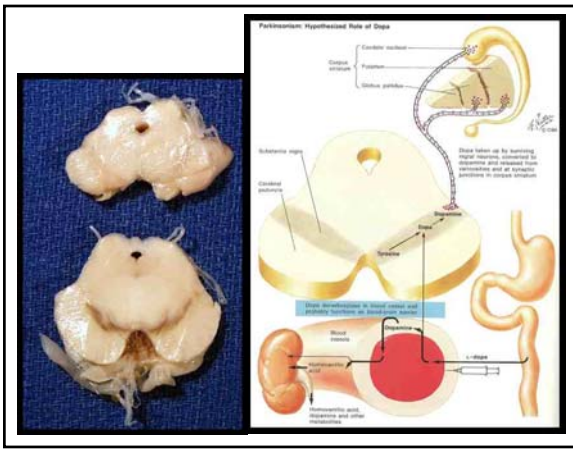
Neuronal Complexity

- Neurodegeneration
  - Progressive loss of dopaminergic neurons in the substantia nigra
  - Formation of Lewy bodies
- Impacts multiple neurochemical pathways
  - dopamine
  - norepinephrine
  - serotonin
  - acetylcholine
  - GABA
  - glutamate

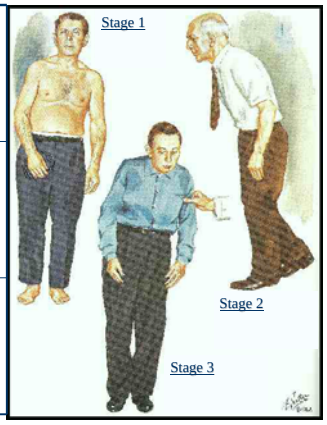


Lewy bodies in Midbrain: Hallmark of PD

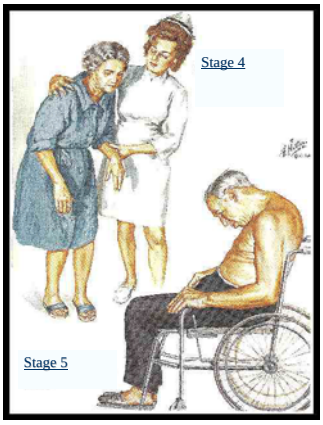




Stage 1	Unilateral involvement; blank faces; affected arm in semiflexed position with tremor; patient leans to unaffected side. Progression to stage 2 in ~18 months.
Stage 2	Bilateral involvement with early postural changes; slow, shuffling gait with decreased excursion in legs; tremor on both sides; rigidity. To stage 3 in ~25 months.
Stage 3	Pronounced gait disturbances and moderate generalized disability; postural instability with tendency to fall; still independent. To stage 4 in ~42 months.



Stage 4	Significant disability; limited ambulation with assistance. Progression to stage 5 in ~17 months.
Stage 5	Complete invalidism; patient confined to bed or chair; cannot stand or walk with assistance.



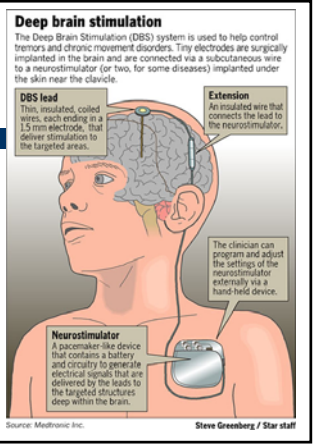
Parkinson's Disease:

- Typical Cognitive Profile:
  - Retention of Problem Solving Abilities with only fluctuations in attention and processing speed
  - Intact learning and memory, although rapid retrieval is compromised
  - Visuoperceptual abilities may be variable
  - Not demented
- Typical Emotional Profile:
  - Depressive symptoms reported or may appear
  - May appear apathetic or report apathetic symptoms.

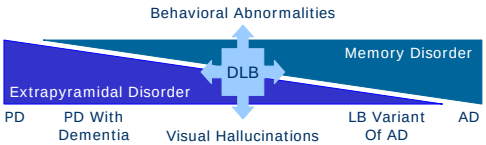
PD: Treatment

The picture for Parkinson's disease is very encouraging.

In 1997, the U.S. Food and Drug Administration (FDA) approved DBS for the treatment of tremor in Parkinson's disease using a single implanted electrode. In January 2002 the FDA approved DBS using two implanted electrodes (bilateral, meaning one on each side of the brain).



