DEMENTIA

Szabolcs Szatmári

Tg. Mureş – Marosvásárhely
Romania

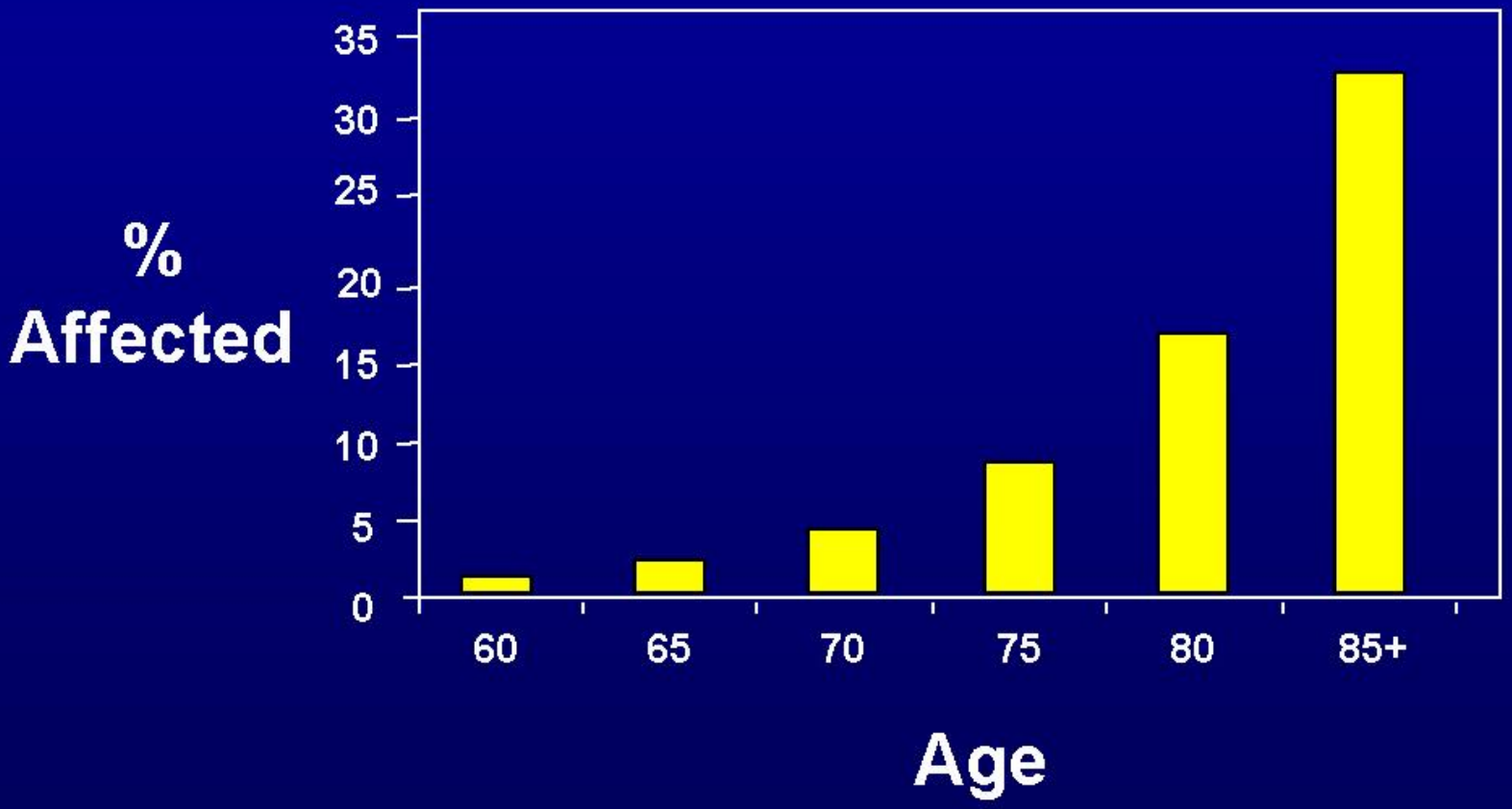

Ronald
Reagan
1911-2004


ROBIN WILLIAMS
1951-2014

Dementia

- from Latin
- *de-* "apart, away"
- + *mens* (genitive *mentis*) "mind"

Dementia Doubles in Frequency Every 5 Years After Age 60



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Evans et al. *JAMA*. 1989.
Jorm et al. *Acta Psychiatr Scand*. 1987.

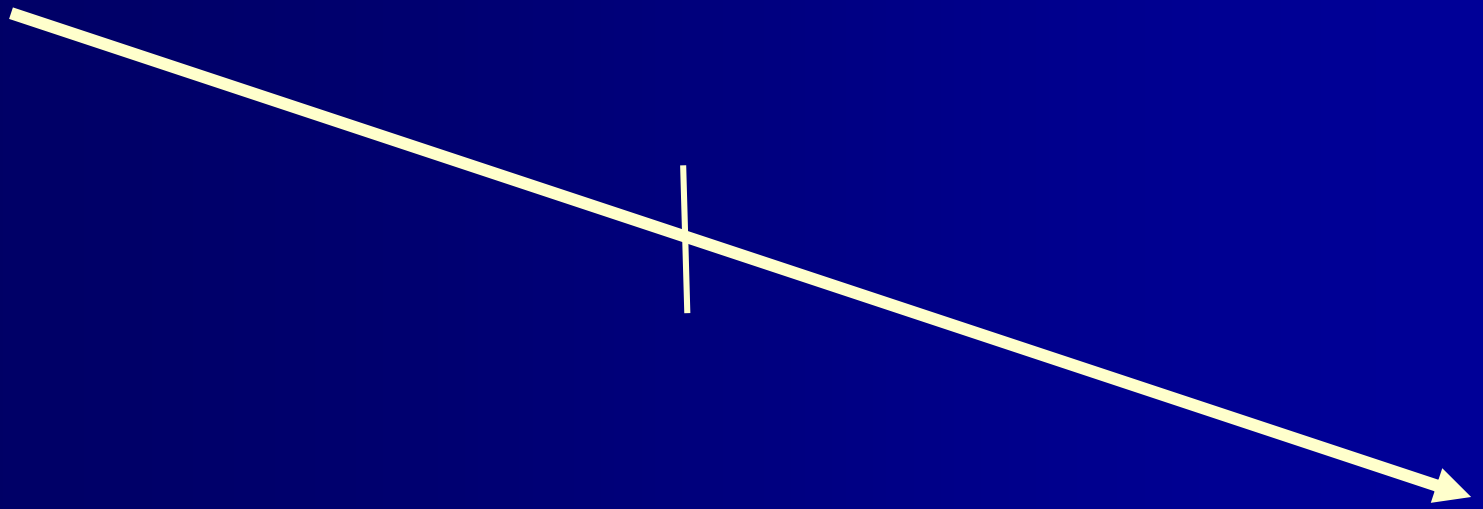
MORE GRAY HAIR AND LESS GRAY MATTER

Daryl R. Gress

Cognitive decline

minor neurocognitive disorder

major neurocognitive disorder



“PREDEMENTIA”

DEMENTIA

DSM-IV criteria for the diagnosis of dementia

The development of multiple cognitive deficits manifested by both

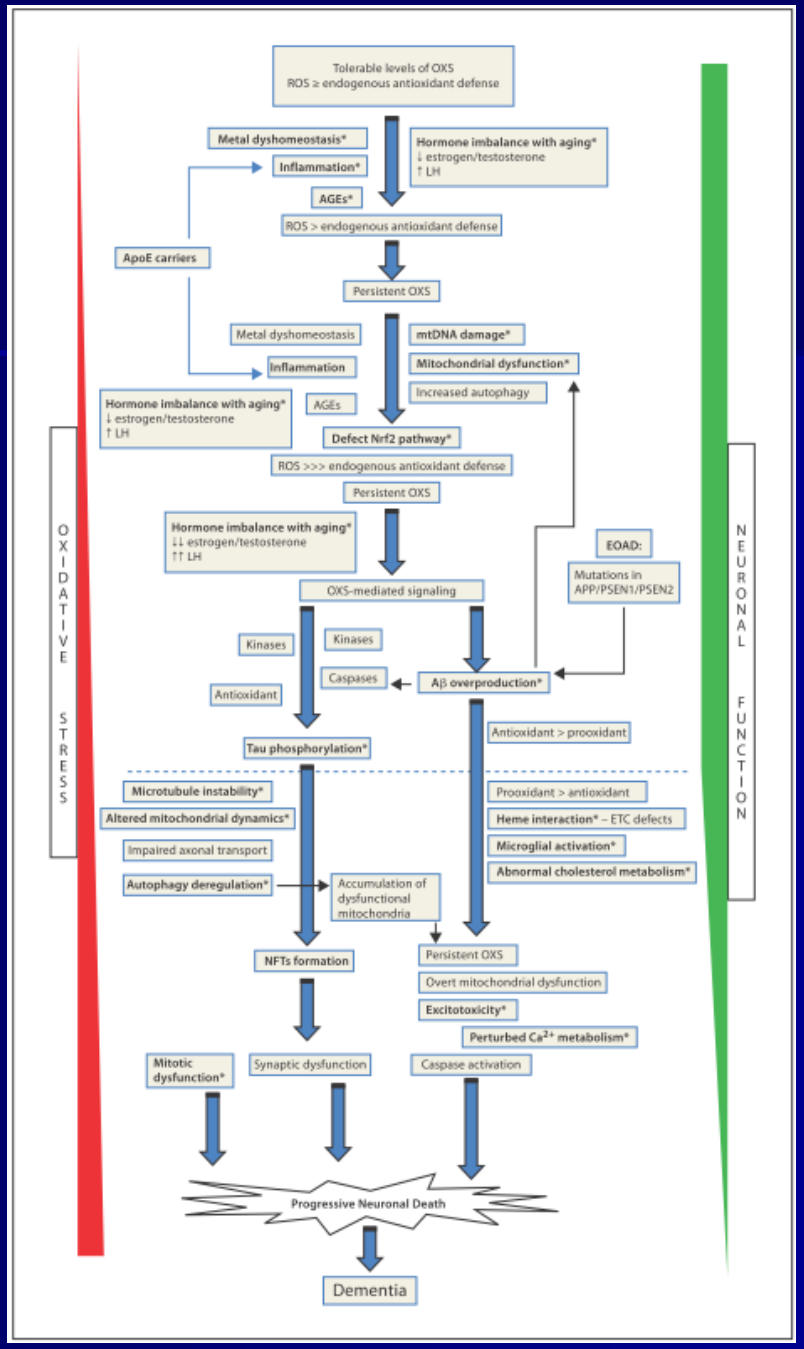
- memory impairment
- and at least one of the following:
  - aphasia
  - apraxia
  - agnosia
  - executive dysfunction
- causing significant impairment in social or occupational functioning
- and which do not exclusively occur during delirium

