

Encephalopathy Delirium Dementia

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ENCEPHALOPATHY

- Delirium
- Dementia

ENCEPHALOPATHY

- Delirium
 - reversible
 - the structure is OK
- Dementia
 - irreversible
 - brain damage

ENCEPHALOPATHY

- Delirium
 - reversible
 - the structure is OK
- Dementia
 - irreversible
 - brain damage
- Radio analogy
 - delirium is like a weak battery
 - dementia is like frayed wires

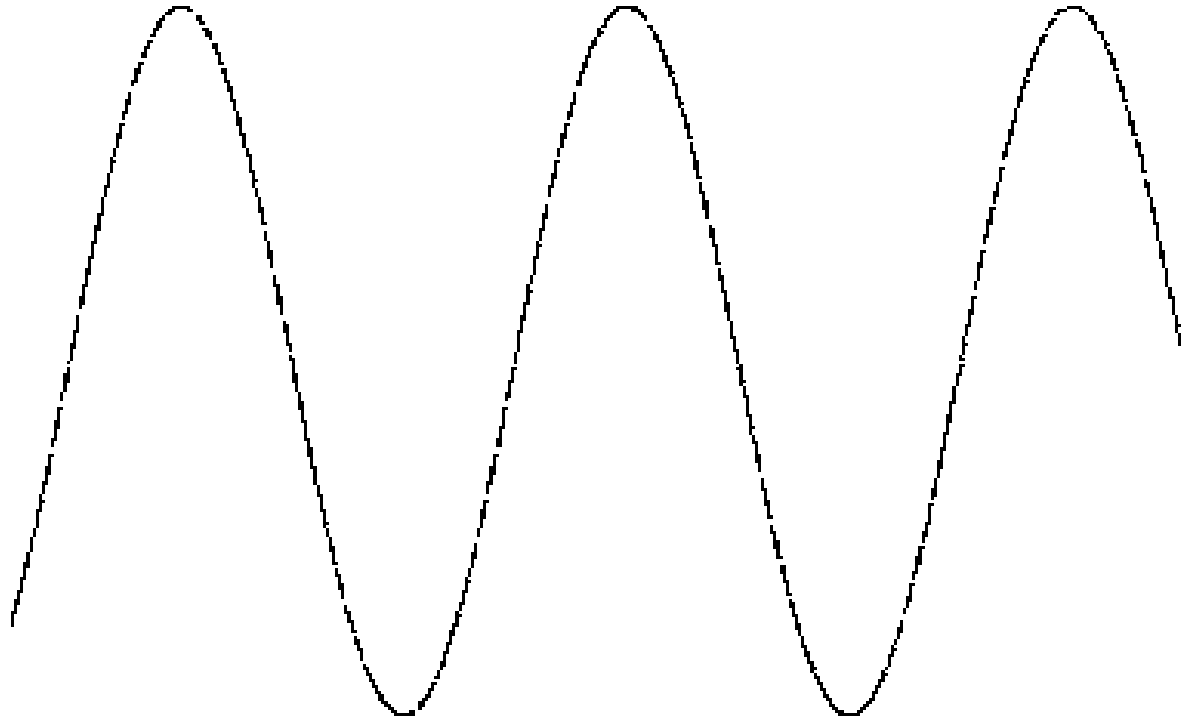
DIAGNOSTIC CRITERIA FOR DELIRIUM

1. **Disturbance of consciousness** with reduced ability to focus, sustain, or shift **attention**.
2. A change in cognition or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving condition.
3. The disturbance develops over a **short period of time** and tends to **fluctuate** during the course of a day.
4. Evidence from the history, physical examination, or laboratory findings indicate that the disturbance is caused by direct physiological consequences of a **general medical condition**.

DELIRIUM

- Confusion
- Altered level of consciousness
- Prominent inattention
- Acute (or subacute) onset
- Fluctuation
- Usually non-focal neurological exam
- Usually caused by a medical condition