Clinical Spectrum of Lewy Body Disorders



Modified from Arch Neurol 2001; 58:186

Dementia Syndromes

- Parkinson's Disease
- Parkinson's Disease with Dementia
- Parkinson's Disease Plus Syndromes
  - Progressive Supranuclear Palsy (PSP)
  - Multiple System Atrophy
  - Diffuse Lewy Body Disease
  - Cortical Basal Degeneration
- Small Vessel Vascular Dementia
- Alzheimer's Disease
- Frontotemporal Dementia
  - Pick's Disease
  - Progressive Non-Fluent Aphasia
  - Semantic Dementia
  - Dysexecutive Syndrome
- Creutzfeld Jacob Disease (CJD)

PD with Dementia

- Cardinal Characteristics
  - Typically over age 70
  - Often has cardiovascular risk factors (hypertension, diabetes)
  - May retain response to Levodopa treatment
  - Cognitive Symptoms of PD with:
    - Pronounced intellectual decline relative to premorbid estimates
    - Impairment in one other domain:
      - Impaired Learning and Memory
      - Impaired Language Difficulty
      - Impaired Abstract Reasoning

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Parkinson's Plus Syndromes

Cardinal Features of PD +

- poor or short-lived response to levodopa
- autonomic dysfunction
- dementia
- ophthalmoplegia
- amyotrophy
- dystonia
- depression
- ataxia

Multiple Systems Atrophy (MSA)

Most patients do not receive the correct diagnosis during their lifetime because of the difficulty in differentiating MSA from other disorders (eg, Parkinson disease, pure autonomic failure (PAF), other rare movement disorders)

Figure 1. Pronounced anteocollis in one patient with parkinsonian multiple system atrophy

Multiple Systems Atrophy

- Cardinal Features
  - Onset: Early – age 40 or older (mean age is 54)
  - Progression: Fast; life expectancy is shorter than PD (6 year survival).
  - First symptoms: Autonomic and/ or urinary dysfunction
  - May mimic PD symptoms
  - *Typically, No dementia*

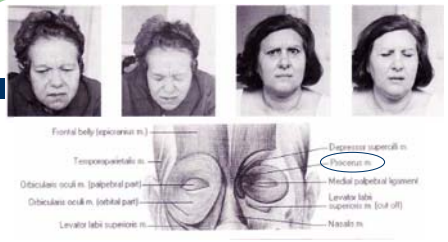
MSA vs. PD

Characteristic	MSA	PD
Response to chronic levodopa therapy	Poor or unsustained motor response because of loss of postsynaptic dopamine receptors	Good
Progression of Disability	Relatively fast disability; 40% of patients in a wheelchair within 5 years	Relatively Slow Disability
Instability and Falling	Early	Late
Lewy Bodies	Not Present	Primarily in substantia nigra
Thermoregulation	Cold hands and slow to warm after a cold pack	Normal

Progressive Supranuclear Palsy (PSP)

The disorder's long name indicates that the disease begins slowly and continues to get worse (*progressive*), and causes weakness (*palsy*) by damaging certain parts of the brain that control eye movements (*supranuclear*).

- Cardinal Features
  - Vertical supranuclear gaze
  - Spastic or drunken-like speech
  - Dizziness and balance disturbance
  - Head tilt backward; Falls backward
  - Typically little to no Lewy Bodies
  - Presents with frontal function difficulties due to both subcortical disturbance and bilateral frontal cortical atrophy.



A typical facial expression in PSP: described as "astonished," "worried," or "reptile-like".

The expression may be due to a focal dystonia of the procerus muscle as well as to a combination of very reduced blinking, lid retraction and gaze palsy.

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Questions:

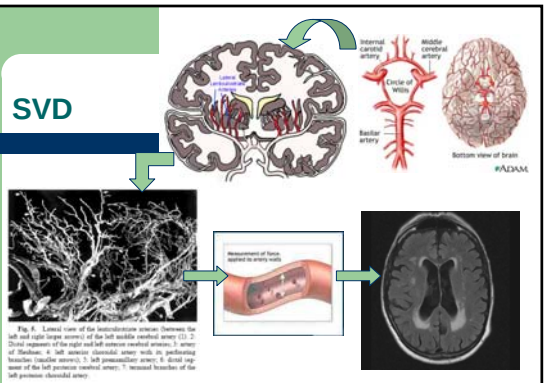
Small Vessel Vascular Disease is:

- The same thing as Multi-Infarct Dementia:
  - True
  - False
- Involves a step-wise progression:
  - True
  - False