CAUSES OF DEMENTIA

- INTRACRANIAL:
  - DEGENERATIV:
    - *Alzheimer, Pick, Lewy,*
    - *Parkinson, Huntington,*
  - VASCULAR, POST-STROKE
  - TUMORS, POST-TRAUMATIC,
    - *Tumor, metastasis, subdural haematoma, hydrocephalus*
  - INFECTIONS
    - *AIDS, prion: Creutzfeldt-Jakob,* ***PESS,*** *neurosyphilis, Lyme, meningitis*

CAUSES OF DEMENTIA

- EXTRACRANIAL:
  - INTOXICATIONS
    - Alcohol, drogs, CO
  - GENETIC
    - Wilson
  - ORGAN INSUFF.
    - liver, renal failure, cardiac, thyroid
  - DEFICIENCY STATES
    - B12, folate


Tolerable levels of OXS
ROS ≥ endogenous antioxidant defense
Metal dyshomeostasis*
Inflammation*
AGEs*
Hormone imbalance with aging*
↓ estrogen/testosterone
↑ LH
ROS > endogenous antioxidant defense
ApoE carriers
Persistent OXS
Metal dyshomeostasis
Inflammation
mtDNA damage*
Mitochondrial dysfunction*
Increased autophagy
Hormone imbalance with aging*
↓ estrogen/testosterone
↑ LH
AGEs
Defect Nrf2 pathway*
ROS >>> endogenous antioxidant defense
Persistent OXS
Hormone imbalance with aging*
↓↓ estrogen/testosterone
↑↑ LH
EOAD:
Mutations in APP/PSEN1/PSEN2
OXS-mediated signaling
Kinases
Kinases
Caspases
Aβ overproduction*
Antioxidant
Tau phosphorylation*
Antioxidant > prooxidant
Microtubule instability*
Altered mitochondrial dynamics*
Impaired axonal transport
Autophagy deregulation*
Accumulation of dysfunctional mitochondria
Prooxidant > antioxidant
Heme interaction* – ETC defects
Microglial activation*
Abnormal cholesterol metabolism*
NFTs formation
Persistent OXS
Overt mitochondrial dysfunction
Excitotoxicity*
Perturbed Ca2+ metabolism*
Mitotic dysfunction*
Synaptic dysfunction
Caspase activation
Progressive Neuronal Death
Dementia
OXIDATIVE STRESS
NEURONAL FUNCTION

When to assess the patient for cognitive impairment?

- memory complaints
- family alerted
- other diseases (hospitalized elderly patients)
- sent by the family doctor
- screening!!!

Minimal program for investigation of cognitive impairment

- anamnesis and heteroanamnesis
- general exam
- neurological exam
- psychiatric exam
- Mini Mental State Examination and/or other short cognitive test
- laboratory tests
- CT or MRI

REPEAT IF NECESSARY DEPENDING ON THE EVOLUTION!!!

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History, anamnesis, heteroanamnesis:

- risk factors:
  - alcohol, hypertension, stroke, diabetes mellitus, atrial fibrillation, dislipidemia
  - head trauma
  - depression
  - dementia in the family

History, anamnesis, heteroanamnesis:

- activity of daily living:
  - alimentation, washing, dressing, shopping, handling money, orientation, accommodation
  - incontinency
    - urine, fecal
    - emotional
- education, prior level of knowledge

Questions to ask family members about patients with memory problems

- Can you give some examples of times when the patient had trouble with memory?
- Does he or she have trouble remembering names or faces of familiar people?
- Has he or she got lost while driving or walking in familiar areas?

Questions to ask family members to determine the nature of cognitive impairment in patients with memory loss

Aphasia

Does the patient:

- have any difficulties with finding the right word to say?
- use frequently "what-d'ye-call-it" instead of names?
- break off in midsentence?
- use circumlocutions in his/her speech?

Questions to ask family members to determine the nature of cognitive impairment in patients with memory loss

Apraxia

Does he or she have any difficulty with:

- dressing or bathing alone?
- using a brush or comb?
- feeding himself or herself?

Questions to ask family members to determine the nature of cognitive impairment in patients with memory loss

Agnosia

Does he or she have any trouble recognizing:

- familiar people or places?
- familiar objects or personal items?

Executive dysfunction

- Has he or she had any difficulty understanding what is going on around him or her,
  - such as following a church activity or planning an upcoming event?
- Has he or she had any problems figuring out how to use familiar objects,
  - such as appliances or tools, or how to operate with new devices, such as a new television remote control or microwave oven?

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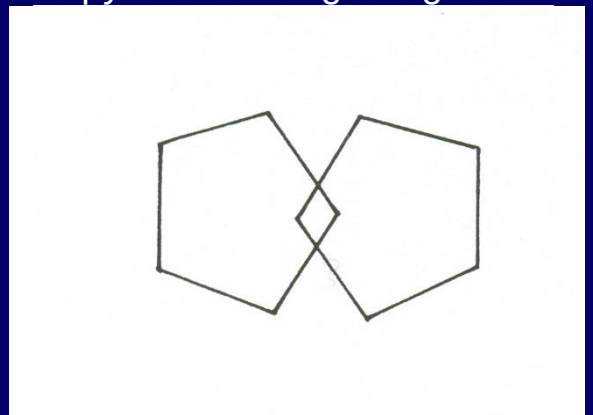
Mini-Mental State Examination

Folstein MF, Folstein SE, McHugh PR 1975

Maximum score	Score	
		Orientation
5	__	What is the (year) (season) (date) (day) (month)?
5	__	Where are we: (state) (county) (town or city) (hospital) (floor)?
		Registration
3	__	Name three common objects (e.g., "apple," "table," "penny"):
		Attention and calculation
5		Spell "world" backwards. The score is the number of letters in correct order.
	__	(D___L___R___O___W___)
		Recall
3	__	Ask for the three objects repeated above.
		Language
2		Name a "pencil" and "watch."
	__	Repeat the following: "No ifs ands or buts."
1	__	Follow a three-stage command:
3	__	"Take a paper in your right hand, fold it in half and put it on the floor."
1	__	Close your eyes.
1	__	Write a sentence.
1		Copy the following design.



Total score

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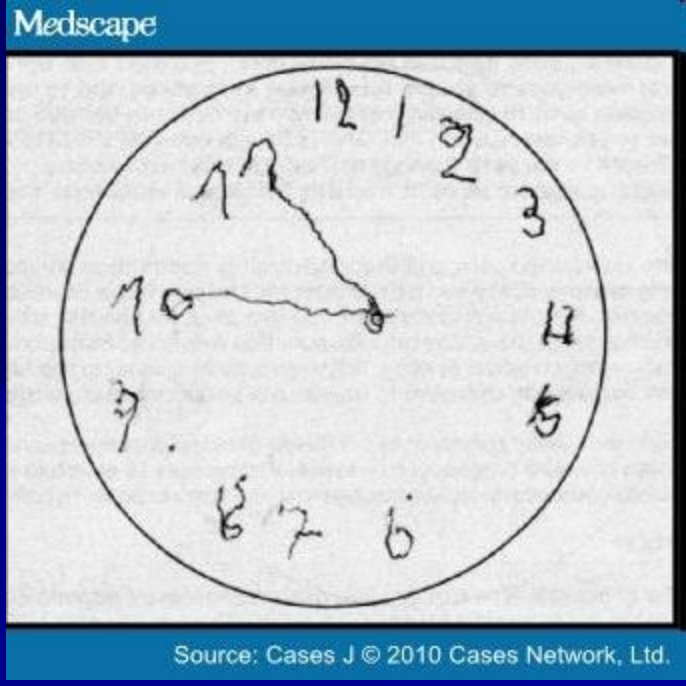
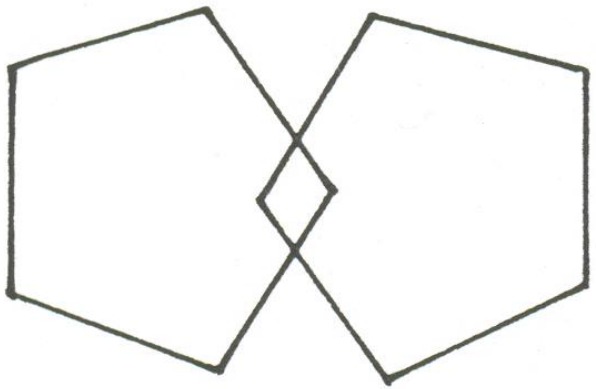
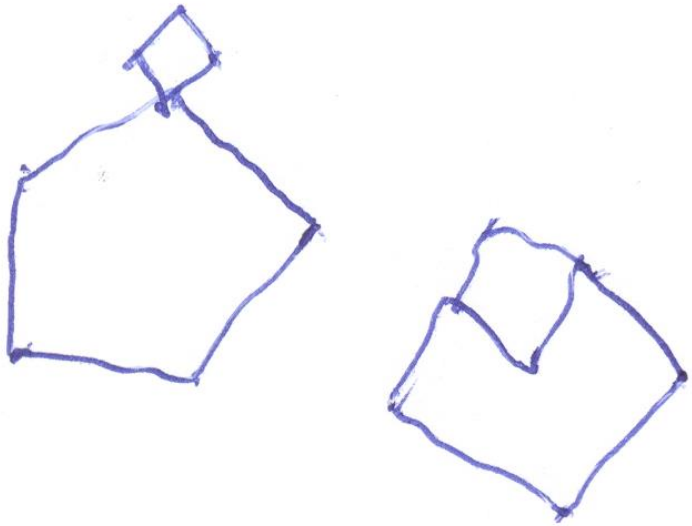
Clock Drawing Test