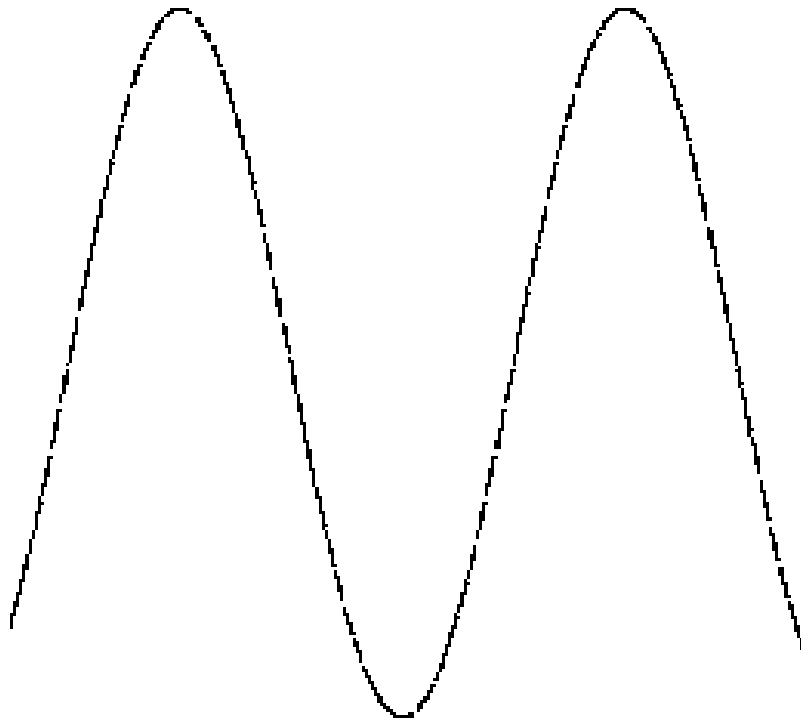
DELIRIUM IS MARKED BY FLUCTUATION



FLUCTUATION

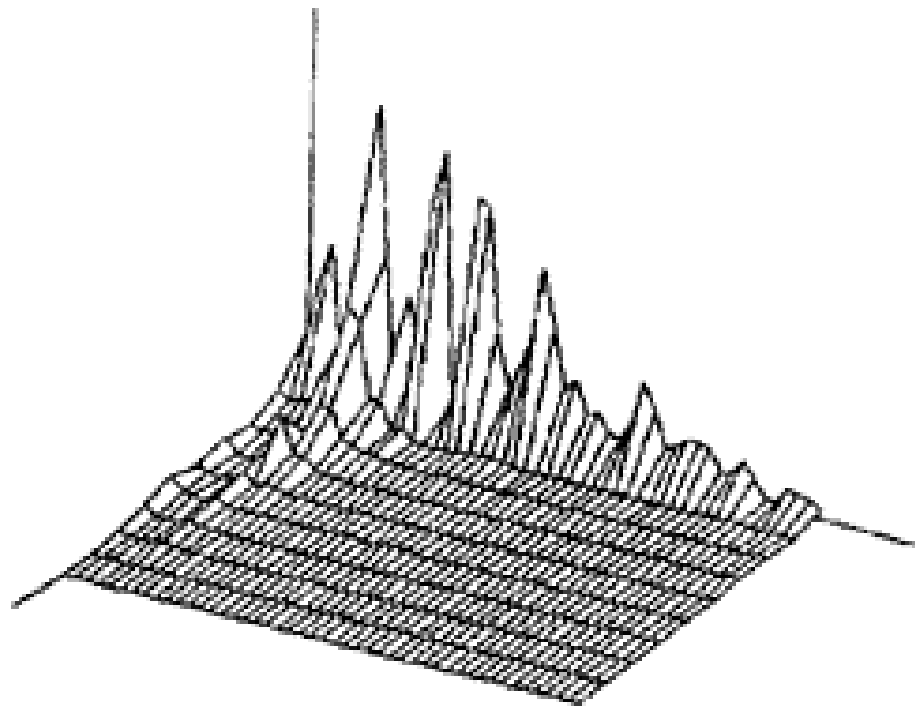
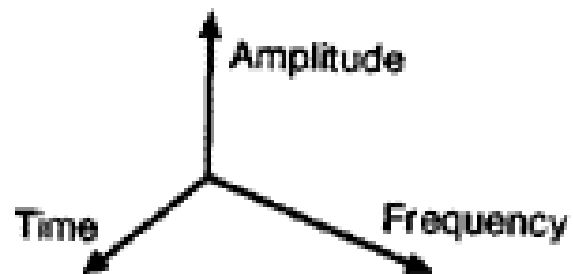


FLUCTUATION



- Alertness
- Attention
- Memory
- Language
- Visuospatial orientation
- Executive function
- Personality

FLUCTUATION



CAUSES OF DELIRIUM

- Delirium is usually caused by a medical condition.
 - Metabolic derangement
 - Drugs
 - Other

CAUSES OF DELIRIUM

- Metabolic derangement
 - Decompensation of chronic disease
 - Inadequate treatment of chronic disease
 - New problem

CAUSES OF DELIRIUM

- Drugs
 - Drugs by prescription
 - Maintenance
 - PRN
 - “Recreational” drugs, including alcohol
 - Drug withdrawal
 - OTC drugs

CAUSES OF DELIRIUM

- Drugs well-known to cause delirium
 - (The “anti-” drugs)
 - Anti-pain (narcotics)
 - Anticholinergics
 - Antibiotics (especially quinolones)
 - Anti-no sleep (sedatives)
 - Anti-anxiety
 - Anti-Parkinson

Drugs Commonly Causing Delirium or Confusional States

Analgesics

Opioids (especially meperidine)
Nonsteroidal antiinflammatory agents

Antibiotics

Acyclovir
Amphotericin B
Cephalosporins
Chloroquine
Cycloserine
Isoniazid
Mefloquine
Nalidixic acid
Penicillin
Piperazine
Quinolones
Rifampin
Streptomycin
Sulfonamides
Tobramycin

Anticholinergics

Atropine
Benztropine
Trihexyphenidyl
Scopolamine

Anticonvulsants

Carbamazepine
Phenytoin
Valproate
Vigabatrin

Antidepressants

Selective serotonin reuptake inhibitors
Tricyclic antidepressants

Cardiovascular drugs

Amiodarone
Beta blockers
Digoxin
Disopyramide
Diuretics

Corticosteroids

Dopamine agonists

Amantadine
Bromocriptine
Levodopa
Pergolide
Pramipexole
Ropinirole

Histamine 2 receptor antagonists

Cimetidine
Famotidine
Ranitidine

Miscellaneous

Baclofen
Disulfiram
Donepezil
Interferons
Interleukin-2
Nitrous oxide
Oral hypoglycemics

Sedatives/Hypnotics

Barbiturates
Benzodiazepines
Clozapine
Lithium
Phenothiazines

DRUGS

DELIRIUM

- Neurotransmitter imbalance
 - Acetylcholine deficiency
 - Dopamine excess
 - Either absolute or relative to each other

ACETYLCHOLINE DEFICIENCY

- Effects of anticholinergic drugs
- Effects of cholinergic drugs
- Atropine animal model
- Serum anticholinergic activity correlates with severity of the delirium.

DOPAMINE EXCESS

- Effects of dopaminergic drugs
- Effects of neuroleptic drugs

IMPORTANCE OF RECOGNIZING DELIRIUM

- **Delirium**

- Increases patient morbidity
- Increases patient mortality
- Increases staff or caregiver stress
- Increases the potential for injury
- May be the sign of progressive condition
- **May be an emergency!**

CAUSES OF DELIRIUM

- Other
 - Sleep deprivation
 - Infection
 - Injury
 - Neurological conditions
 - Etc.