Subcortical Vascular Dementia

- Cardinal Features
  - Cardiovascular Risk Factors (hypertension)
  - Cognitively: Progressive Subcortical Profile *but* no dominant motor symptoms (not PD like)
    - Difficulty sustaining "mental set" over time
    - Difficulty switching from one task to the other
    - Learning and memory is compromised by attention disturbance, is not a pure anterograde amnesia like AD.
    - Mood disturbances are minimal – include depression.
  - MRI demonstrates white matter abnormalities and no focal strokes

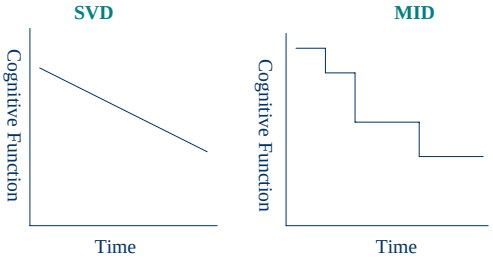
SVD



Multi-Infarct Dementia

- Cardinal Features
  - Cardiovascular Risk Factors
  - Cognitively: Step-wise decline
    - Decline occurs with each successive stroke
    - Cognitive abilities typically involve frontal symptoms, but can also include other cognitive difficulties depending on stroke region.
  - MRI demonstrates focal strokes – multiple lacunes within the subcortical and even cortical regions

Subcortical Vascular Dementia vs. Multi-Infarct Dementia



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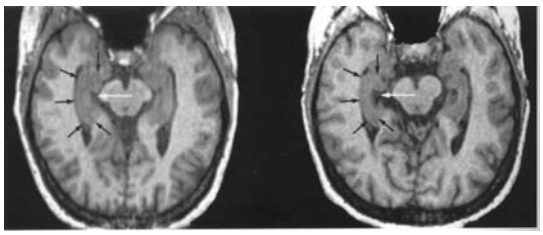
Alzheimer's Disease

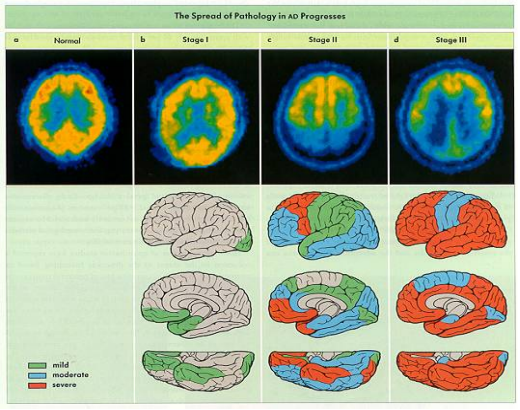
- Cardinal Features
  - First Symptom = Anterograde Memory Impairment (*think MCI amnestic*)
  - Progresses outward in a spiral – to include the temporal, parietal and frontal lobes
    - Symptoms are often accompanied by:
      - Loss of meaning (loss of semantic knowledge) for both words and gestures.
      - Visuoperceptual and visuoconstruction difficulties
      - WITH relatively intact attention, self-monitoring
  - Personality Changes, Hallucinations, Delusions during moderate stage
  - Retain sensory and motor abilities until the final stages.

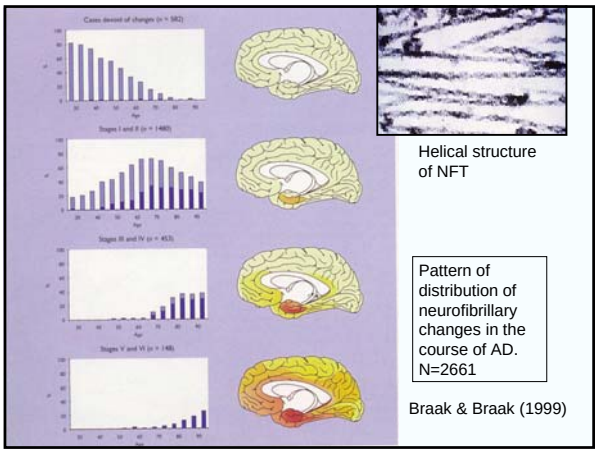
Hippocampal Area: Axial View



LEFT - normal control (left) RIGHT – AD patient

-d Leon, Convit, Tarshish, DeSanti, & Bobinski (1999)