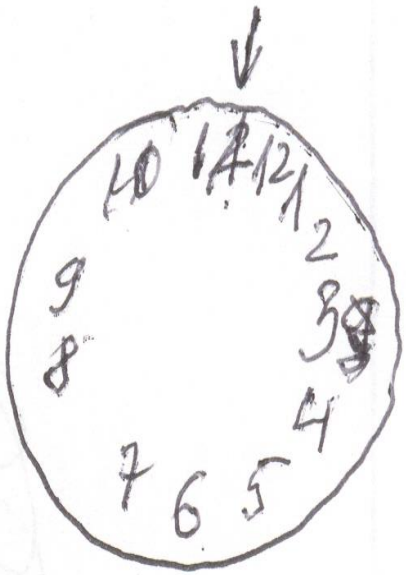


- "Without looking at your watch, draw the face of a clock, and mark the hands to show 10 minutes to 11:00."
  - This task requires intact memory, visuospatial skills, and executive functioning.
- Scoring:
  - the clock numbers are
    - generally intact (6 to 10 points)
    - not intact (1 to 5 points).
  - a score of 5 or less is suggestive of dementia


6 moles
9 liters



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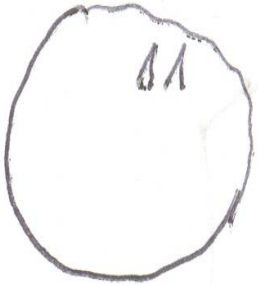
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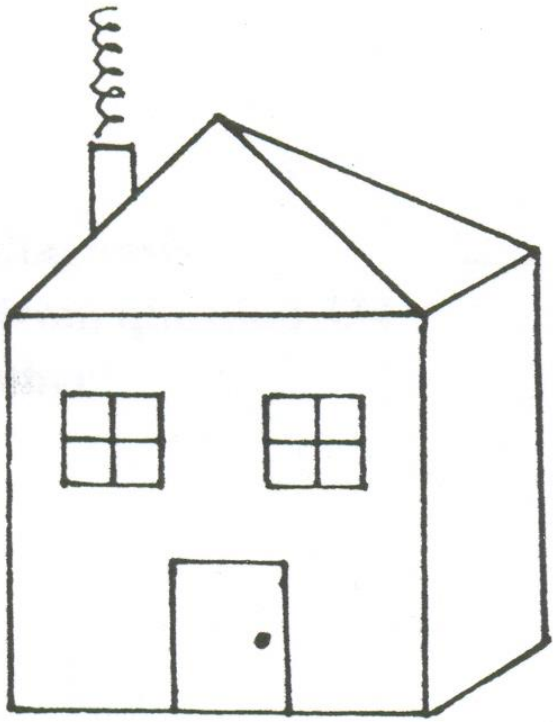

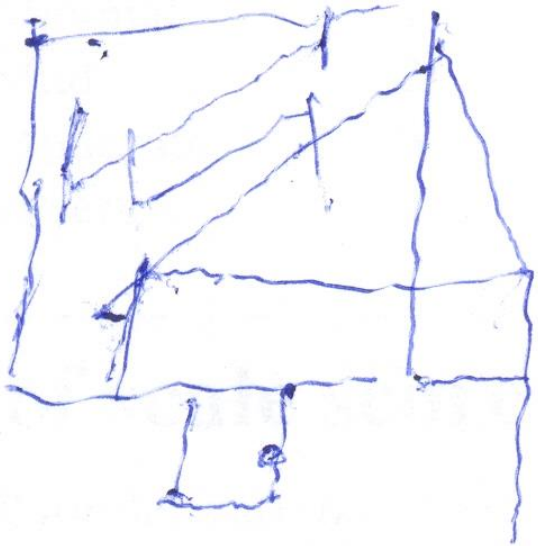

Minimal program for investigation of cognitive impairment

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REPEAT IF NECESSARY DEPENDING ON THE EVOLUTION!!!

LABORATORY TESTS FOR THE EVALUATION OF DEMENTIA

- Thyroid function tests
- Serum vitamin B_{12}
- Serum glucose level
- Complete blood cell count
- Serum electrolyte levels
- Serum liver function tests
- Serum kidney function tests
- Erythrocyte sedimentation rate
- Chest radiography
- Electrocardiography
- Toxicology screening
- Urinalysis and microscopy
- Serologic tests for syphilis

Additional Tests to Consider in the Diagnostic Work-Up of Dementia

Test	Indication
Electroencephalography	Possible seizures; Creutzfeldt-Jakob disease
Lumbar puncture	Onset of dementia within the preceding six months; dementia rapidly progressive
Heavy metal screen	History of potential exposure
Human immunodeficiency virus	History of potential exposure
Lyme disease titer	History of exposure and compatible clinical picture
Ceruloplasmin, arylsulfatase, electrophoresis	Wilson's disease, metachromatic leukodystrophy, multiple myeloma
Slit lamp examination	History and examination suggest Wilson's disease
Apolipoprotein E	Need to increase likelihood that diagnosis of Alzheimer's disease is correct
Genetic testing for Alzheimer genes, other dementia genes	Family history is strong, and confirmation is clinically necessary

Genetic testing and counselling ????

- Testing positive for APOE ε4 does not mean a person will definitely develop late onset Alzheimer's disease.
- Testing negative for APOE ε4 does not guarantee that they will be free from Alzheimer's
- presenilin – when family history is +

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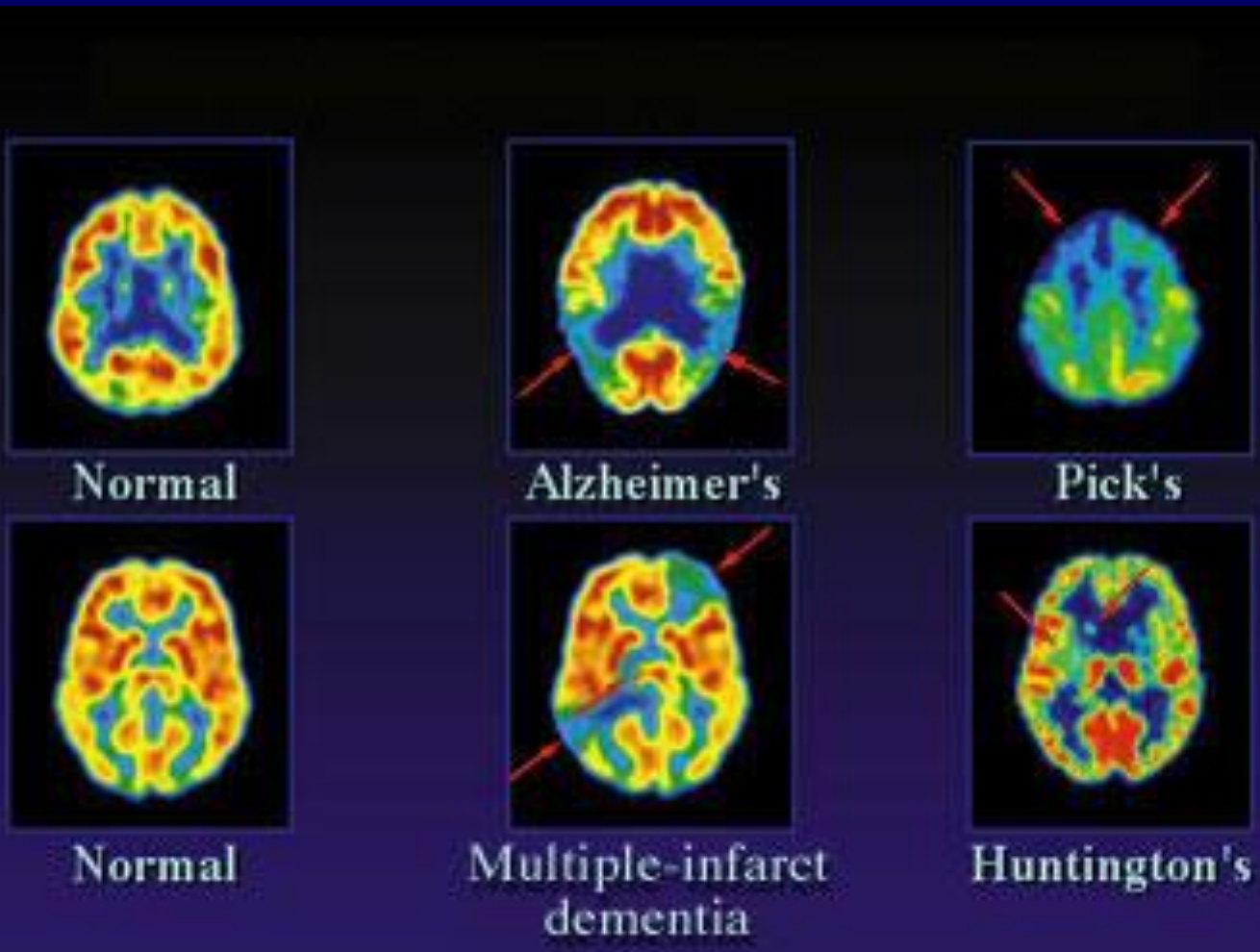
REPEAT IF NECESSARY DEPENDING ON THE EVOLUTION!!!

Neuroradiology - CT/MRI

- Focal neurological signs
- Suspected cerebral lesion
  - tumors
  - subdural haematoma
  - hydrocephalus
  - stroke

!