NEUROLOGICAL CAUSES OF DELIRIUM

- Seizures
- Post-ictal state
- Migraine
- Meningitis
- Stroke
- Intracerebral hemorrhage
- Others

ADDITIONAL CLUES

- Visual hallucinations
- Severe agitation
- Abnormal movements

ABNORMAL MOVEMENTS

- Seizures
- Asterixis
- Myoclonus
- Significant new tremor
- Prominent new nystagmus
- Chorea
- ? Absence of movement

ADDITIONAL CLUES

- Visual hallucinations
- Severe agitation
- Abnormal movements
- Abnormal vital signs
- **Ask the family**
- **Abnormal sleep-wake cycle**

Older age
Male sex
Visual impairment
Presence of dementia
Severity of dementia
Depression
Functional dependence
Immobility
Hip fracture
Dehydration
Alcoholism
Severity of physical illness
Stroke
Metabolic abnormalities

PREDISPOSING FACTORS IN DELIRIUM

Burns, et al. JNNP 2004;75:362

Narcotics
Severe acute illness
Urinary tract infection
Hypoxaemia
Shock
Anaemia
Pain
Physical restraint
Bladder catheter use
Iatrogenic event
Cardiac surgery
Non-cardiac surgery
Intensive care unit admission
High number of hospital procedures

PRECIPITATING FACTORS IN DELIRIUM

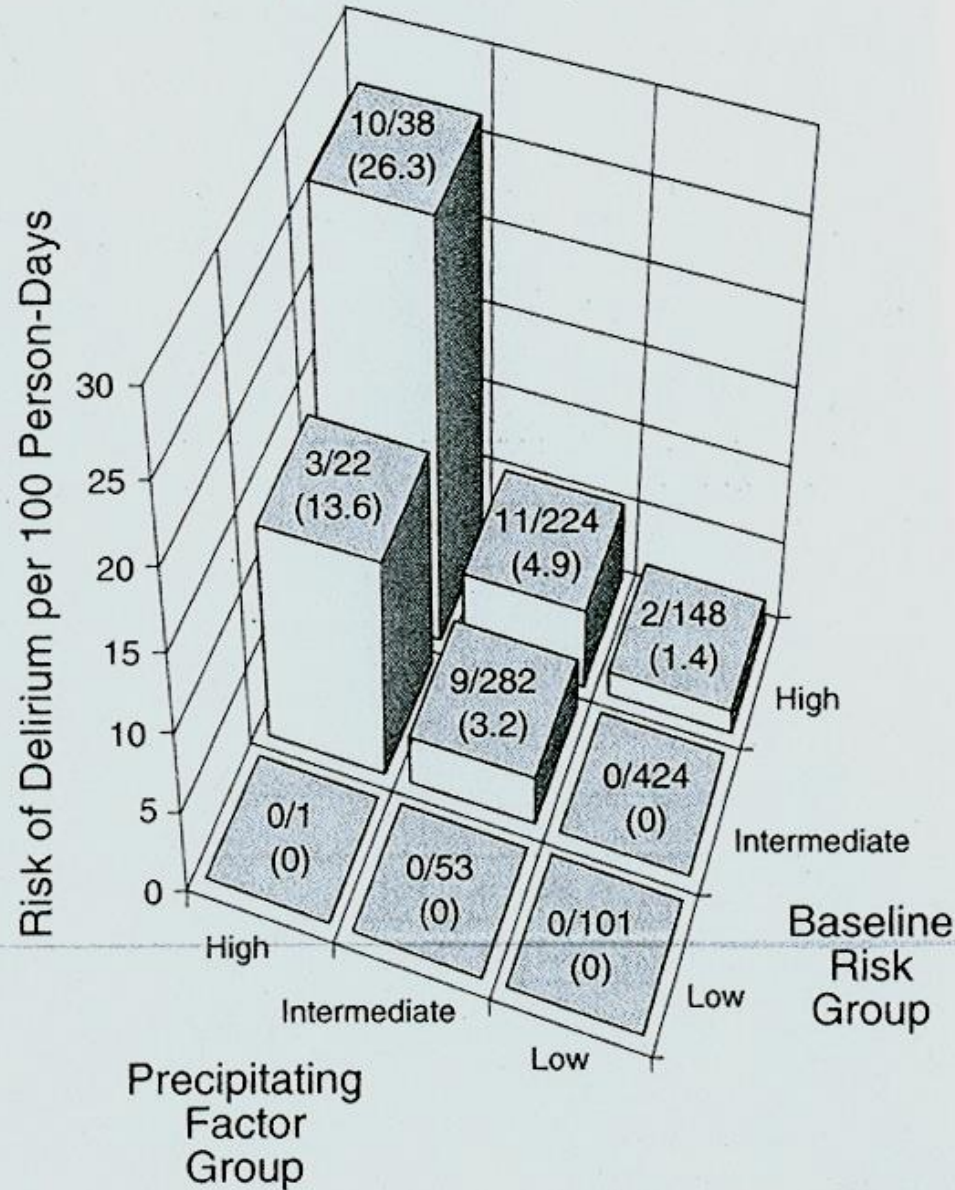
Burns, et al. JNNP
2004;75:362

HOSPITALIZATION RISK FACTORS FOR DELIRIUM

- Use of physical restraints
- Malnutrition (e.g. serum albumin level <3 g/dL)
- >3 medications added
- Use of bladder catheter
- Any iatrogenic event
 - medication toxicity
 - hospital-acquired infections
 - complications of diagnostic or therapeutic procedures
 - pulmonary embolism
 - unintentional injury, such as falls
 - etc., etc.