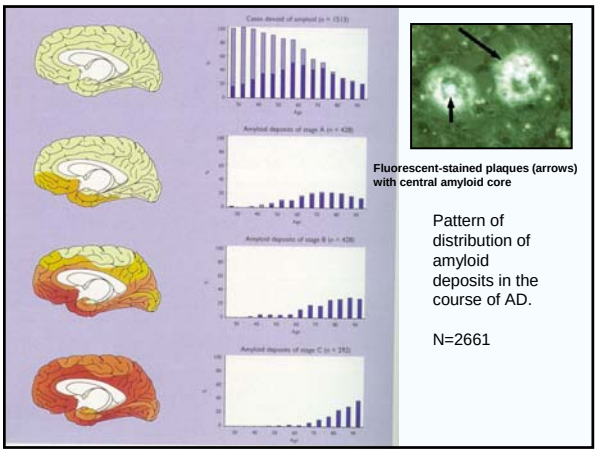




Helical structure of NFT

Pattern of distribution of neurofibrillary changes in the course of AD. N=2661

Braak & Braak (1999)



Fluorescent-stained plaques (arrows) with central amyloid core

Pattern of distribution of amyloid deposits in the course of AD.

N=2661

Are there cortical variants?

- Visual variant of AD:
  - Profound visuoperceptual/visuoconstructional deficits with memory loss
- Frontal variant of AD:
  - Profound frontal signs with memory loss

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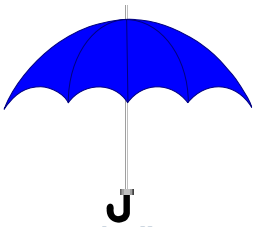
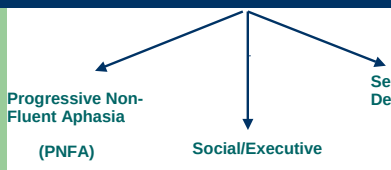
Frontotemporal Dementia (FTD/ FTLD)

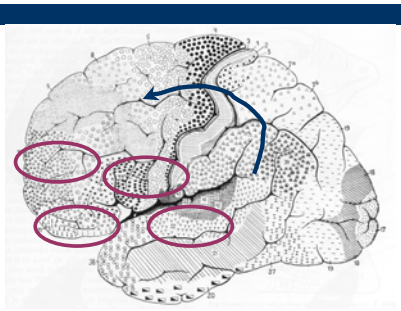


An Umbrella Term

Frontotemporal Dementia

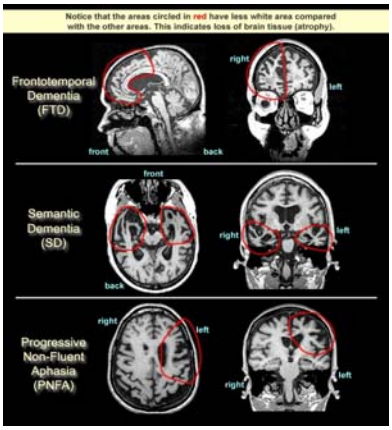


FTD Disease Progression



Clinical features distinguish FTD subgroups

- Dysexecutive
  - behavioral disturbances
  - Disturbances on tests of executive functioning
  - Usually loss of insight into disturbances
- Semantic Dementia & Progressive Non-Fluent Aphasia
  - disruptions of language



(Dysexecutive/ Social; AKA Core FTD)

- Core Features:
  - Decline in social interpersonal conduct
  - Impairment in regulation of personal conduct
  - Emotional blunting
  - Loss of insight
- Supportive Features
  - Behavioral disorder
  - Speech & Language
  - Physical signs
  - Investigations

Symmetrical or asymmetrical frontal atrophy in dorsolateral or ventrofrontal regions

Semantic Dementia

- Core Features
  - Fluent spontaneous speech
  - Loss of word meaning
    - Naming
    - Comprehension
    - Semantic Paraphasias
  - Associative Agnosia and/or Prosopagnosia
  - Preserved abilities:
    - perceptual matching & drawing
    - Single-word repetition
    - Read/Write to dictation
- Supportive Features
  - Speech & Language
  - Behavior

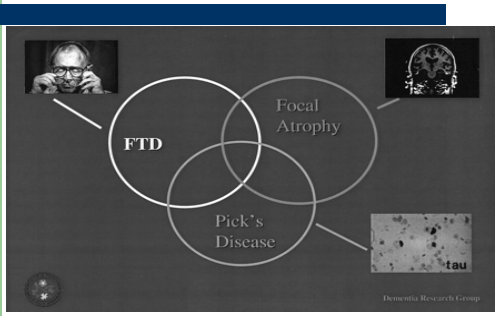
Left ventral temporal - or – bilateral temporal
Preserved inferior frontal gyri

