SISTEMA SANITARIO REGIONALE

AZIENDA OSPEDALIERA UNIVERSITARIA
POLICLINICO UMBERTO I

Internal Medicine and General Surgery II

Geriatric Medicine
Cognitive impairment

Dott.ssa F. Moscucci
Geriatra
Dottorato di Ricerca in Fisiopatologia ed Imaging Cardio-Toraco-Vascolare
Sapienza

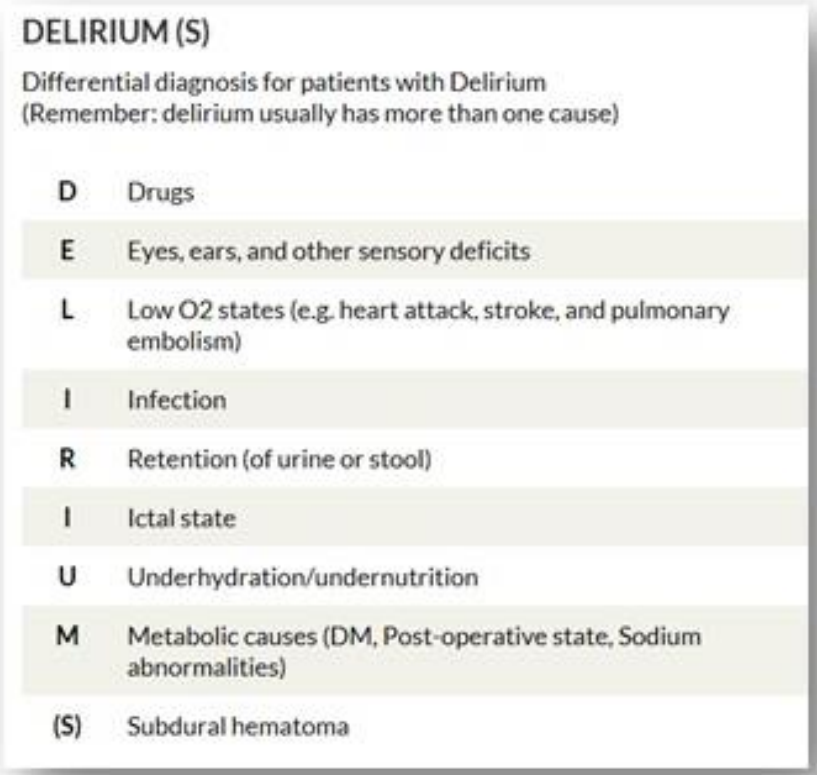
Effect of normal aging in intellectual functioning

	Preserved cognitve functions	Functions showing decline
General intellectual functioning	Crystallized, verbal intelligence	Fluid, nonverbal intelligence, speed of information processing
Attention	Sustained attention, primary attention span	Divided attention
Executive functions	“real world” executive function	Novel executive tasks
Memory	Remote memory, procedural memory, semantic recall	Learning and recall of new informantion
Language	Comprehension, vocabulary, syntactic ablities	Spontaneous words finding, verbal fluency
Visuospatial skill	Construction, simple copy	Mental rotation, complex copy, mental assembly
Psychomotor functions		Reaction time

“*A man is as old as his arteries*”

Thomas Sydenham 1624-1689

Many common age-related medical conditions could affect cognitive status



DELIRIUM (S)

Differential diagnosis for patients with Delirium
(Remember: delirium usually has more than one cause)

D	Drugs
E	Eyes, ears, and other sensory deficits
L	Low O2 states (e.g. heart attack, stroke, and pulmonary embolism)
I	Infection
R	Retention (of urine or stool)
I	Ictal state
U	Underhydration/undernutrition
M	Metabolic causes (DM, Post-operative state, Sodium abnormalities)
(S)	Subdural hematoma

- Acute onset and Fluctuating symptoms

- Inattention

- Disorganized thinking

- Altered level of consciousness

- Complete recovery, if correctly treated

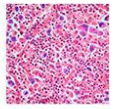
Frailty!

PREDISPOSING FACTORS

HEALTHY AGING

Increasing of predisposing factors

FRAILTY or DEMENTIA



Immunosenescence
Inflammaging

Microvasculature changes

Altered body composition
Oxidative stress

Neuroendocrine dysfunction
Neuroanatomical abnormalities

The lower the burden of predisposing factors, the higher the intensity of the stressor required to cause Delirium

Acute stressors

The higher the burden of predisposing factors, the lower the intensity of the stressor required to cause Delirium

PRECIPITATING FACTORS

DELIRIUM

Impaired neuro-vascular coupling: hypoxia, hypoglycemia

Neuroinflammation

Microglia and Astrocytes activation

Physical and/or psychological stress

Neurostransmitter alterations

Medications

Deteriorating health

POOR HEALTH-RELATED OUTCOMES

Disability
Institutionalization
Hospitalization
Death

The CAM-ICU-7 Delirium Severity Scale

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; RASS: Richmond Agitation Sedation Scale; SAS: Sedation-Agitation Scale; GCS: Glasgow Coma Scale

Neurodegenerative Diseases

Alzheimer Disease

Probability!! The diagnosis is certain only after authopsy!

Diagnostic criteria (DSMV):

1)Dementia as noted on clinical examination and established by neuropsychological testing;

2)Significant impairment in two or more areas of cognition;

3)Progressive memory decline;

4)Absence of other medical or psychiatric conditions, including delirium, as the cause for memory impairment.

Alzheimer Disease

Potential diagnostic tools:

- Cerebrospinal fluid markers (beta amyloid or tau proteins)
- Structural and functional changes on brain scan
- Genetic factors.

Alzheimer Disease

Neuropsychological assessment:

Cognitive functions:

Mini Mental State Examination (MMSE)

Severe Impairment Battery (SIB)

Milan Overall Dementia Assessment (MODA)

Alzheimer's Disease Assessment Scale- (ADAS-Cog)

Functional status:

Barthel Index

Basic Activity of Daily Living (BADL)

Instrumental Activity of Daily Living (IADL)

Bedford Alzheimer Nursing Severity Scale (BANSS)

Scala di Tinetti

Physical Performance Test (PPT)

Cognitive symptoms:

UCLA Neuropsychiatric Inventory

Geriatric Depression Scale (GDS)

Cornell Depression Scale

Comorbidities:

Cumulative Illness Rating Scale (CIRS)

Caregivers burn out:

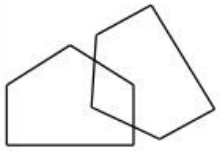
Caregiver burden Inventory (CBI)

Severity evaluation:

Clinical Dementia Rating Scale

MMSE

Essendo tale test molto diffuso e reperibile anche su internet, si è ritenuto idoneo riproporlo qui interamente sicuri di non violare alcuna norma di copyright.