Weber, et al. Intern Med J 2004;34:115

Development Cohort
1293 Hospital-Days Among 196 Patients



RISK OF DEVELOPING DELIRIUM IN HOSPITALIZED PATIENTS

Inouye. JAMA
1996;275:852

DELIRIUM SUMMARY

- Confusion
- Altered level of consciousness
- Prominent inattention
- Acute (or subacute) onset
- Fluctuation
- Usually non-focal neurological exam
- Usually caused by a medical condition
- May be an emergency!

The treatment of delirium



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NONPHARMACOLOGICAL TREATMENT

- Interpersonal contact
- Environmental manipulation
- Reorientation
- Family involvement
- Sensory input (glasses, hearing aids)
- Remove restraints
- Optimize sleep hygiene

TREATMENT OF DELIRIUM

- The basics
- Prevention
- Educate the caregiver and staff.
- Nonpharmacological intervention
- **How serious is the delirium?**

HOW LIKELY IS INJURY?

- Not likely?
 - Nonpharmacological management

HOW LIKELY IS INJURY?

- Not likely?
 - Non-pharmacological management
- Possible?
 - Restraints?
 - Drugs

HOW LIKELY IS INJURY?

- Not likely?
 - Non-pharmacological management
- Possible Probable?
 - Restraints?
 - Drugs

DRUGS TO TREAT DELIRIUM

- (Withdraw those that may be causing the delirium.)
- No drugs have the FDA indication for the treatment of delirium.

ANTIPSYCHOTIC MEDICATIONS

- Tranquilize with relatively less sedation
- Potential for side effects
- Oral
 - Conventional
 - Atypical
- Parenteral
 - Conventional
 - Atypical

ORAL ANTIPSYCHOTICS

- Conventional
 - haloperidol
- Atypicals
 - quetiapine (Seroquel)
 - olanzapine (Zyprexa)
 - risperidone (Risperdal)
 - aripiprazole (Abilify)
 - ziprasidone (Geodon)

PARENTERAL ANTIPSYCHOTICS

- haloperidol
- olanzapine (Zyprexa) (IM only)
- ziprasidone (Geodon) (IM only)
- aripiprazole (Abilify) (IM only)
- (droperidol)

PHARMACOLOGICAL INTERVENTION

- Typical antipsychotics
 - “The best-established medications for delirium are the typical antipsychotics; generally, the most practical is haloperidol.”
 - haloperidol: PO, IM, IV
 - risks of EPSs and QT prolongation

Continuum: Lifelong Learning in Neurology

SIDE EFFECTS OF ANTIPSYCHOTICS

- Extrapiramidal side effects
- Akasthisia
- Neuroleptic malignant syndrome
- QTc prolongation
 - ziprasidone
 - parenteral haloperidol and droperidol
- Others

BENZODIAZEPINES

- Relatively safer than the antipsychotics

PHARMACOLOGICAL INTERVENTION

- Benzodiazepines have three roles in the management of delirium.
 - alcohol, barbiturate, or benzodiazepine withdrawal
 - adjunctive to antipsychotics (“a functional potentiation of effects”)
 - promote sleep

BENZODIAZEPINES

- Relatively safer than the antipsychotics
- Potential for side effects
- Oral and parenteral forms

PHARMACOLOGICAL INTERVENTION

- Benzodiazepines
 - lorazepam: PO, IM, IV
 - midazolam (not mentioned): IM, IV

Continuum: Lifelong Learning in Neurology

SIDE EFFECTS OF BENZODIAZEPINES

- Sedation
- Worsened delirium
- Disinhibition
- Ataxia
- Respiratory depression (if parenteral)
- Others

PHARMACOLOGICAL TREATMENT OF DELIRIUM

- Consider a neuroleptic as first line.
- Consider a hypnotic.
- Consider a cholinergic drug ???

PRECEDEX

Wikipedia

- **Dexmedetomidine** is an anxiety reducing, sedative, and pain medication. Dexmedetomidine is notable for its ability to provide sedation without risk of respiratory depression (unlike other commonly used sedatives such as propofol, fentanyl, and midazolam) and can provide cooperative or semi-arousable sedation.
- Similar to clonidine, it is an agonist of α_2 -adrenergic receptors in certain parts of the brain.

A PRECAUTION

- Delirium should be reversible and of limited duration.
- If medications are used, they should therefore be prescribed for only a short time.

INDICATIONS FOR PHARMACOLOGIC INTERVENTION IN DELIRIUM

- in order to carry out essential investigations or treatment
- to prevent patients endangering themselves or others
- to relieve distress in a highly agitated or hallucinating patient

Potter J, Clinical Medicine 2006;6:303

DELIRIOGENIC, PSYCHOTOXIC DRUGS

- All psychotropic drugs have this potential, including
 - neuroleptics
 - benzodiazepines
- Side effects
 - delirium
 - nursing home placement syndrome

Tom Ala (unpublished observations)

DEMENTIA

BASIC DEMENTIA DEFINITION

- Impairment of memory and at least one other cognitive domain
- Impairment of social or occupational functioning
- Delirium has been ruled out.
- Depression has been ruled out.
- (an acquired condition)

DSM-IV

DEMENTIA IN A YOUNGER PERSON

- Trauma
- Drug overdose
- Strokes
- Cardiac or respiratory arrest
- Multiple sclerosis
- Many others
- ~~Degenerative~~

DEMENTIA IN THE ELDERLY

- Alzheimer's disease 60-75%
- Dementia with Lewy bodies 10-25%
- Vascular dementia ~10%
- Frontotemporal dementia ~10%
- Others ~5%

THE DEGENERATIVE DEMENTIAS CAUSE LOSSES IN ALL THE COGNITIVE DOMAINS.