- acute, subacute onset
- trauma weeks ago
- general signs of malignancy



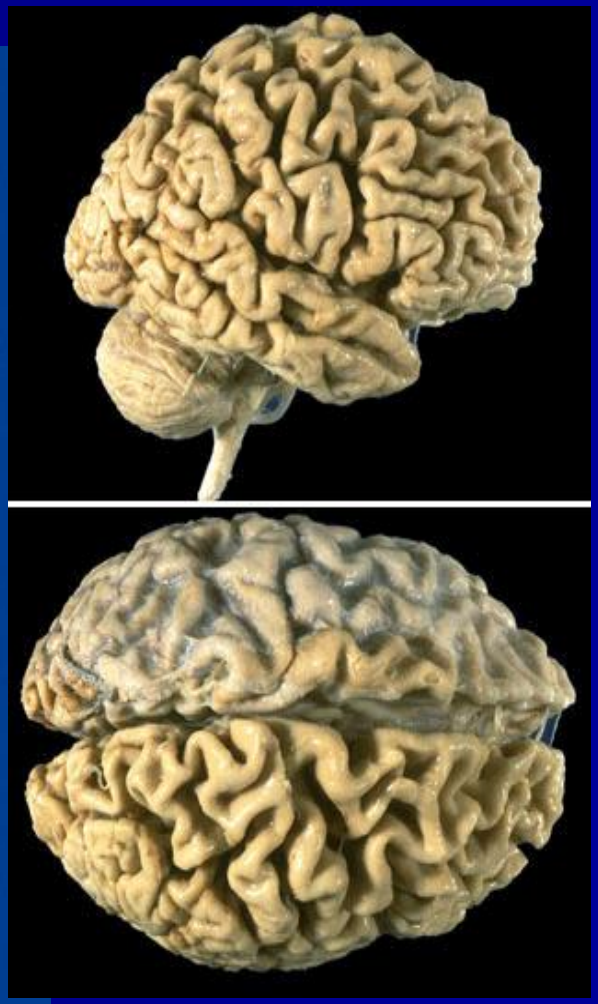
Dr. Gary W. Small

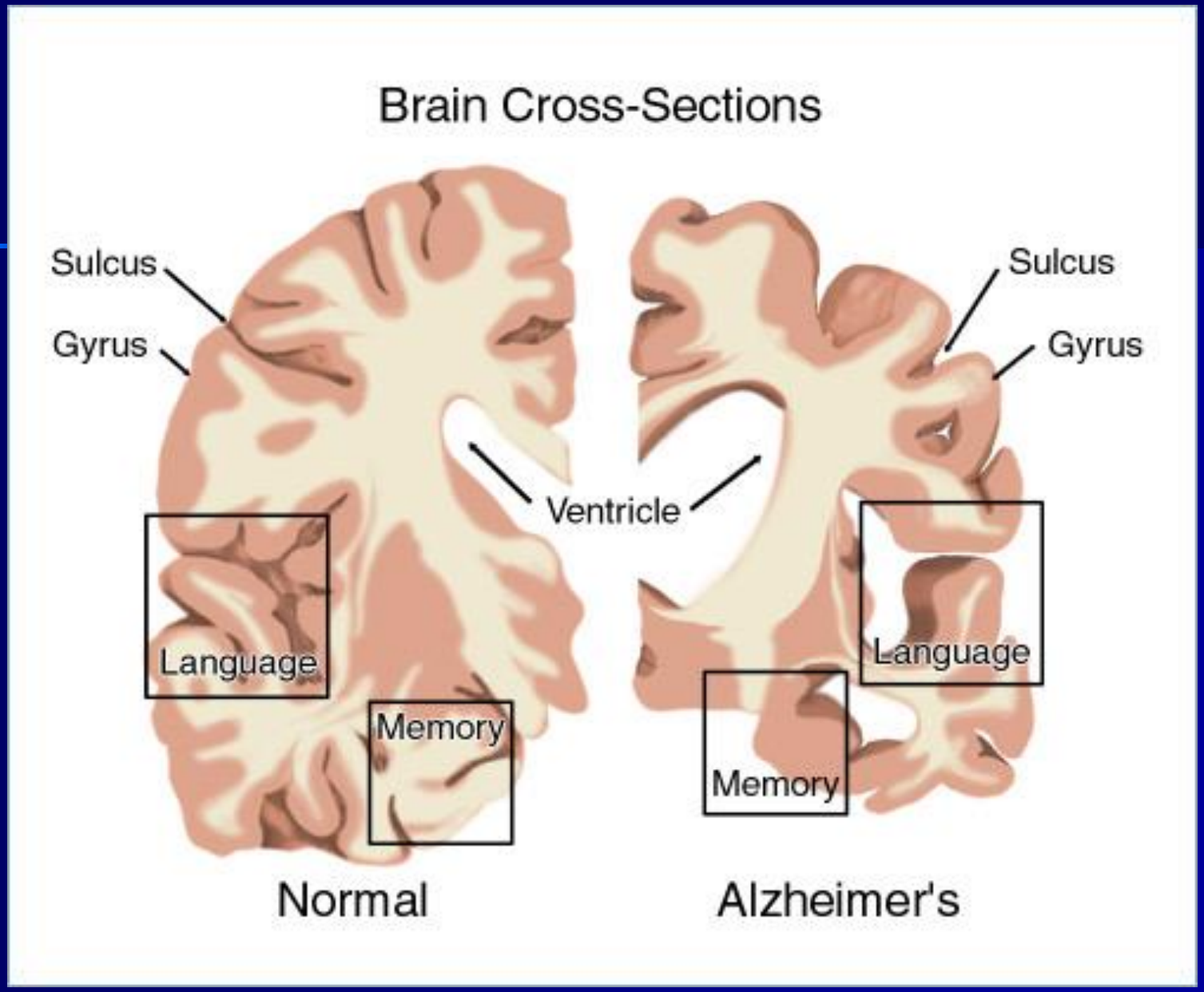
ALZHEIMER's DISEASE

- Characteristic:
  - **dementia**
  - **no other causes**
  - slow progression
  - cortical signs
  - no neurological signs
  - CT/MRI: atrophy

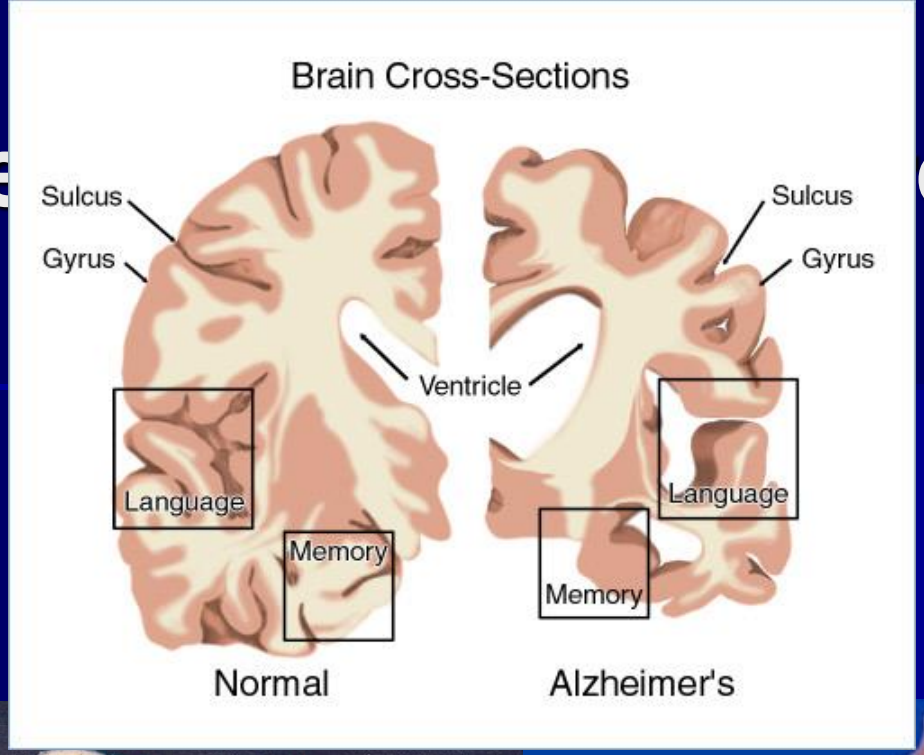
- Not characteristic:
  - acute onset, focal signs, epilepsy, other CT/MRI signs