Chiedere al paziente il giorno del mese, l'anno, il mese, il giorno della settimana e la stagione. [0] [1] [2] [3] [4] [5]	**Orientamento temporale**
Il paziente sa riferire il luogo in cui si trova, a quale piano, in quale città, regione, stato. [0] [1] [2] [3] [4] [5]	**Orientamento spaziale**
L'esaminatore pronuncia ad alta voce tre termini (casa, pane, gatto) e chiede al paziente di ripeterli subito. L'esaminatore deve ripeterli fino a quando il paziente non li abbia imparati (max 6 ripetizioni). [0] [1] [2] [3]	**Memoria**
Far contare per sette all'indietro, partendo da 100. Fermarsi dopo le prime 5 risposte. [0] [1] [2] [3] [4] [5] Se il paziente avesse difficoltà di calcolo, far scandire all'indietro la parola CARNE una lettera alla volta. [0] [1] [2] [3] [4] [5]	**Attenzione e calcolo**
Richiamare i tre termini precedentemente imparati. [0] [1] [2] [3]	**Richiamo delle tre parole**
Come si chiama questo? (indicando una matita). Come si chiama questo? (indicando un orologio). Il paziente deve riconoscere due oggetti. [0] [1] [2]	**Denominazione**
Invitare il paziente a ripetere la frase "tigre contro tigre" [0] [1]	**Ripetizione**
Invitare il paziente ad esguire correttamente i seguenti ordini: a) prenda un foglio con la mano destra, b) lo pieghi a metà, c) e lo butti per terra. [0] [1] [2] [3]	***Esecuzione di un compito su comando orale***
Presentare al paziente un foglio con la seguente scritta: "Chiuda gli occhi". Invitare il paziente ad eseguire il comando indicato. [0] [1]	***Esecuzione di un compito su comando scritto***
Far scrivere al paziente una frase formata almeno da soggetto e verbo. [0] [1]	**Scrittura**
Far copiare al paziente il disegno indicato (*vedi qui sotto*) [0] [1] 	**Prassia costruttiva**

Clinical presentation

With progression:

Behavioural disorders (aggressiveness, incontinence)
Affective disorders
Pyramidal signs (rigidity, dyskinesia, lethargy)
Difficulties in ADL and IADL

Final presentation:

Total foreignness to the environment and complete dependence
Wasting
Dysphagia
General decline
High susceptibility to infections and sepsis

Genetic risck factors

- Mutations of chromosomes 1, 14, 21
- Rare early-onset (before age 60) familial forms of dementia
- Down syndrome
- Apolipoprotein E4 on chromosome 19
- Late-onset AD
- APOE*4 allele ↑risk & ↓onset age in dose-related fashion
- APOE*2 allele may have protective effect

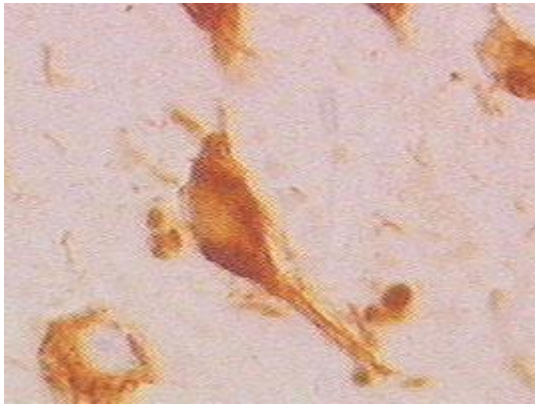
Pathology

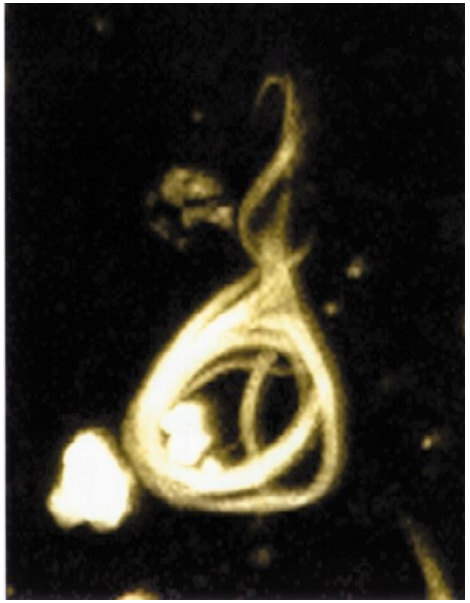
- There are 3 consistent neuropathological hallmarks:
  - Amyloid-rich senile plaques
  - Neurofibrillary tangles
  - Neuronal degeneration

- These changes eventually lead to clinical symptoms, but they begin years before the onset of symptoms

NeurofibrillaryTangles

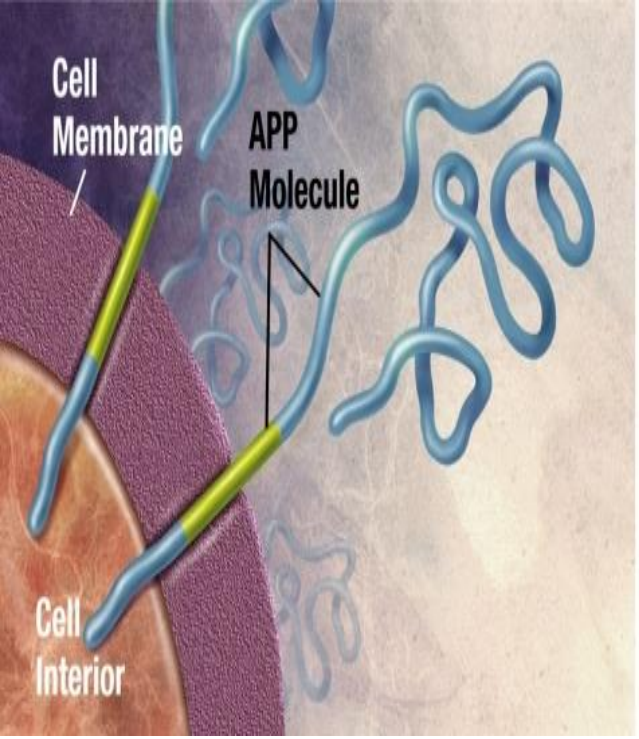
Immunocytochemical staining of neurofibrillary tangles in the isocortex of the brain of a human with AD (anti-tau antibody)