- Memory
- Attention
- Visuospatial organization
- Language
- Personality
- Executive ability
- (Psychomotor speed)

LATE DEMENTIA

- Unable to care for self
- Behavioral problems
- Disordered sleep
- Incontinence
- Delusions
- Agitation
- Hallucinations
- Etc.

AD

ALZHEIMER'S DISEASE

- Memory impairment
- One or more of the following
 - Aphasia
 - Apraxia
 - Agnosia
 - Disturbance in executive functioning
- (Onset usually > 65)

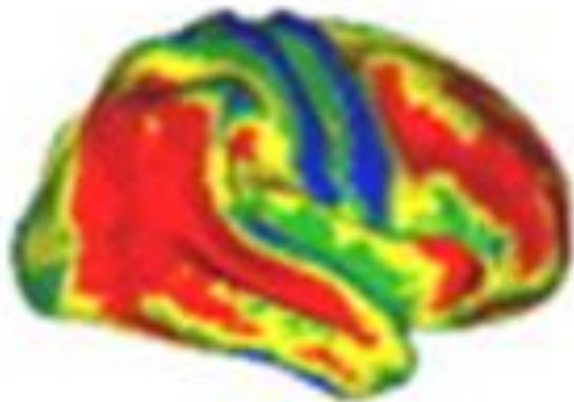
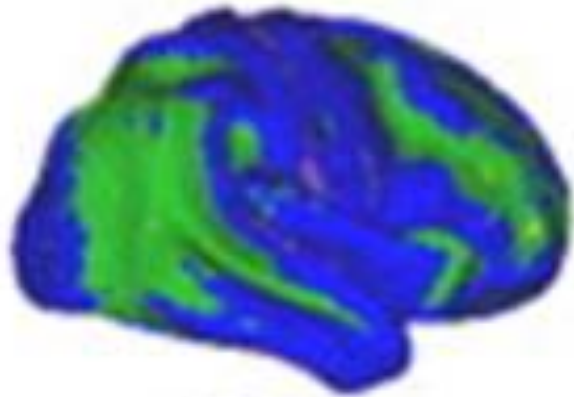
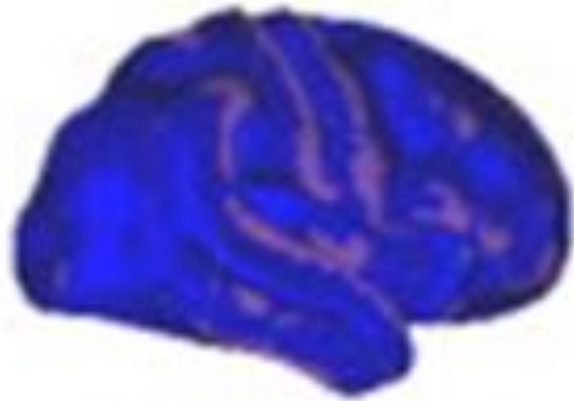
DSM-IV. 1994, p 1420

ALZHEIMER'S DISEASE

- Memory impairment
- Loss of ability to do something they were able to do in the past
- (Onset usually > 65)