Alzheimer's disease: narrow gyri, large sulci




Brain Cross-Sections
Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

Alzhe ophy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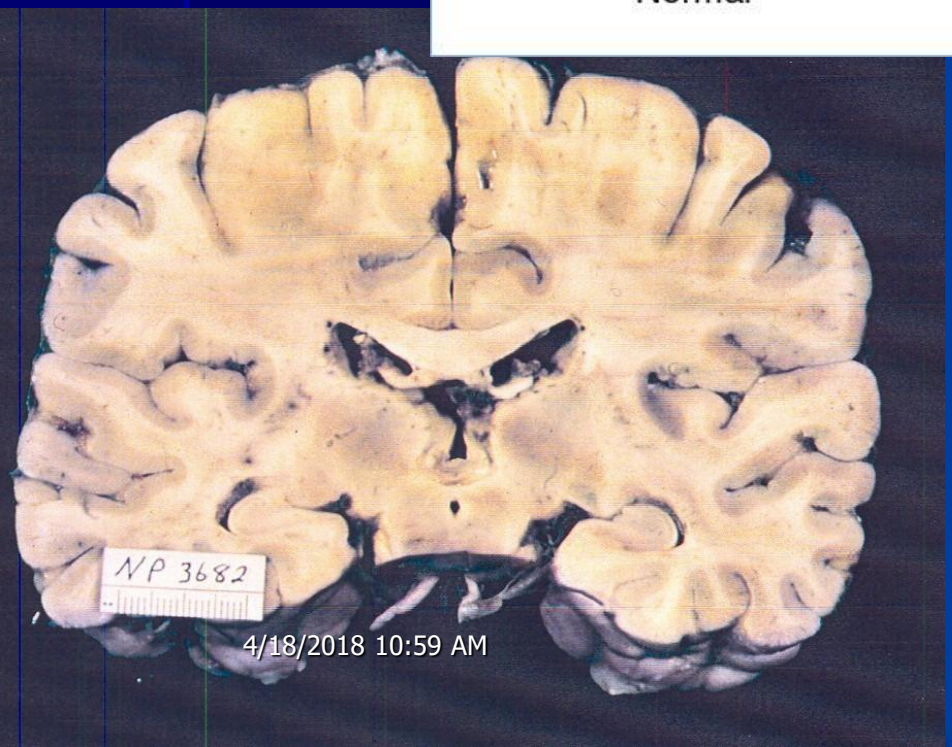
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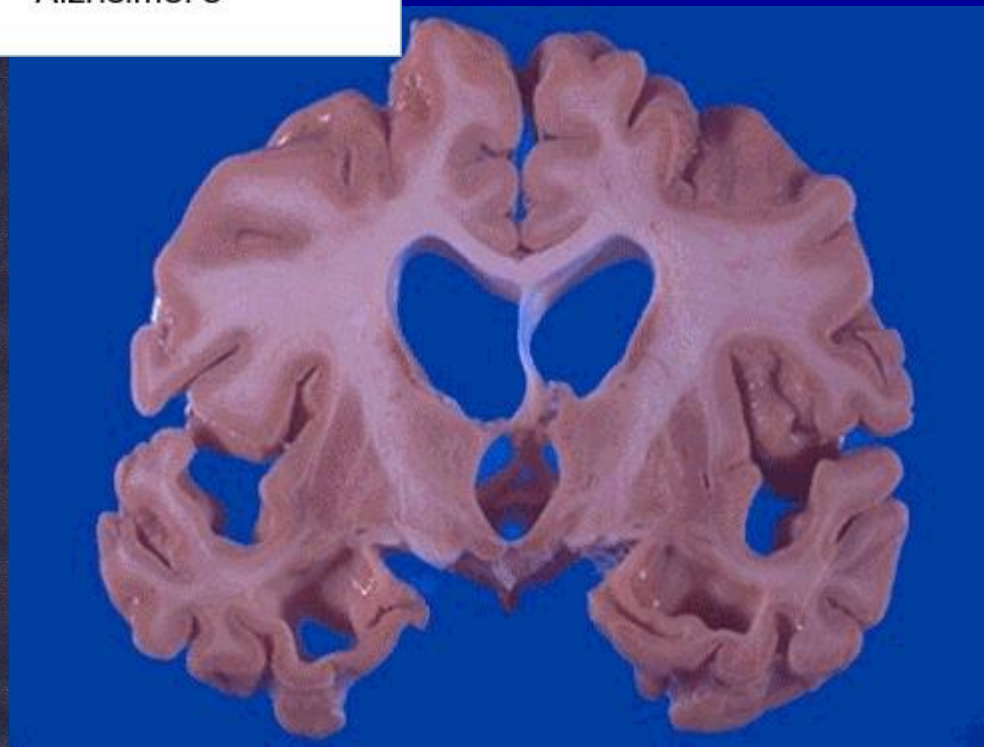
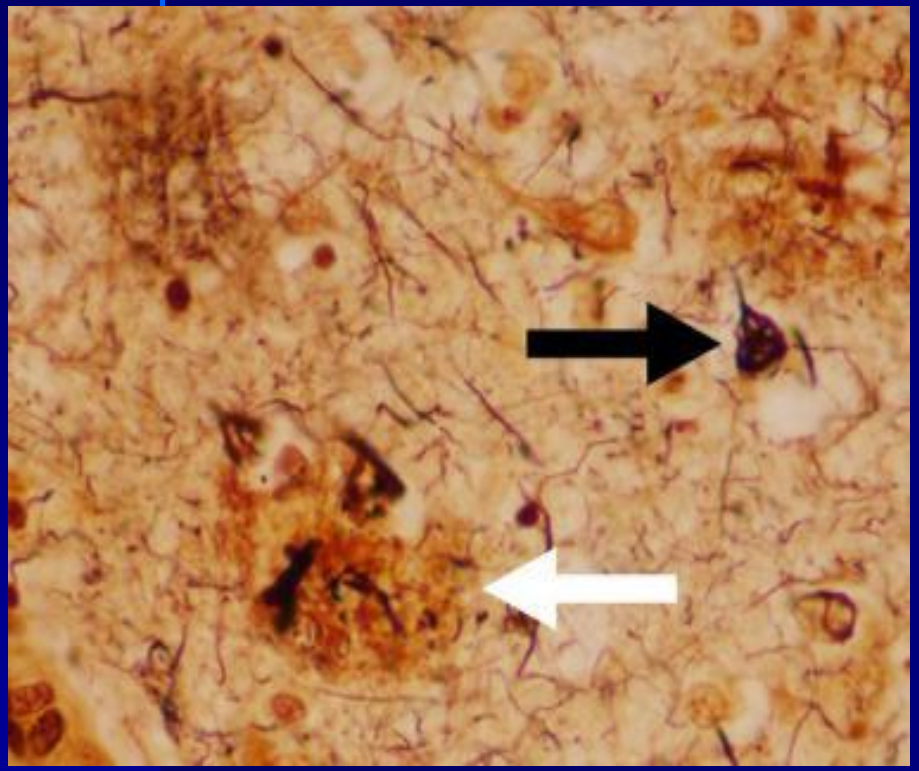
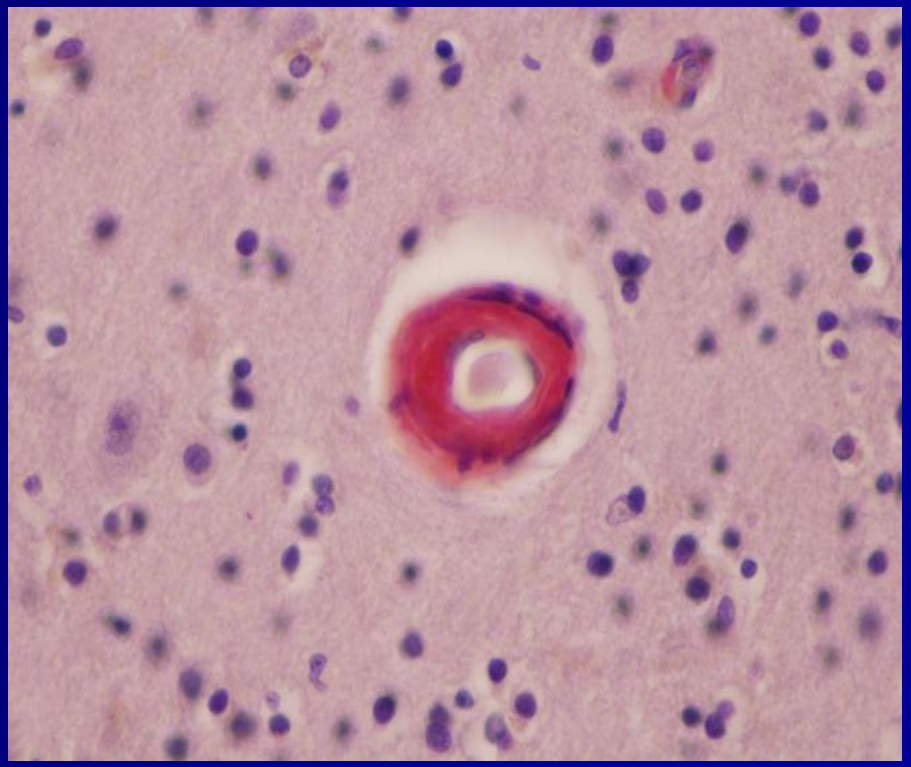
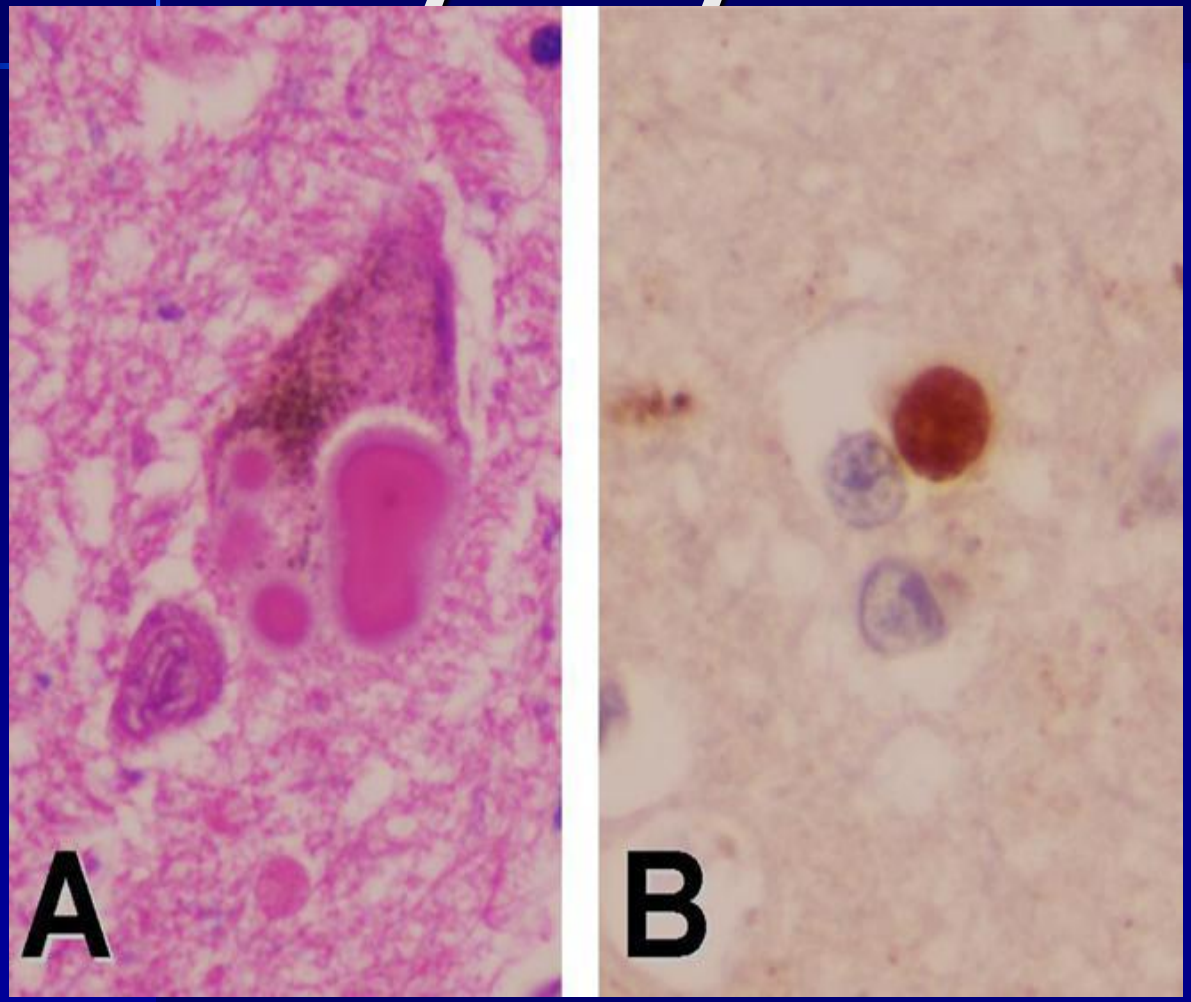