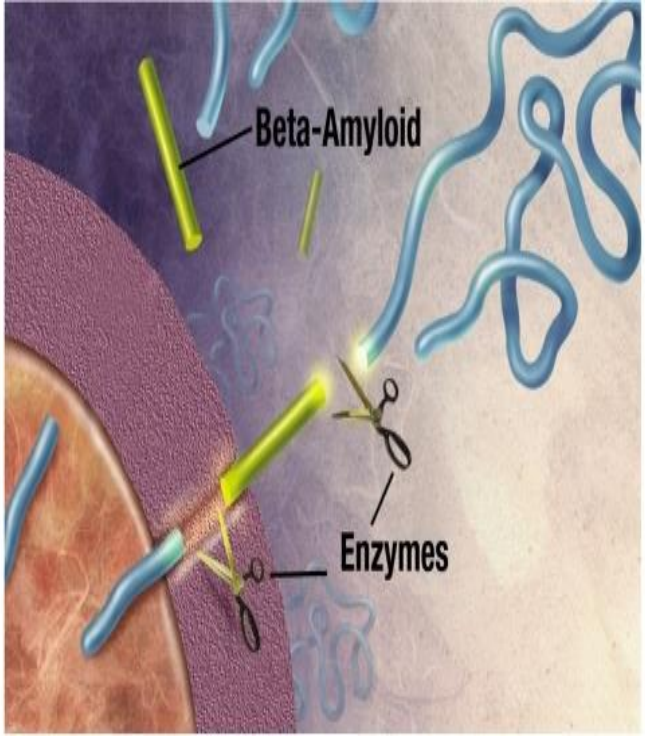


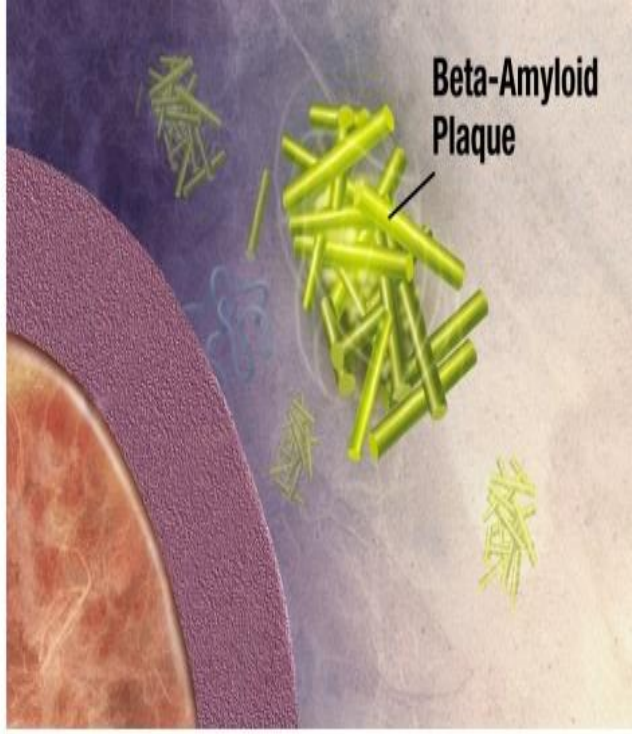


AD

- Alzheimer's disease is characterised by **loss of neurons** and **synapses** in the **cerebral cortex** and certain subcortical regions. This loss results in gross **atrophy** of the affected regions, including degeneration in the **temporal lobe** and **parietal lobe**, and parts of the **frontal cortex** and **cingulate gyrus**.
- Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD.
- ***Plaques*** are dense, mostly insoluble deposits of amyloid – beta peptides and cellular material outside and around neurons.
- **Tangles** (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves.
- Although many older individuals develop some plaques and tangles as a consequence of ageing, the ***brains of AD patients have a greater number of them in specific brain regions such as the temporal lobe***.





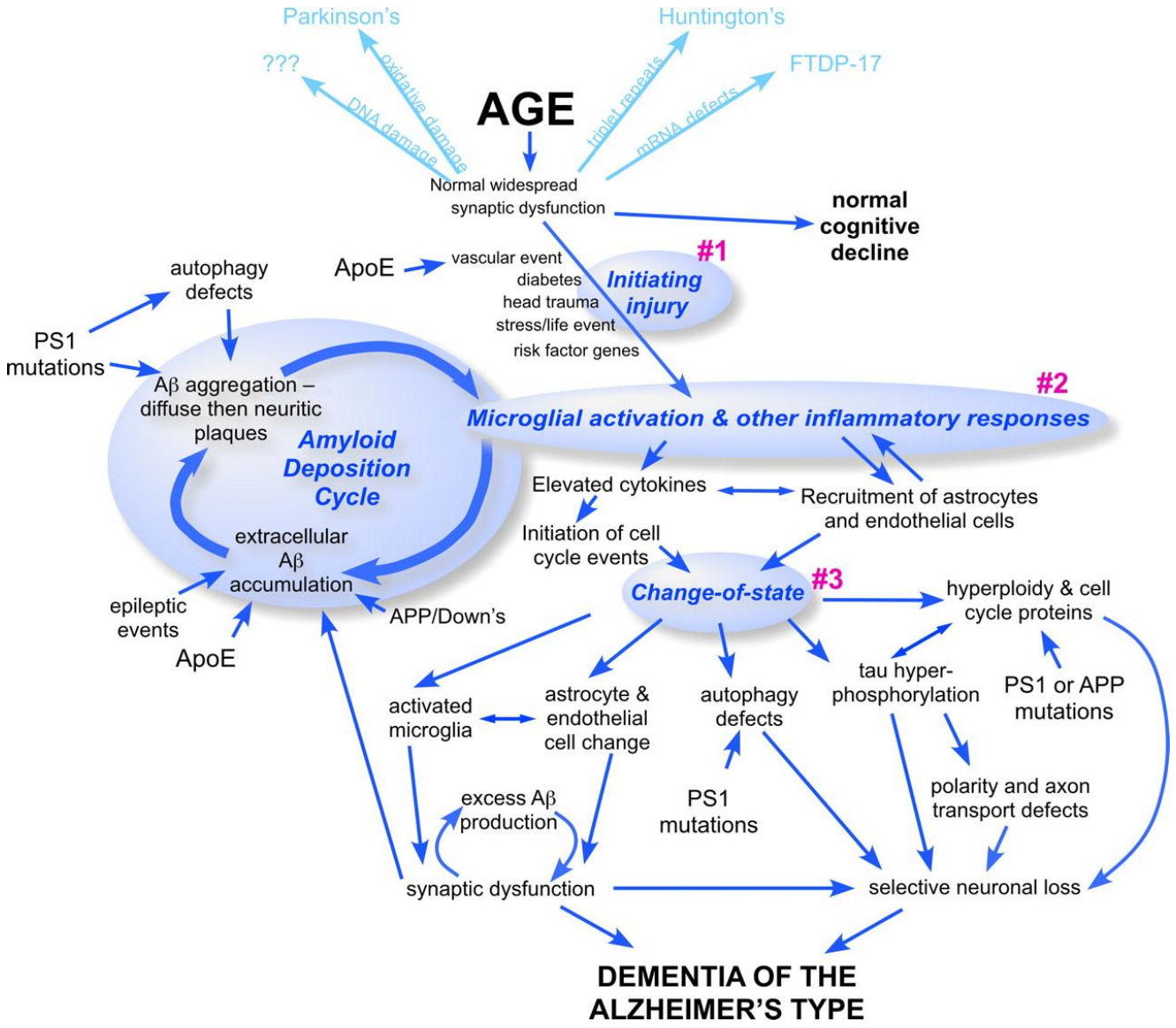


Enzymes act on the APP (amyloid precursor protein) and cut it into fragments. The beta-amyloid fragment is crucial in the formation of senile plaques in AD.

Cholinergic Hypothesis

- Acetylcholine (ACh) is an important neurotransmitter in areas of the brain involved in memory formation
- Loss of AChactivity correlates with the severity of AD

Inflammation Hypothesis



Reference

Xiaoguang Du, Xinyi Wang, and Meiyu Geng

- Alzheimer's disease hypothesis and related therapies

Transl Neurodegener. 2018; 7: 2.

ASSESSMENT: LABORATORY

Laboratory tests should include:

- **Complete blood cell count**
- **Blood chemistries**
- **Liver function tests**

>Serologic tests for:

Syphilis, TSH, Vitamin B12level

ASSESSMENT: BRAIN IMAGING

Use imaging when:

- Onset occurs at age < 65 years
- Symptoms have occurred for < 2 years
- Neurologic signs are asymmetric
- Clinical picture suggests normal-pressure hydrocephalus

Consider:

- Noncontrast computed topography head scan
- **Magnetic resonance imaging**
- Positron emission tomography

TREATMENT & MANAGEMENT

- **Primary goals: to enhance quality of life & maximize functional performance by improving cognition, mood, and behavior**

–Nonpharmacologic

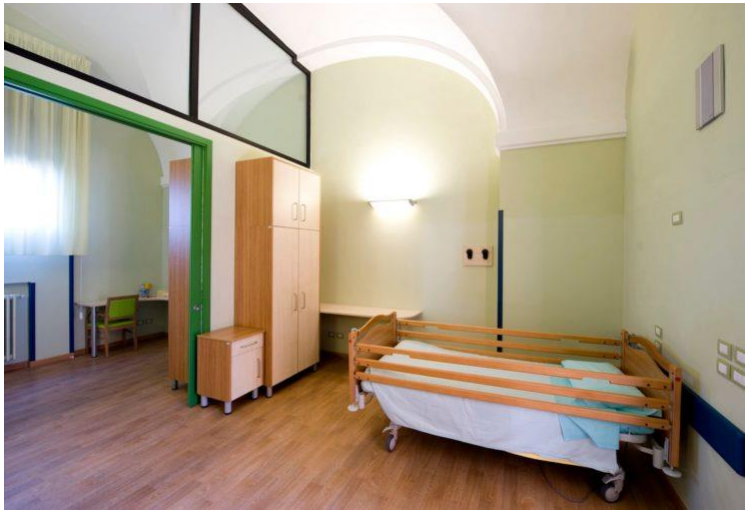
–Pharmacologic

–Specific symptom management

–Resources

NONPHARMACOLOGIC

- Cognitive enhancement
- Individual and group therapy
- Regular appointments
- Communication with family, caregivers
- Environmental modification
- Attention to safety