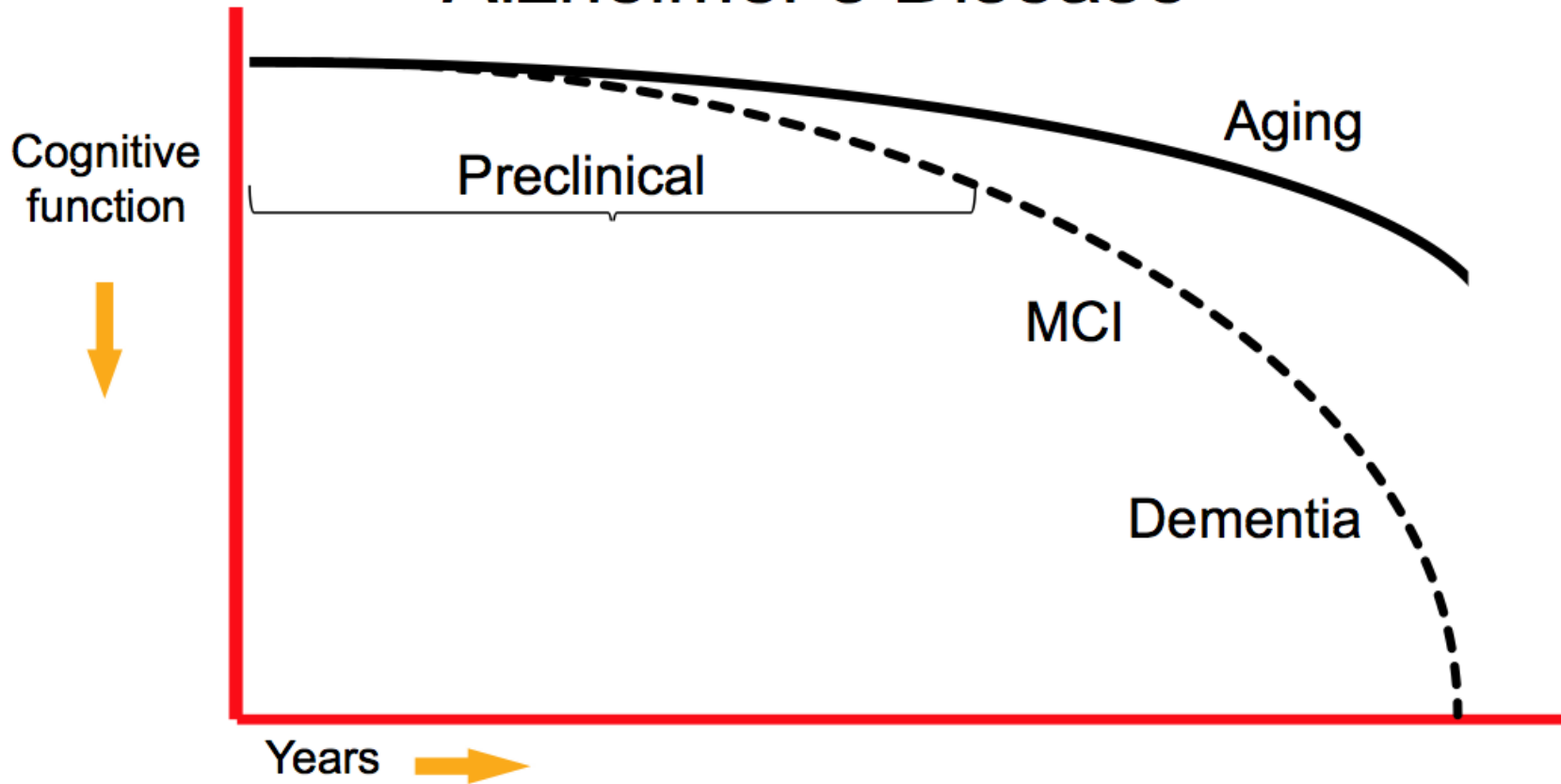
DSM-IV. 1994, p 1420

ACCUMULATION OF AMYLOID IN ALZHEIMER'S DISEASE



Vlassenko. *Biochimica Biophysica Acta*
2012;1822:370

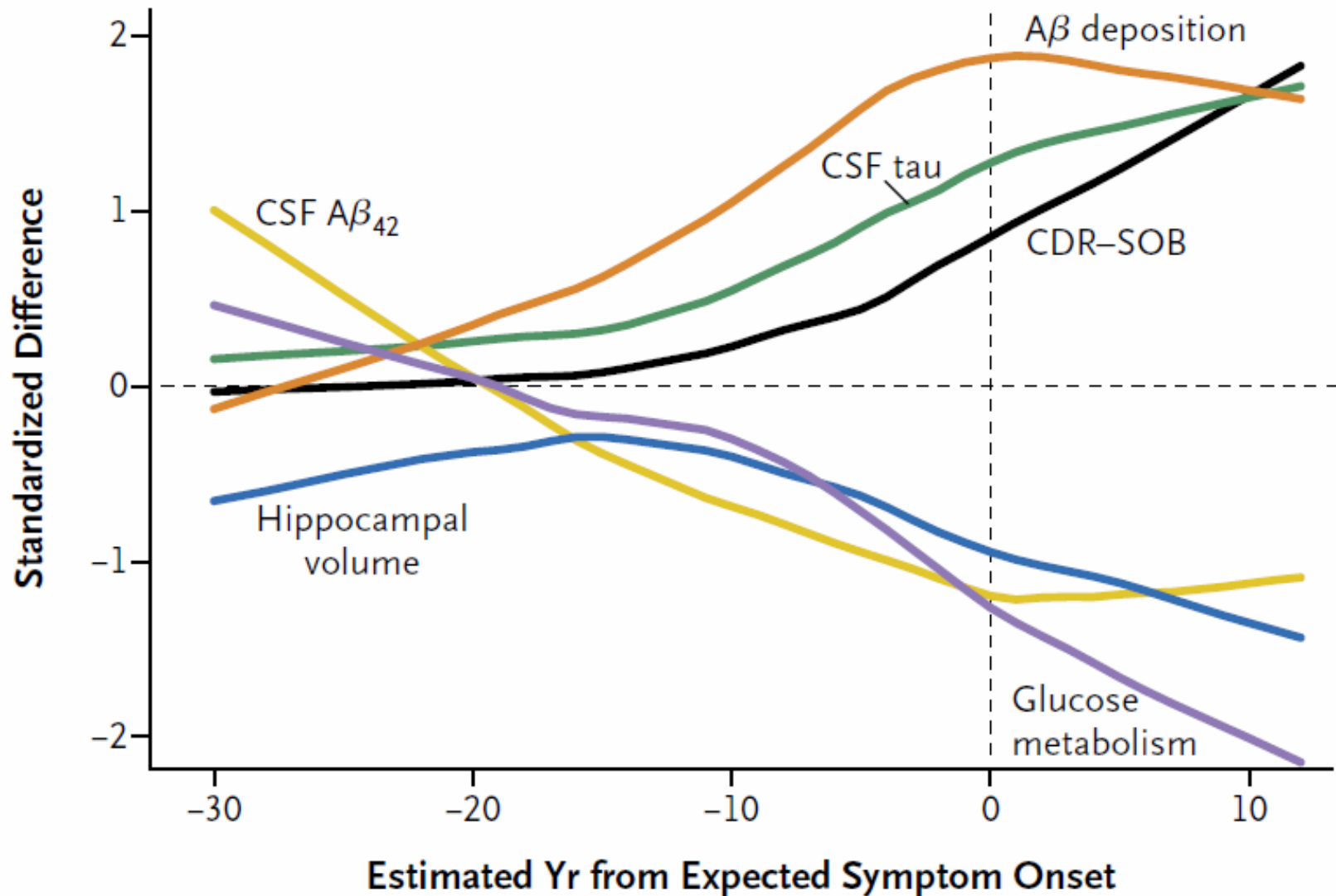
Alzheimer's Disease



Recommendations to Update Diagnostic Criteria, 2010
http://www.alz.org/research/diagnostic_criteria/