Progressive Non-Fluent Aphasia

- Core Features
  - Non-fluent spontaneous speech
    - Agrammatism
    - Phonemic paraphasias
    - Anomia
- Supportive Features
  - Speech & Language
  - Behavior
  - Physical signs

- Asymmetrical to Left Hemisphere
- Atrophy of left frontal near Broca's

FTD Core vs. Picks



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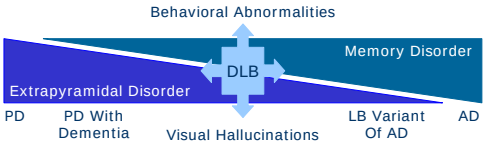

Diffuse Lewy Body Disease

- Cardinal Features
  - Shares similarities with Alzheimer's disease and Parkinson's disease.
  - Includes prominent memory loss, aphasia, and apraxia initially and executive deficits (e.g, disinhibition, loss of initiative, incontinence) later.
  - Cognitive symptom severity vary on a day to day basis.
  - Up to 81% of patients with diffuse Lewy body disease have unexplained periods of markedly increased confusion that lasts days to weeks and closely mimics delirium.
  - Visual Hallucinations – usually of animals or people.

PD	LBD	AD
Midbrain Lewy bodies	Cortical Lewy bodies	Cortical neuritic plaques, neurofibrillary tangles
Autonomic dysfunction sometimes seen	Autonomic dysfunction often seen	Autonomic dysfunction rare
Hallucinations only in response to antiparkinsonian drugs	Incidence of hallucinations 80%, usually early in illness	Incidence of hallucinations 20%, usually in moderate to late stages.
Bradykinesia, rigidity, and falls and resting tremor	Bradykinesia, rigidity, falls – but no resting tremor	Typically, none of these symptoms.
Relatively stable	Prominent day-to-day variability	Relative stability of impairment
Robust response to levodopa and carbidopa (Madopar, Sinemet)	Marginal response to levodopa and carbidopa	NA; medications are typically anticholinesterase inhibitors.
Executive dementia sometimes occurs late in illness	Executive, memory, language and visual disturbances possible	Prominent memory and language disturbances

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Corticobasal Degeneration (CBD)

- Cardinal Features:
  - Chronic progressive course
  - Asymmetric onset of extrapyramidal dysfunction
  - Higher cortical dysfunction *and* symptoms of a movement disorder
    - Apraxia, Acalculia, right-left disorientation
    - "Alien limb" ("My hand/leg has a mind of its own.")
  - Rigid/akinetic syndrome resistant to therapeutic doses of levodopa
  - Dystonic limb posturing (not purely action induced)
  - Occasional action tremor
  - Unusual presentations, for example, primary progressive aphasia and progressive buccofacial apraxia
  - Usually no hallucinations; if present – may be LBD.
  - Hisopathologies in the white matter, subcortical and cortical structures

Creutzfeldt-Jakob Disease

- Cardinal Features
  - Progression = extremely rapid
  - Myoclonus (muscle contractions in the form of "jerks" or twitches) is the most constant physical sign
  - visual abnormalities or cerebellar dysfunction including muscle incoordination and gait and speech abnormalities.
  - abnormal reflexes, spasticity, tremors and rigidity
  - behavioral changes with agitation, depression or confusion.
  - akinetic mutism during the terminal stages of the illness.

Creutzfeldt-Jakob Disease

- Rare disorder - affecting only one person per million population.
- Cases have been recorded in patients as young as 17 years and as old as 83 years
- There are three major categories of CJD:
  - sporadic CJD, hereditary CJD, and acquired (variant) CJD.
    - Variant CJD has been linked to consuming beef products contaminated with central nervous system tissue from cattle infected with Bovine Spongiform Encephalopathy (BSE, often called mad cow disease).

Creutzfeldt-Jakob Disease

- CJD is characterized as a prion disease because it is caused by an infectious protein particle known as a prion that binds with cells, altering their composition.
- Prions are the only known pathogens that are devoid of nucleic acid (prions contain no DNA or RNA). Unlike Alzheimer's disease, which is not transmissible, CJD can be transmitted through exposure to the pathogenic form of the prion protein molecule that causes it.
- Widening of sulci, atrophy of gyri

Video Cases