PHARMACOLOGIC

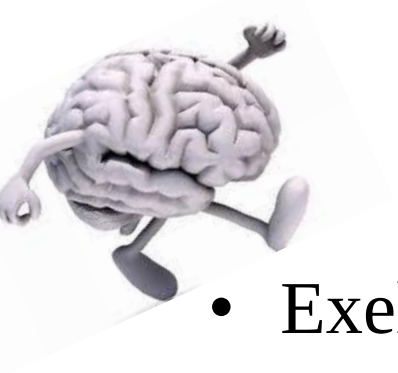
- Cholinesterase inhibitors: donepezil, rivastigmine, galantamine
- Other cognitive enhancers: estrogen, NSAIDs, ginkgo biloba, vitamin E
- Antidepressants
- Antipsychotics

Mild/Moderate AD:

Cholinesterase inhibitors increase the levels of acetylcholine in the brain, which plays a key role in memory and learning. This kind of drug postpones the worsening of symptoms for 6 to 12 months in about half of the people who take it. Cholinesterase inhibitors most commonly prescribed for mild to moderate Alzheimer's disease include Aricept (donezepil HCL), Exelon (rivastigmine), and Razadyne (galantamine).

Exelon (Rivastigmine)

- Exelon is FDA approved for mild and moderate stages of the disease; it is also approved for the treatment of mild to moderate dementia due to Parkinson's disease.
- Exelon is available as a capsule, liquid, and patch.



- Exelon is a cholinesterase inhibitor that prevents the breakdown of acetylcholine and butyrylcholine in the brain by blocking the activity of two different enzymes. Acetylcholine and butyrylcholine play a key role in memory and learning.

- When given orally, bioavailability is about 40% in the 3 mg dose. The compound can cross the blood-brain barrier.

Aricept (Donepizel)

- One of the most widely used drugs to treat the symptoms of Alzheimer's disease. Aricept is FDA-approved for mild, moderate, and severe stages of the disease.
- Aricept is available in tablet form or an orally disintegrating tablet form, and is commonly **started at 5 mg** a day.
- Can cross the blood-brain barrier.

Moderate/Severe AD:

Ebixa(memantine) regulates glutamate in the brain, which plays a key role in processing information. This drug is used to treat moderate to severe Alzheimer's disease and may delay the worsening of symptoms in some people. It may allow patients to maintain certain daily functions a little longer than they would without the medication.

Drugs in AD

- **Aricept**
  Donepezil

  Used to delay or slow the symptoms of AD
  • Loses its effect over time
  • Used for mild, moderate and severe AD
  • Does not prevent or cure AD

- **Citalopram**

  Used to reduce depression and anxiety
  • May take 4 to 6 weeks to work
  • Sometimes used to help people get to sleep

- **Depakin**
  Sodium Valproate

  Used to treat severe aggression
  • Also used to treat depression and anxiety

- **Exelon**
  Rivastigmine

  Used to delay or slow the symptoms of AD
  • Loses its effect over time
  • Used for mild to moderate AD
  • Can get in pill form or as a skin patch
  • Does not prevent or cure AD

Ebixa Memantine	**Used to delay or slow the symptoms of AD** • Loses its effect over time • Used for moderate to severe AD • Sometimes given with Aricept®, Exelon® • Does not prevent or cure AD
Reminyl Galantamine	**Used to prevent or slow the symptoms of AD** • Loses its effect over time • Used for mild to moderate AD • Can get in pill form or as a skin patch • Does not prevent or cure AD
Zoloft Sertraline	**Used to reduce depression and anxiety** • May take 4 to 6 weeks to work • Sometimes used to help people get to sleep
Trileptal Oxcarbazepine	**Used to treat severe aggression** • Also used to treat depression and anxiety
Tegretol Carbamazepine	**Used to treat severe aggression** • Also used to treat depression and anxiety
Remeron Mirtazepine	**Used to reduce depression and anxiety** • May take 4 to 6 weeks to work • Sometimes used to help people get to sleep

Future Trends

- Alzheimer's as a multifactorial syndrome
- Pendulum of history
- Vaccine
- Genetic therapy

D DRUGS

E EMOTIONAL

M METABOLIC

E EYES & EARS

N NUTRITIONAL

T TUMOR-TOSSIC-TRAUMA

I INFECTIONS

A ATHEROSCLEROSIS

Table 1 Comparison of Alzheimer's disease and the frontal/subcortical dementias

Alzheimer's disease	Frontal/subcortical dementia
▶ Affects mainly parietal and temporal cortex	▶ Affects prefrontal cortex, white matter, basal ganglia, thalamus
▶ Recent memory severely affected	▶ Recent memory often normal or only mildly impaired
▶ Aphasia, apraxia, agnosia common	▶ Executive dysfunction common
▶ Various behavioral problems common	▶ Loss of drive, disinhibition common
▶ MMSE accurately reflects severity	▶ MMSE useless, often near-normal

MMSE = Mini Mental State Exam.

Source Created for Geriatrics by JT Stewart, MD.

Vascular Dementia

-Generally clinicians look for

Stepwise progression, prolonged plateaus or fluctuating course

Focal cognitive deficits **but not necessarily memory impairment**

Impaired executive function (difficulty problem solving, difficulty with judgement)