Pathology: neurofibrillary tangles, neuritic plaques, amiloid depositions





Pathology: Lewy-body



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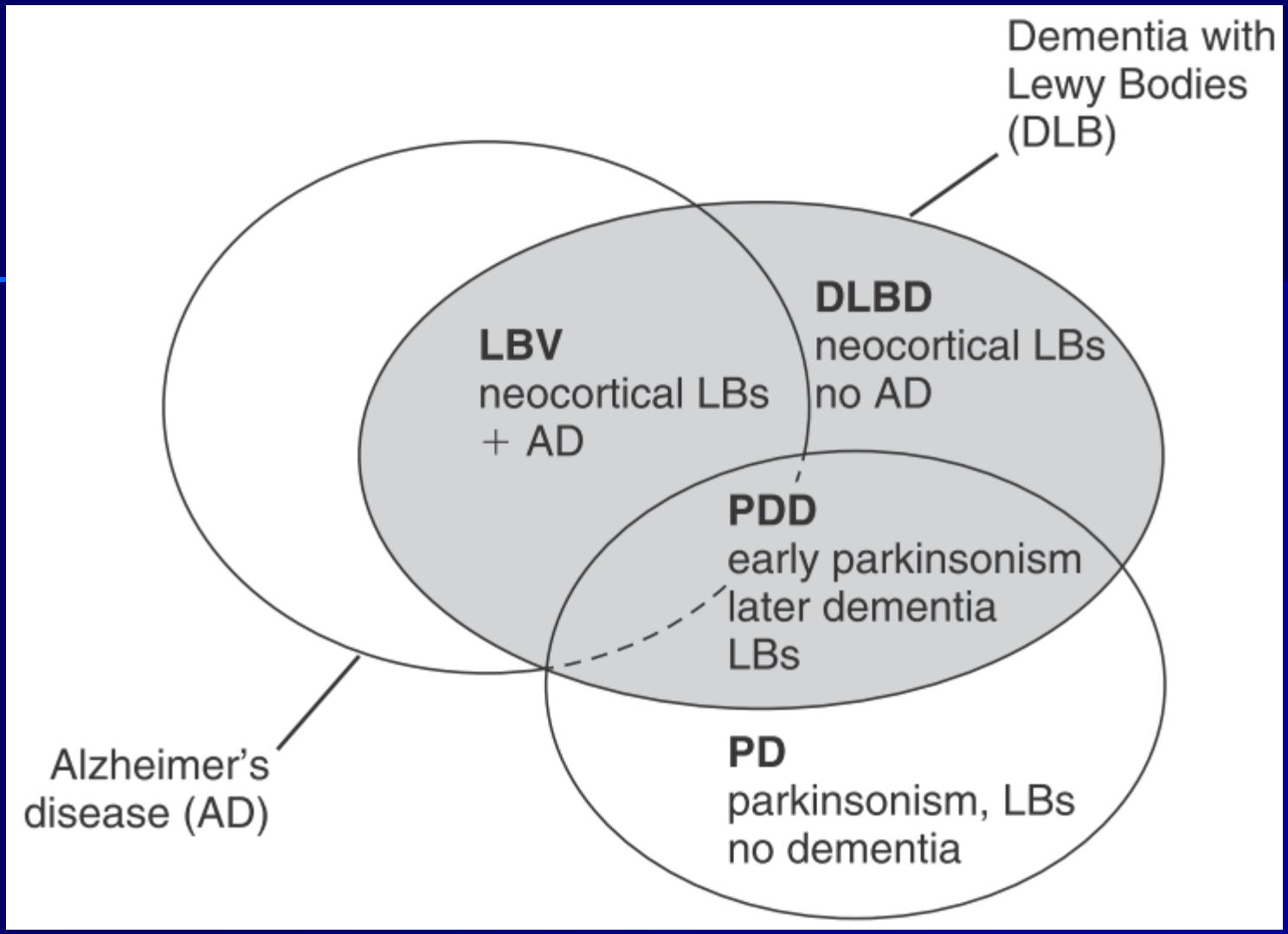
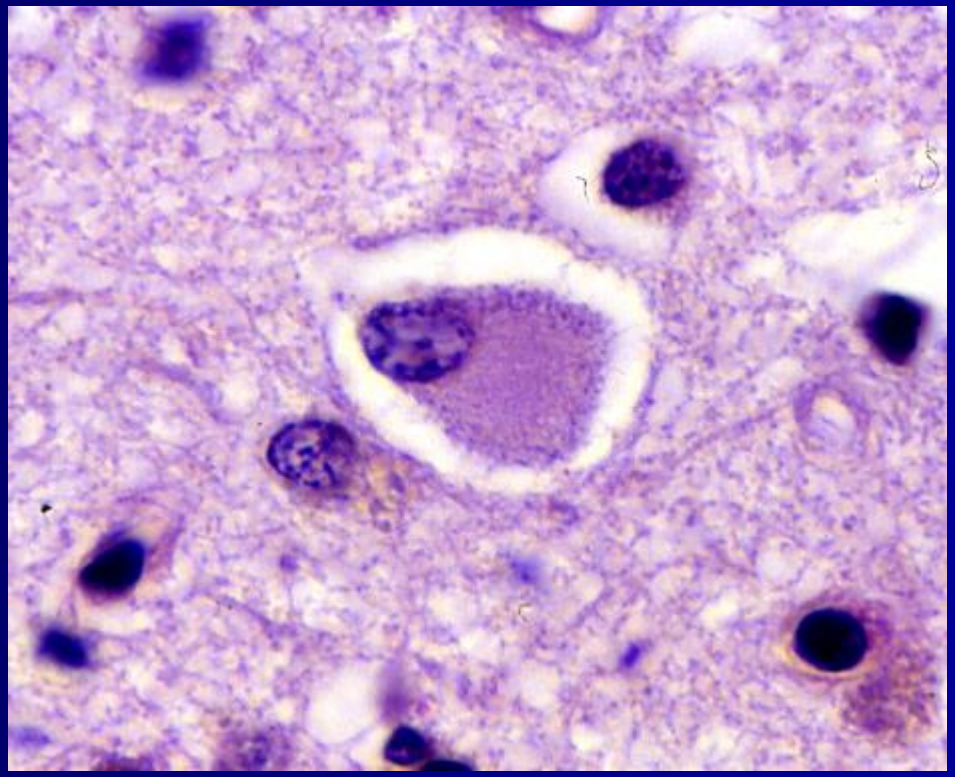
Clinical criteria

- Dementia
  - Attention
  - Visuospatial
  - Executive
- Characteristic:
  - Fluctuation
  - Hallucinations
  - parkinsonism



Lewis, KA et al: Abnormal neurites containing C-terminally truncated α -synuclein are present in Alzheimer's disease without conventional Lewy body pathology. The American Journal of Pathology 177(6) 3037–3050, 2010

Pathology: Pick-cells



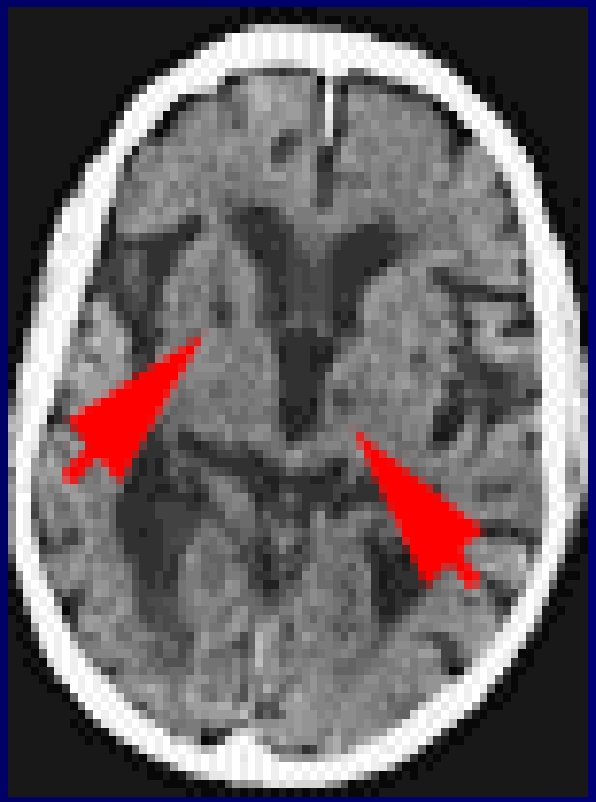
VASCULAR DEMENTIA

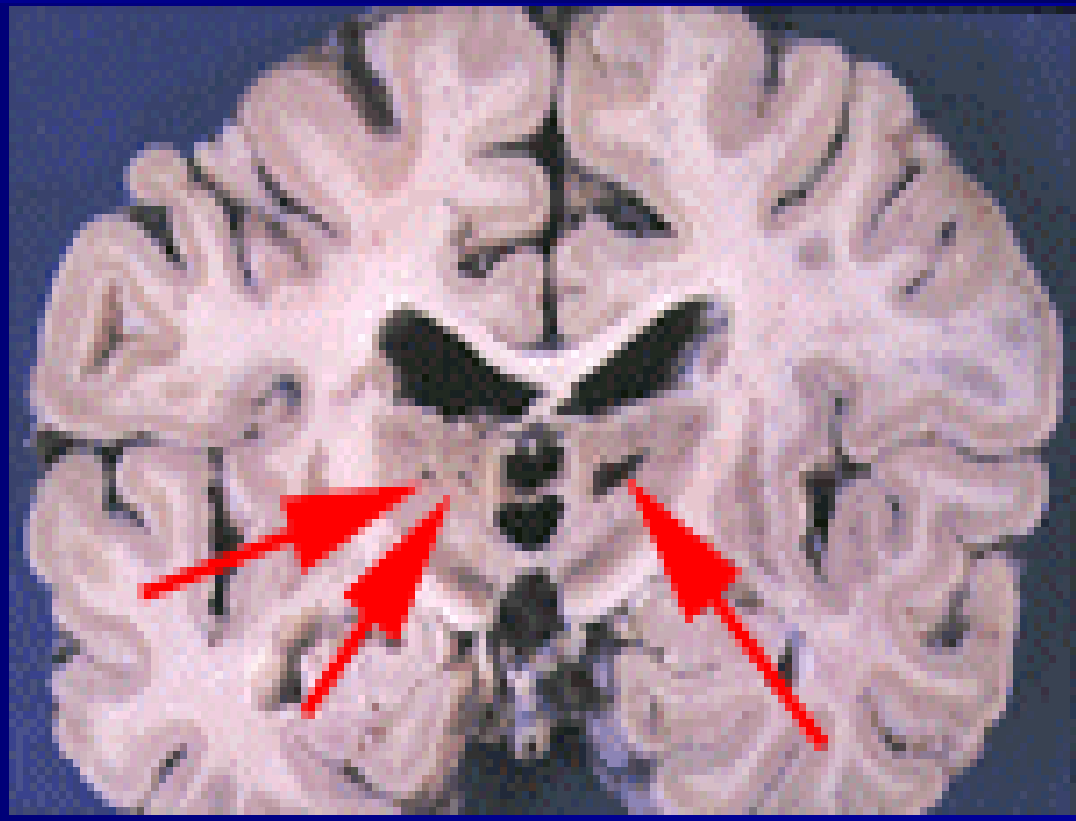
- Dementia
- Cerebrovascular disease (risk factors, stroke, CT/MRI)
- relationship