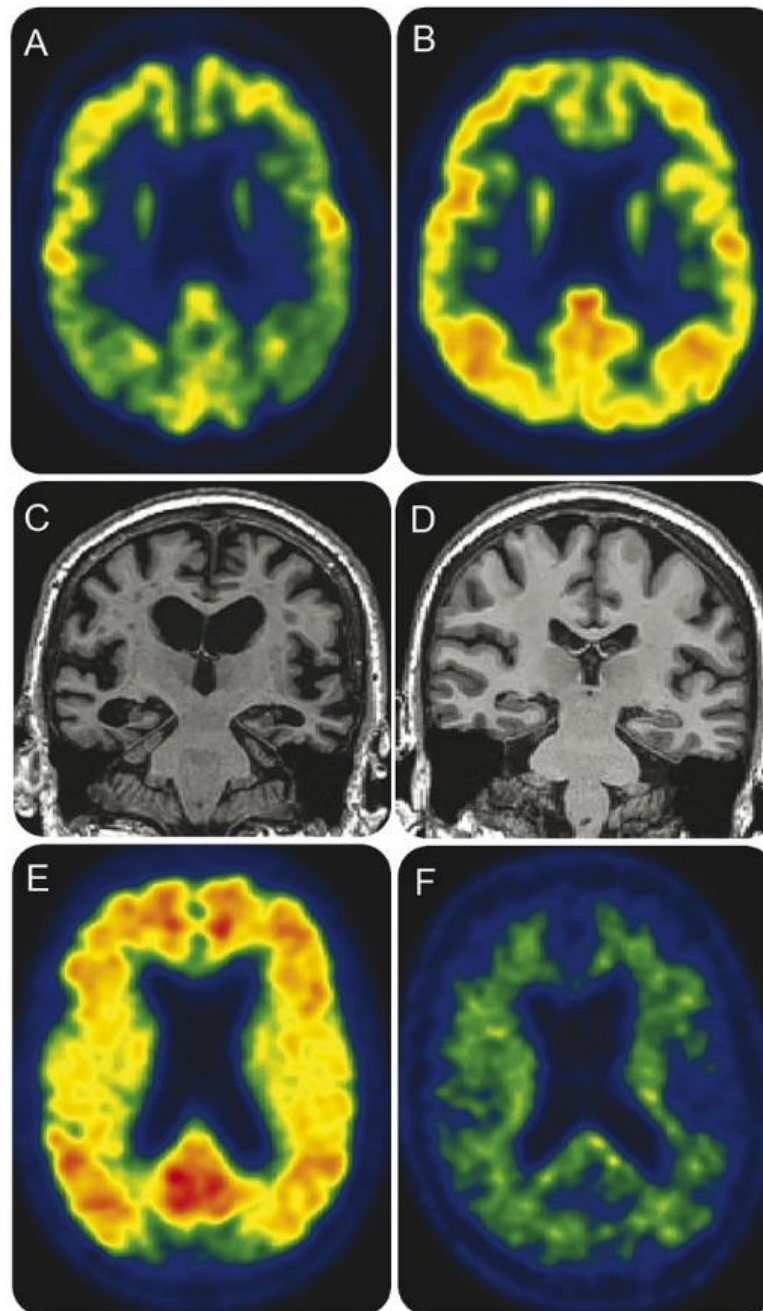
CURRENT AD RESEARCH DIRECTION

- Treat Alzheimer's before too much damage is done.
- Treat Alzheimer's before the patient has symptoms.
- How do you identify those patients?
- A biomarker is needed!