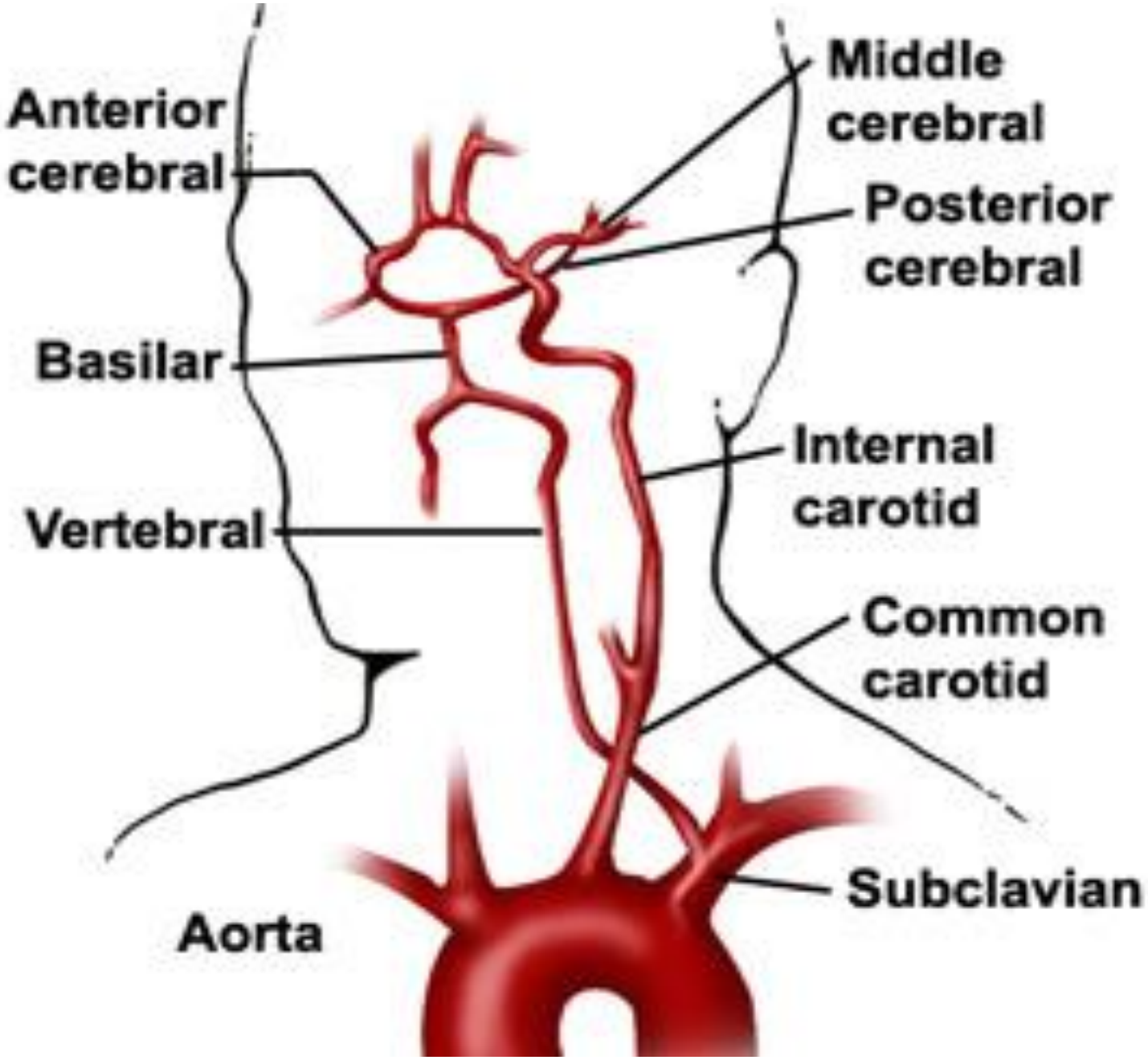
-Diagnosis strengthened by

Focal neurological signs (weakness on one side, difficulty with speech)

Neuroimaging (CT or MRI) consistent with ischemia

CV risk factors, concurrent peripheral vascular disease, coronary artery disease etc

Large Vessel Vascular Dementia
Small Vessel Vascular Dementia
Ischemic-Hypoxic Vascular Dementia
Hemorrhagic dementia


Anterior cerebral
Middle cerebral
Posterior cerebral
Basilar
Internal carotid
Vertebral
Common carotid
Subclavian
Aorta

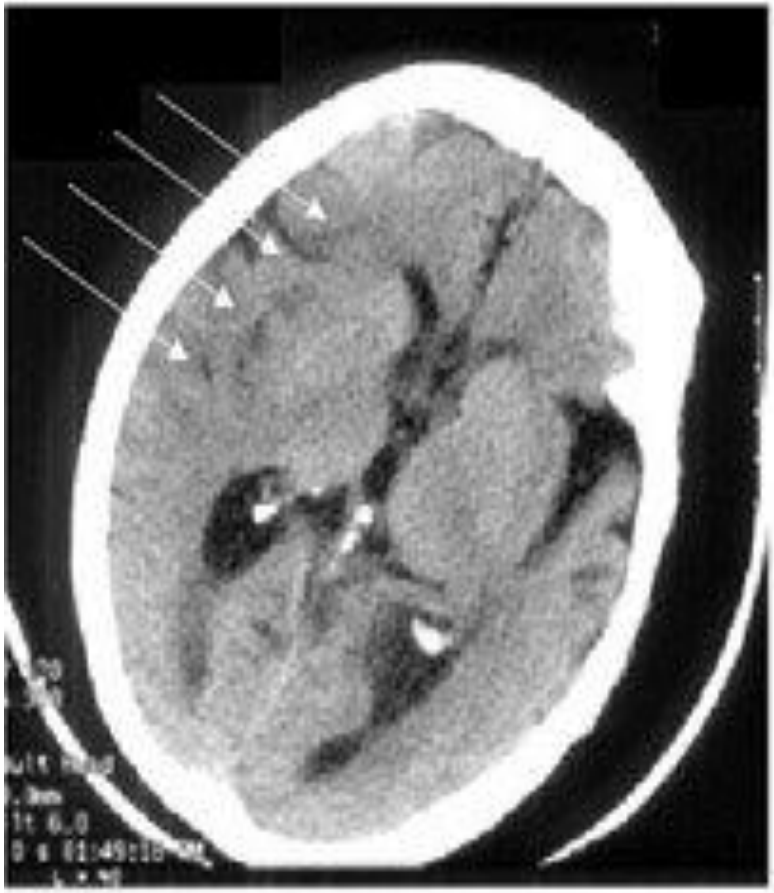
EPIDEMIOLOGY

-Incidence estimates (3 months post CVA) vary: 25-41%

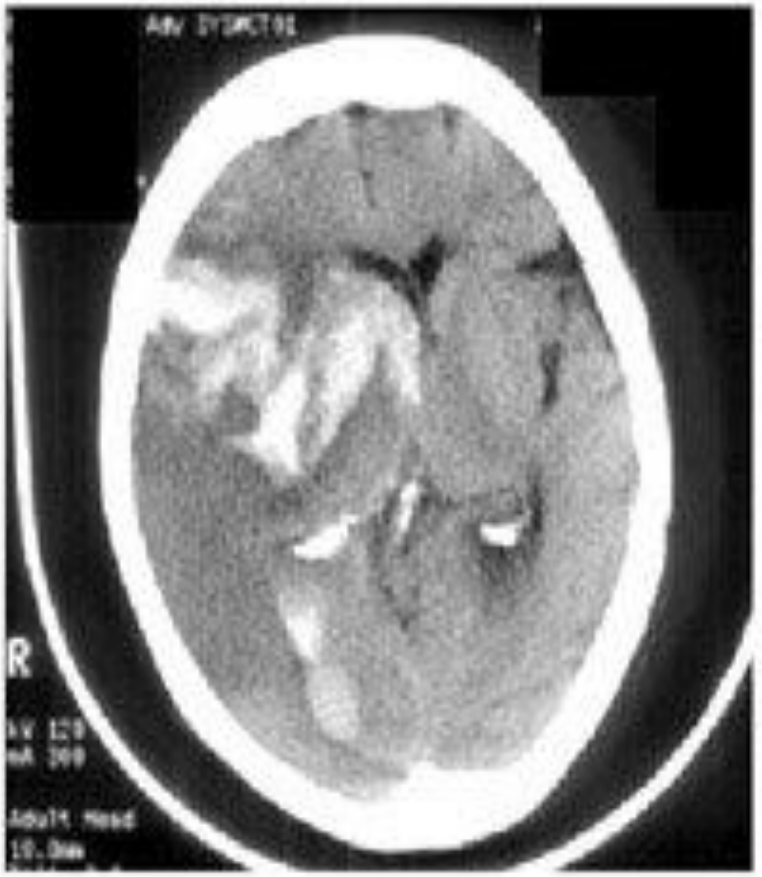
-Clinical features will depend largely on what part of the brain was damaged