VASCULAR DEMENTIA

- Commonly: multiinfarct (MID), multilacunar
- Characteristic:
  - anamnestic: stroke, TIA
  - Signs after stroke: neurological exam and CT/MRI
  - Pseudobulbar syndrome,
  - Incontinency: emotional, urine
  - gait disorders (astasia, abasia),
  - depression
- Not characteristic:
  - normal CT/MRI,
  - lack of vascular risk factors

CT: multiple lacunar infarcts



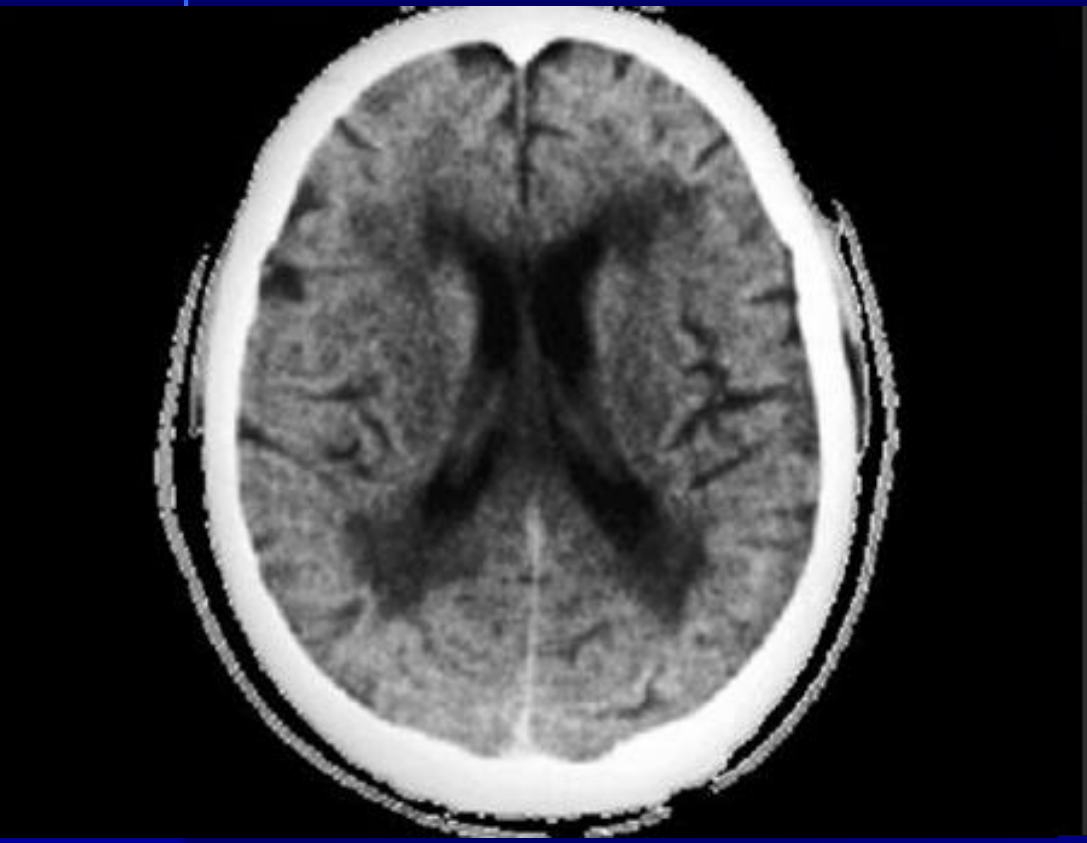


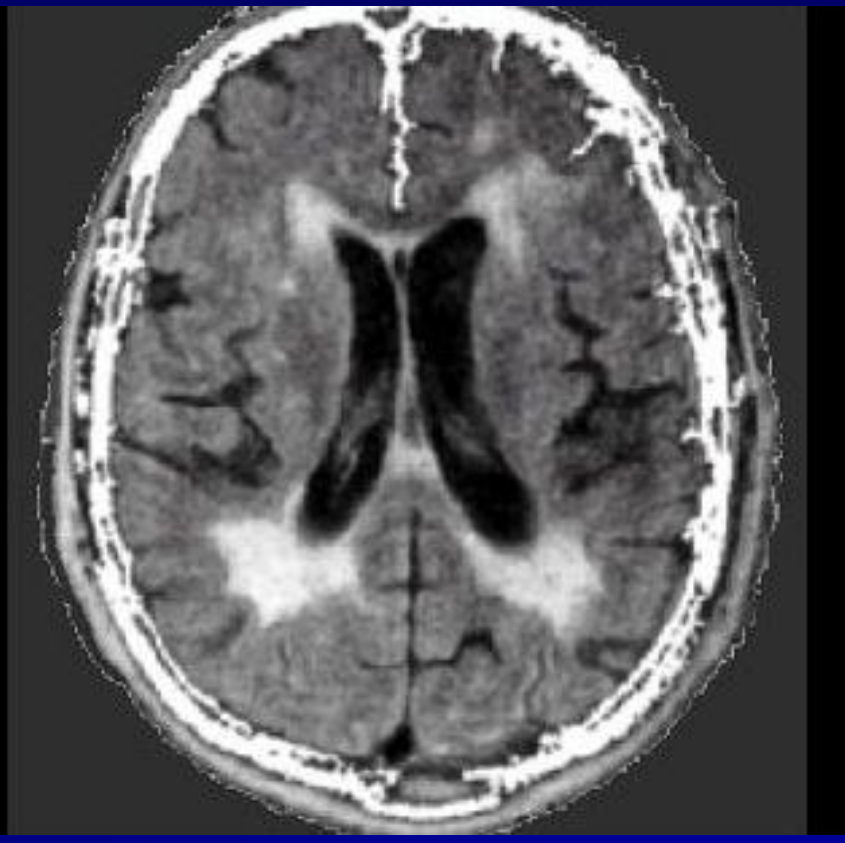
Hegedűs, 2001

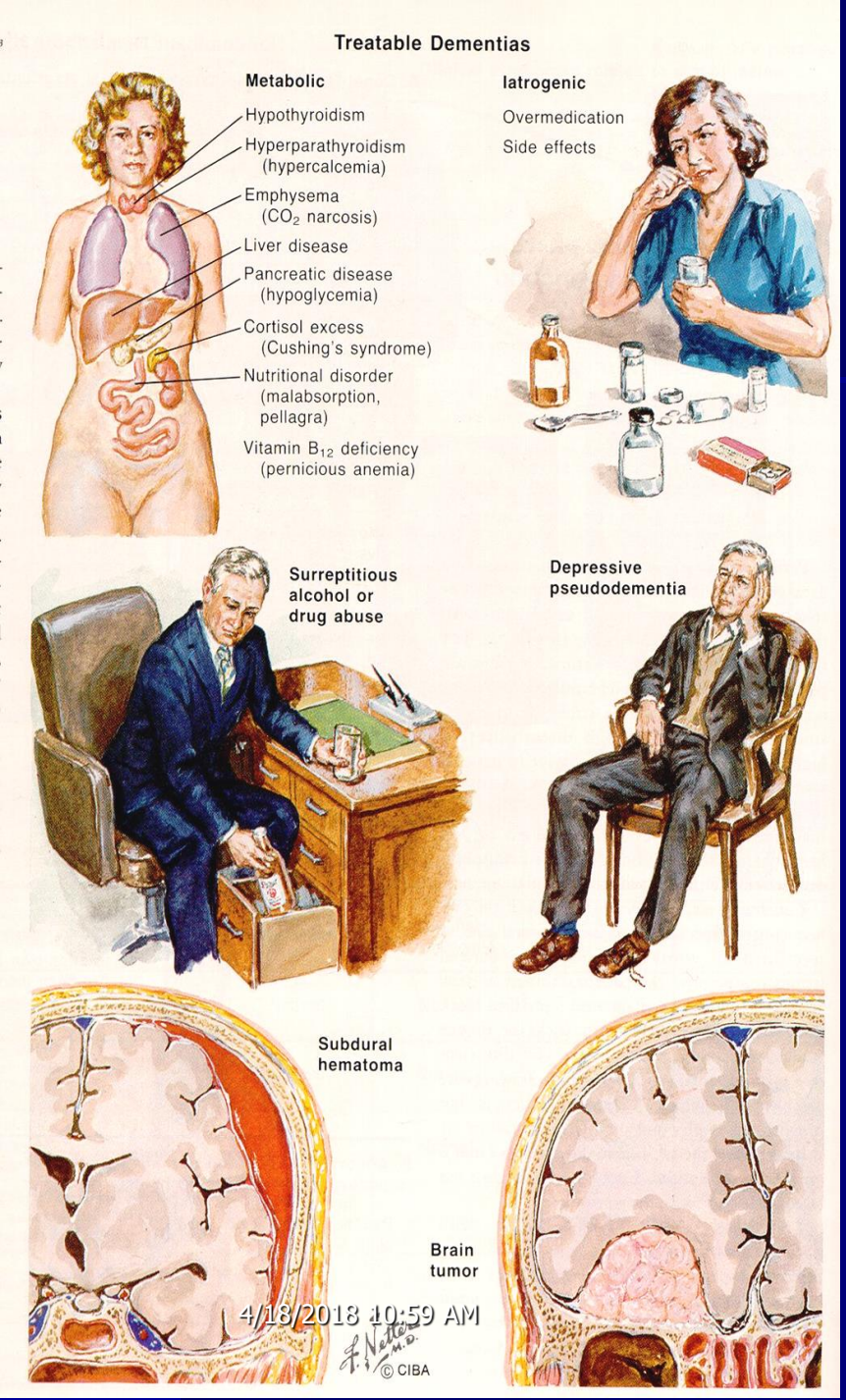
VASCULAR DEMENTIA

- Special:
  - Binswanger's disease (encephalitis subcorticalis chronica progressiva)
    - hypertension, dementia, unsteady gait, incontinency
    - ~ ≠ leucoaraiosis
  - CADASIL *(cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy)*