-Depression common

-Location of vascular lesion is likely more important than how much tissue died

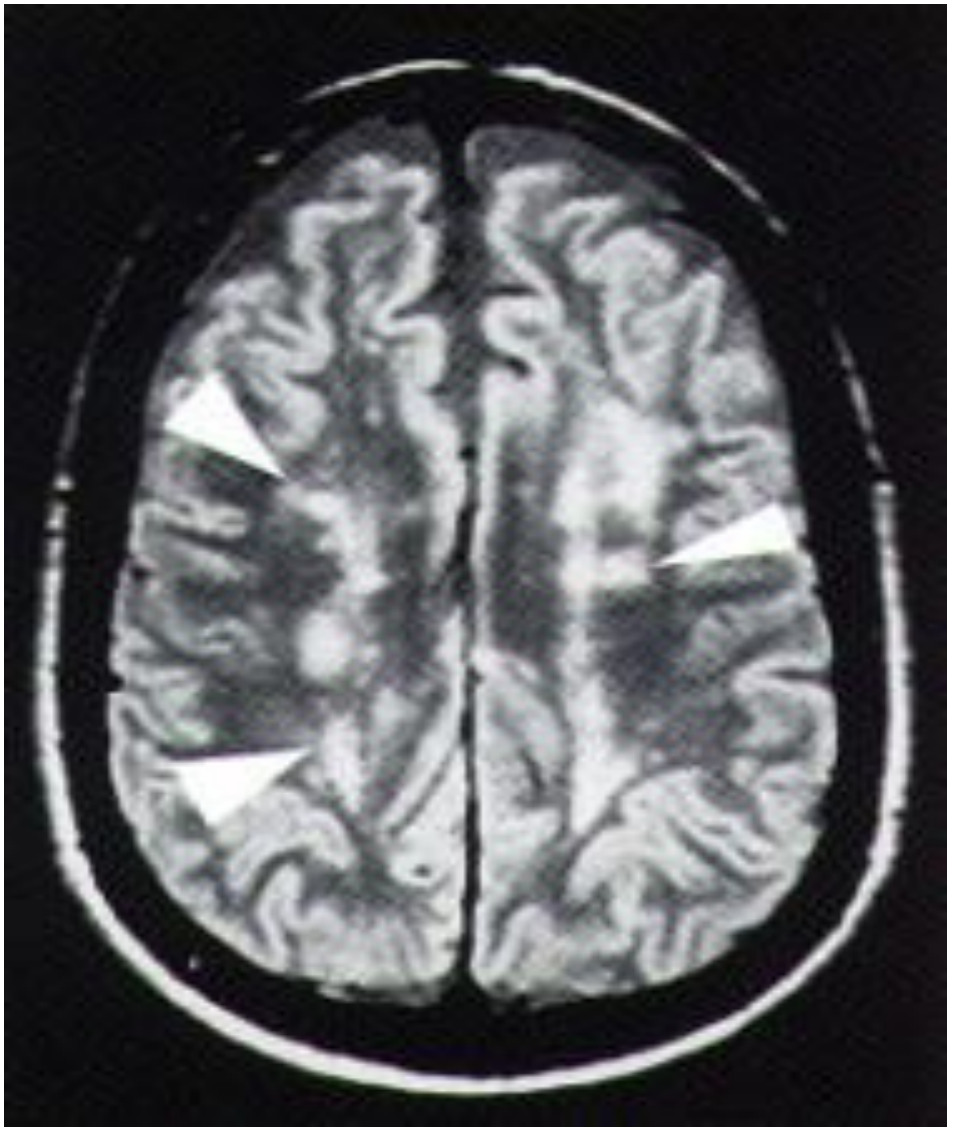


Six hours
subtle R MCA infarct



24 hours - the infarct has undergone extensive haemorrhagic transformation after thrombolysis

Magnetic resonance image of the brain, T2 axial view without contrast enhancement. Note the areas of increased signal bilaterally, known as periventricular hyperintensity (arrows).



Mixed Dementia

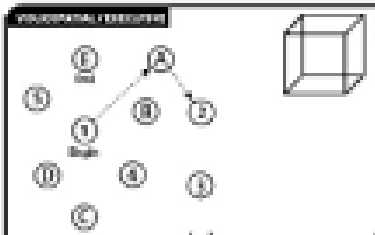
- Vascular lesions may have synergistic effect with AD pathology
- If evidence of cerebrovascular disease present, the density of plaques and tangles needed to cause dementia is lower than that needed for “pure AD”

Diagnosis

- MMSE not adequate because of lack sensitivity in VCI, as it isn't a sensitive test for executive function, inattention, mood or personality changes
- Montreal Cognitive Assessment (MoCA)
  - Increasingly popular
  - Designed for vascular dementia
  - http://mocatest.org/

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSPATIAL/EXECUTIVE



Copy cube

Draw CLOCK. (Ten past eleven)

NAMING

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if normal on trial 1.

	FACE	VELVET	CHURCH	DAISY	RED
no. of trials required					

ATTENTION

Read list of digits (1 digit/sec).

Subject has to repeat them in the forward order

Subject has to repeat them in the backward order

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

Serial subtraction starting at 100

LANGUAGE

Repeat: I only know that John is the one to help today.

The cat always hid under the couch when dogs were in the room.

Verbal fluency / Name maximum number of words in one minute that begin with the letter F

ABSTRACTION

DELAYED RECALL

	FACE	VELVET	CHURCH	DAISY	RED
no cue required					
Optional: category cue					
Optional: multiple choice cue					

ORIENTATION

TOTAL /30

Add 1 point if ≤ 12 yrs edu

Treatment

- Primary prevention:
  - Treatment of HTN, DM, hypercholestrolemia
- Secondary prevention:
  - More aggressive control of HTN, DM and hypercholestrolemia
  - Anti-platelet agents like Aspirin and Plavix
  - Warfarin/NOAC in patients with Atrial fibrillation
  - Possible surgery in patients with documented carotid artery stenosis

Secondary prevention

- STOP SMOKING!!!
- Avoid orthostatic hypotension
- Good control of congestive heart failure and obstructive sleep apnea

Pharmacological treatment

- **Acetyl cholinesterase inhibitors (AChEI)** – may have mild - moderate benefit, patients with VaD are more likely to experience side effects with AChEI than AD patients and so may be more likely to discontinue the drug

- **Memantine** – may be useful as an adjunct to AChEI in patients with moderate to severe dementia, not covered by Pharmacare

- **Anti depressants** (specifically SSRIs)

- **Atypical antipsychotics**

Lewy Body disease

Eosinophilic inclusions in Cortex, Ippocampus e Basal nuclei

- ✓Cognitive disorders: fluctuating state of consciousness
- ✓ HALLUCINATIONS: visual ones
- ✓ extrapyramidal signs (Parkinsonism)
- ✓ urinary incontinence
- ✓ Falls
- ✓ Syncope-like episodes

Pathology

- Degeneration of substantia nigra
- Degeneration of the cortical areas of the brain with many or all of the features seen in Alzheimer's disease
- Remaining nerve cells contain abnormal structures called ‘Lewy bodies’