Leucoaraiosis

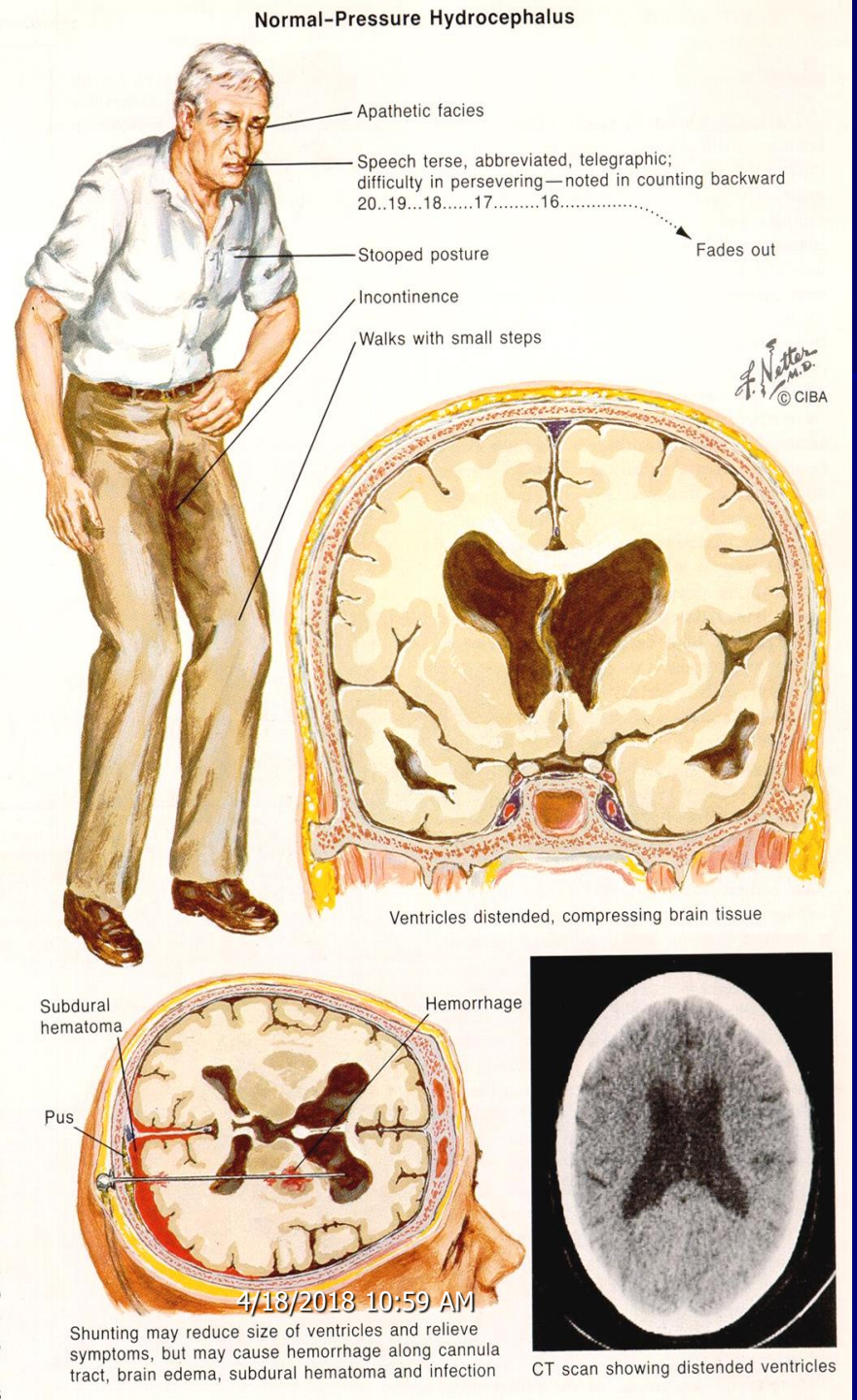






Potentially reversible causes of dementia

- subdural hematoma
- tumor (frontal)
- metabolic
- alcohol
- drugs
- Pseudodementia (depression)
- hydrokephalus



Potentially reversible causes of dementia

- hydrokephalus
  - dementia
  - unsteady gait
  - incontinency

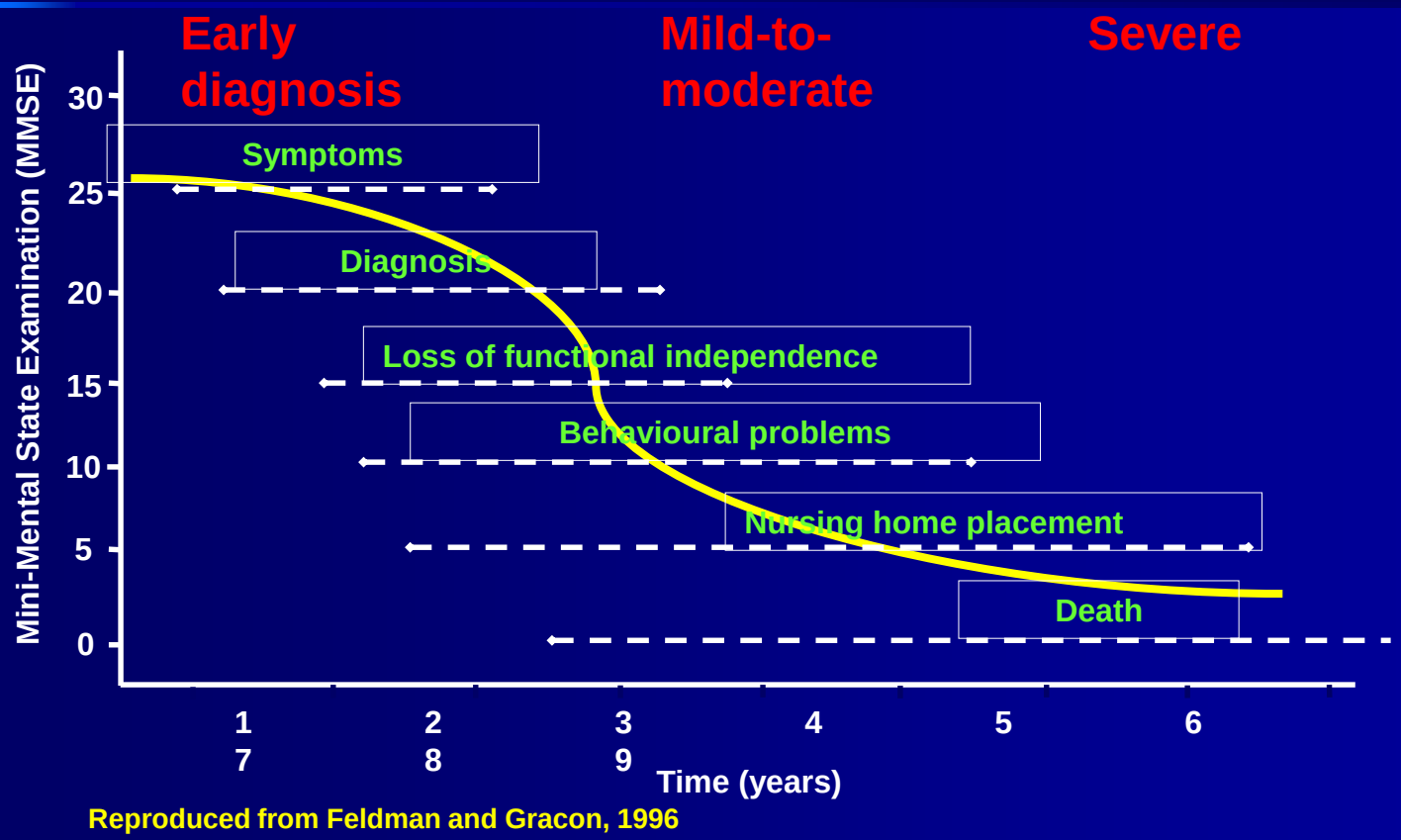
Features Distinguishing Delirium and Dementia

	Delirium	Dementia
Onset	Acute	Insidious
Duration	Days/weeks	Months/years
Attention	Distracted	Usually normal
Level of Consciousness	Increased/decreased	Usually normal
Cognition	Disorganized	Impoverished

Features Distinguishing Dementia and Depressive Pseudodementia:

	Dementia	"Pseudodementia"
Precise onset	Unusual	Usual
Duration	Long	Short
Complaints	Variable	Usual
psych history	Uncommon	Common
"Don't know"	Uncommon	Common
Affect	Labile, blunted	Depressed

Natural history of Alzheimer's disease



Reproduced from Feldman and Gracon, 1996

Alzheimer's Disease Treatment

- Prescription medication
  - cholinesterase inhibitors (CI)
- Other medications
  - vitamin E, gingko biloba, memantine, others
- For behavioral disturbances
  - psychotropic medications
- Nonpharmacologic intervention
  - caregiver support
  - behavioral and environmental modifications

Fillit and Cummings. *Managed Care Interface*. 2000.

Acetylcholinesterase Inhibitors Used in the Treatment of Dementia

Drug	*Dosage*	*Target dosage*	*Minimum therapeutic dosage*
Donepezil (Aricept)	Start at **5** mg once daily, taken at bedtime; after **6** weeks, increase to 10 mg once daily.	**10 mg once** daily	5 mg daily
Rivastigmine (Exelon)	Start at **1.5** mg twice daily, taken with food; at 2-week intervals, increase each dose by 1.5 mg, up to a dosage of 6 mg twice daily.	**6 mg twice** daily	3 mg twice daily
Galantamine (Reminyl)	Start at 4 mg twice daily with food; at 4-week intervals, increase each dose by 4 mg, up to a dosage of 12 mg twice daily.	**12 mg twice** daily	8 mg twice daily

N-methyl-D-aspartat (NMDA) antagonist

- Memantine (Ebixa)
  - for treatment of moderate-to-severe AD
  - Recommended dose:
    - 2x10 mg per day
      - Start at 1x5 mg per day
      - Increase with 5mg per day each week to max. 2x10 mg per day