Body Lewi

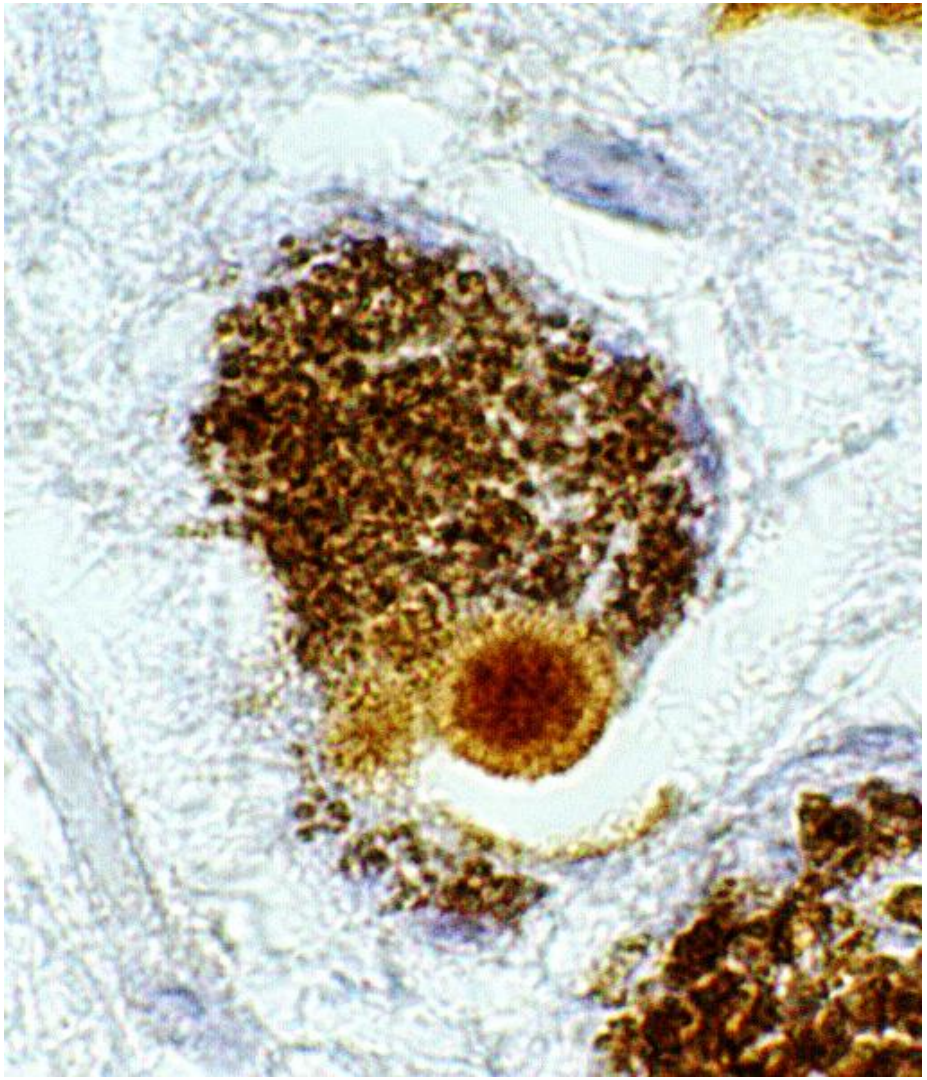
Abnormal aggregation of proteins, including

- alpha-synuclein, neurofilament and ubiquitin
- PD
- Dementia with Lewy bodies
- MSA
- Amyotrophic lateral sclerosis
- Hallervorden-Spatz syndrome

Synucleopathies

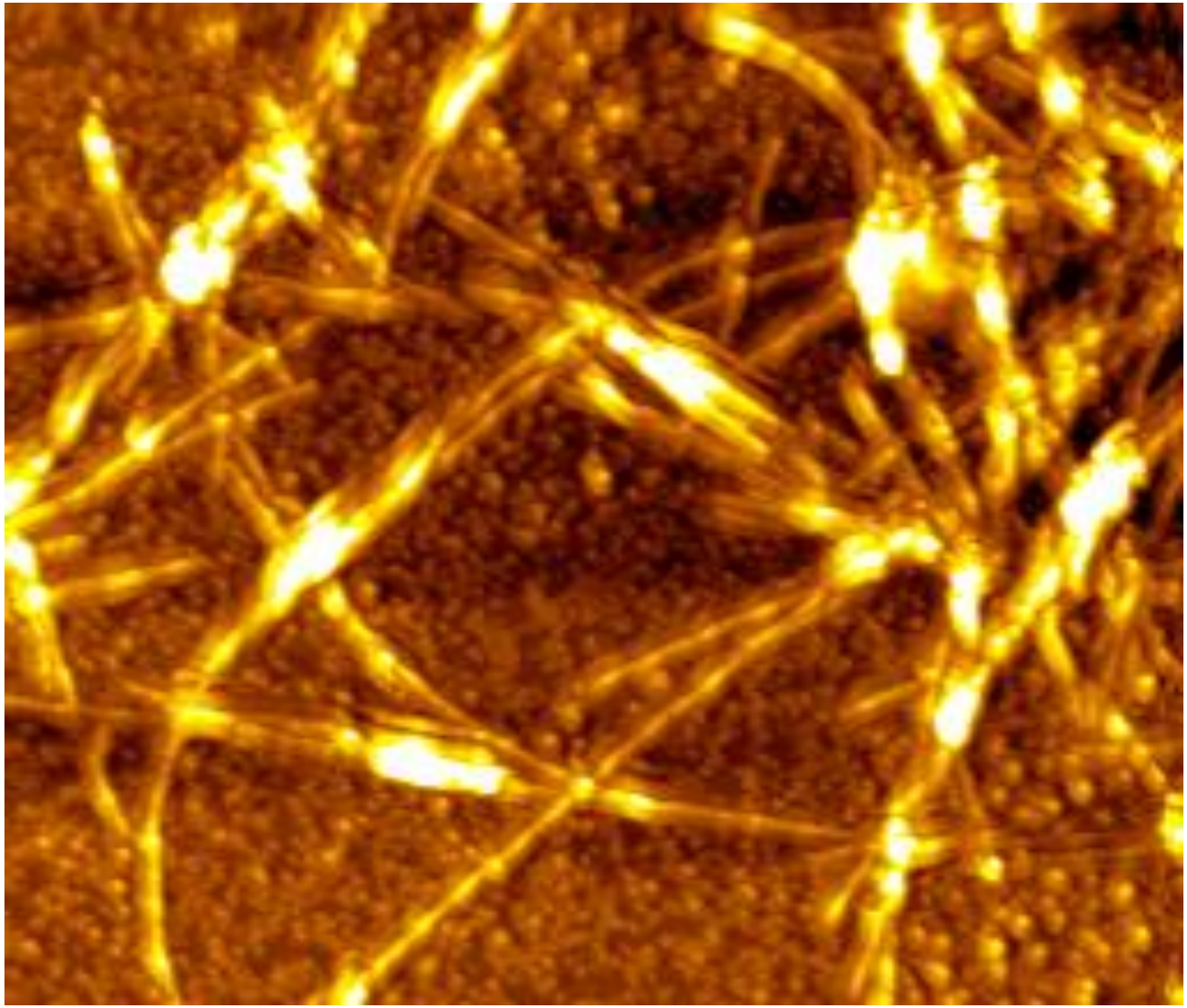
Core, body, halo

Variations in shape



Alpha sinuclein

- Abundant CNS protein
- Composed of 140 amino acids
- Alpha form of synuclein is the only form capable of aggregating into fibrillar structures in vitro
- Beta-synuclein is not localized in Lewy bodies, it may have a role in regulating alpha-synuclein metabolism or aggregation



Role of alpha sinuclein

- Synaptic plasticity
- Negative regulation of dopamine neurotransmission
- Protection at nerve terminals during injury
- Trafficking of cargo in the ER/Golgi complex

In disease

- ‘Ubiquitinated’ with no loss of proteasome function, suggesting there is an excessive accumulation of alpha-synuclein that overwhelms the proteolytic machinery (Tofaris, et al. 2003). This may promote the formation of Lewy bodies

Clinical features

- Dementia normally presenting feature
- Minority present with parkinsonism
- Some with psychiatric disorder without dementia
- Others with orthostatic hypotension, falls or transient disturbances of consciousness
- Sporadic (rarely familial)
- Fluctuation in cognitive performance and functional ability
- Variations in attention and level of consciousness
- Visual hallucinations in two-thirds

TREATMENT

- No cure
- Cognitive symptoms → acetylcholinesterase inhibitors, such as donepezil and rivastigmine
  - May reduce psychiatric and motor symptoms
- Rigidity → levodopa

Frontotemporal dementia

- Definition: clinicopathologic condition consisting of deterioration of personality and cognition assoc. with prominent frontal and temporal lobe atrophy
- Accounts for up to 3-20% of dementias
  - Third behind AD and Lewy Body Dementia in neurodegenerative dementing illnesses

Epidemiology

Mean age of onset 52.8

Male preponderance 14:3 in one study and M=F in others

Dementia prevalence of 81 per 100,000 (95% CI, 62.8 to 104.5) in the 45-64 year age group

Prevalence of AD and FTD in 45-64 age group same at 15 per 100,000 (8.4-27.0)

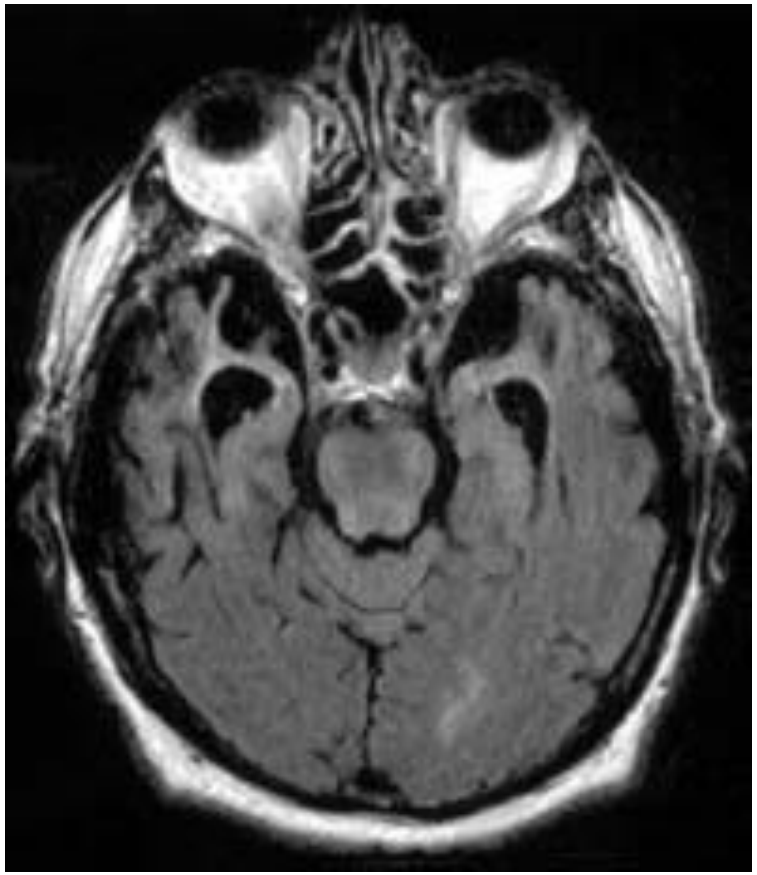
Core features

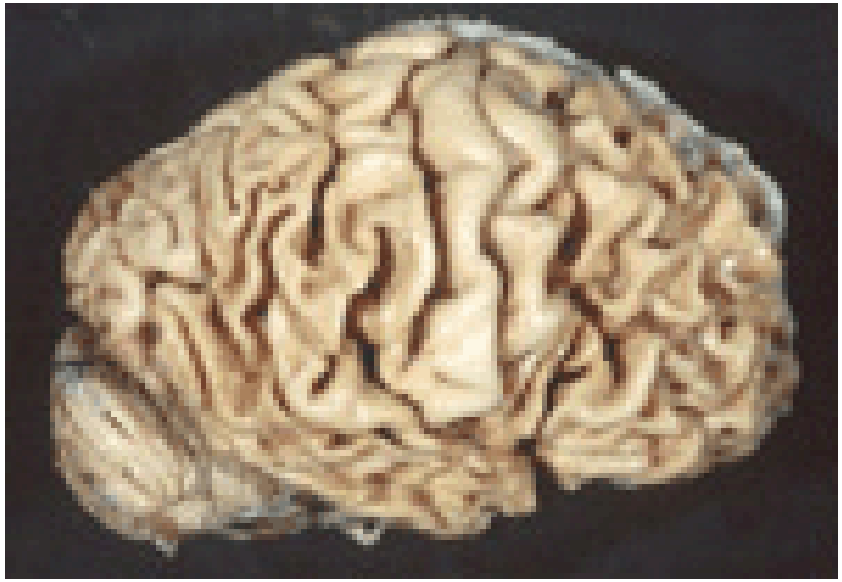
Insidious onset and slow progression

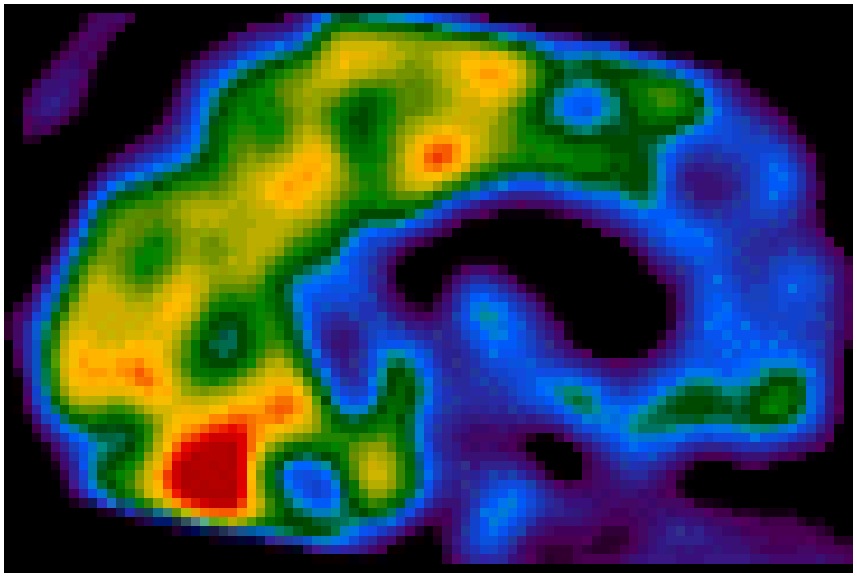
Early decline of
- -Social interpersonal conduct
- -Regulation of personal conduct
- -Insight

Early emotional blunting

MRI







- Prominent frontal and temporal lobar atrophy
- Atrophy may be associated with Pick's bodies, tauopathy, nonspecific superficial cortical neuron loss

Differential diagnosis

- Differs from the other codes including AD, frontal dementia, Pick's disease
  - Use of these codes inappropriate as not capture the age of onset, duration of illness, genetic factors, and impact on caregiver, society, and economics
- AD → older, different duration, less clear genetics
- Frontal dementia → no temporal lobe involvement, genetics differ
- Pick's disease → not capture spectrum of FTD

- Implications for FTD different from other dementias/AD:
  - Greater caregiver burden and increased dependency and health care costs
  - Patients see codes and think they have some other disease

Treatments

No FDA- approved tx

- Neurochemical basis for FTD is unknown
- Abnormalities in serotonin and dopamine

– not cholinergic

- SSRI's

– disinhibition; impulsivity; repetitive behavior; eating disorders; sexual disinhibition

- Trazodone

– agitation; aggression; depression; eating disorder

Treatments

Atypical antipsychotics (olanzapine, quetiapine, aripiprazole)

– agitation

– particularly vulnerable to EPS; use as last resort

– quetiapine with less D2 antagonism

• Stimulants (Methylphenidate,dextroamphetamine)

– apathy; disinhibition

– may cause delirium


"That's all Folks!"
Isberg©