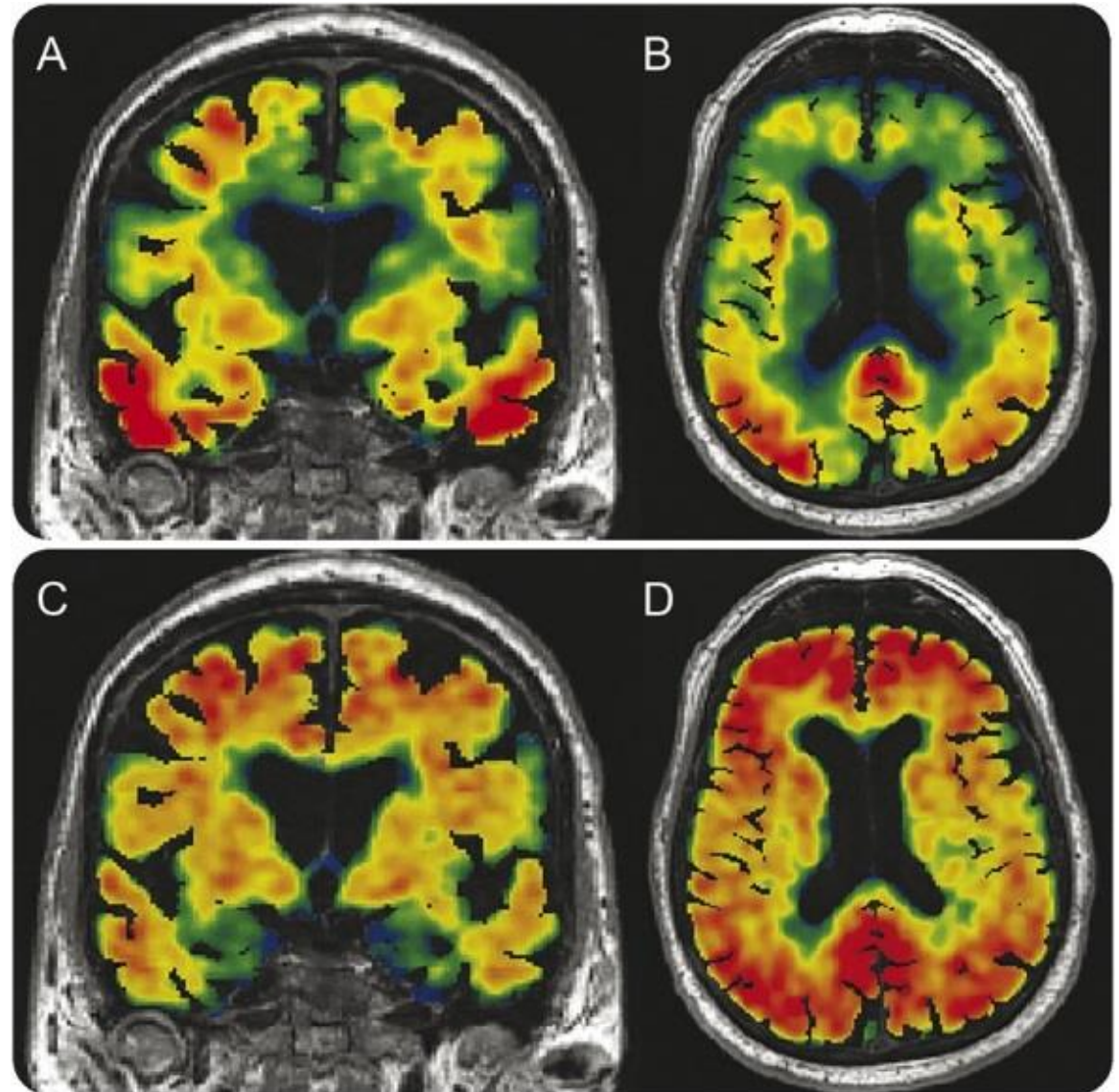


Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset (Bateman. NEJM 2012;367:795)

Individuals with AD dementia are clinically diagnosed participants in Mayo Alzheimer's Disease Research Center study while clinically normal individuals are participants in the Mayo Clinic Study of Aging. **(A) FDG-PET** of 75-year-old man with AD dementia. Hypometabolism in medial parietal and lateral temporal-parietal isocortex with relative preservation of frontal metabolism, which is characteristic of typical (multidomain amnesic) AD. **(B) FDG-PET** of clinically normal 71-year-old man. Uniform FDG uptake is present throughout the isocortex. **(C) MRI** of 71-year-old man with AD dementia. Atrophy is present in the medial temporal allocortex and the basal-lateral temporal isocortex, which is characteristic of typical (multidomain amnesic) AD. **(D) MRI** of clinically normal 71-year-old woman without atrophy. **(E) Amyloid PET** with Pittsburgh compound B of 71-year-old woman with AD dementia. Ligand uptake is seen throughout the isocortex. **(F) Amyloid PET** of clinically normal 93-year-old man showing no ligand uptake in the isocortex. AD = Alzheimer disease; FDG = [¹⁸F]-fluorodeoxyglucose.



A 79-year-old man with a clinical diagnosis of AD dementia. He is a participant in the Mayo Alzheimer's Disease Research Center study. (A, B) Coronal and axial tau PET images (AV1451) superimposed on MRI. (C, D) Coronal and axial Pittsburgh compound B PET images superimposed on MRI. The tau PET images (top) illustrate extensive tracer uptake in basal lateral temporal, parietal, and frontal isocortex with sparing of sensory motor and primary visual cortices. Off-target binding is seen in the basal ganglia, which is characteristic of this tracer. Although areas of spatial overlap between the tau and amyloid tracers are present, abundant amyloid tracer uptake is seen in the frontal lobes, but not with the tau tracer. Conversely, abundant uptake is seen in the medial temporal lobes with the tau ligand but not with the amyloid ligand. AD = Alzheimer disease.



FTD

FRONTOTEMPORAL DEMENTIA

- Two variants
 - Behavioral variant
 - Language variant
- Relative sparing of memory
- Age usually <65

FTD BEHAVIORAL VARIANT

- I. Progressive deterioration of behavior and/or cognition
- II. Requires three of the following:
 - Early behavioral **disinhibition**
 - Early **apathy** or inertia
 - Early **loss of sympathy or empathy**
 - Early perseverative, stereotyped **compulsive/ritualistic behavior**
 - Hyperorality and dietary changes

PRIMARY PROGRESSIVE APHASIA

1. Most prominent clinical feature is difficulty with **language**.
2. These deficits are the principal cause of impaired daily living activities.
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease.

KEY PPA POINTS

- Three variants
 - Nonfluent: Effortful, halting speech
 - Semantic: Impaired single-word comprehension
 - Logopenic: Impaired repetition

CLINICAL DIAGNOSIS OF FTD

- Behavioral variant
- Primary progressive aphasia (PPA)
 - Nonfluent / agrammatic variant
 - Semantic variant
 - Logopenic variant

2011 consensus criteria

DLB

DLB 4TH CONSENSUS REPORT

- Core features
 - Fluctuating cognition
 - Visual hallucinations
 - REM sleep behavior disorder
 - Parkinsonism

McKeith. Neurology 2017;89:88

DLB 4TH CONSENSUS REPORT

- Supportive clinical features
 - Sensitivity to antipsychotics
 - Postural instability
 - Repeated falls
 - Syncope
 - Severe autonomic dysfunction
 - Hypersomnia
 - Other hallucinations
 - Delusions
 - Apathy, anxiety, and depression

DLB 4TH CONSENSUS REPORT

- Indicative biomarkers
 - Reduced dopamine transporter uptake in basal ganglia by SPECT or PET
 - Abnormal ¹²³I-MIBG myocardial scintigraphy
 - Polysomnographic confirmation of REM sleep without atonia

McKeith. Neurology 2017;89:88

DLB 4TH CONSENSUS REPORT

- Probable DLB

- Two or more core clinical features +/- indicative biomarkers
- Only one core clinical feature + one or more indicative biomarkers
- Cannot be diagnosed only with biomarkers

DLB 4TH CONSENSUS REPORT

- Core features
 - Fluctuating cognition
 - Visual hallucinations
 - REM sleep behavior disorder
 - Parkinsonism

VAD

VASCULAR DEMENTIA

- Dementia associated with a clinical stroke*
- Strokes on CT or MRI
- Abnormal neurological exam

* Within three months

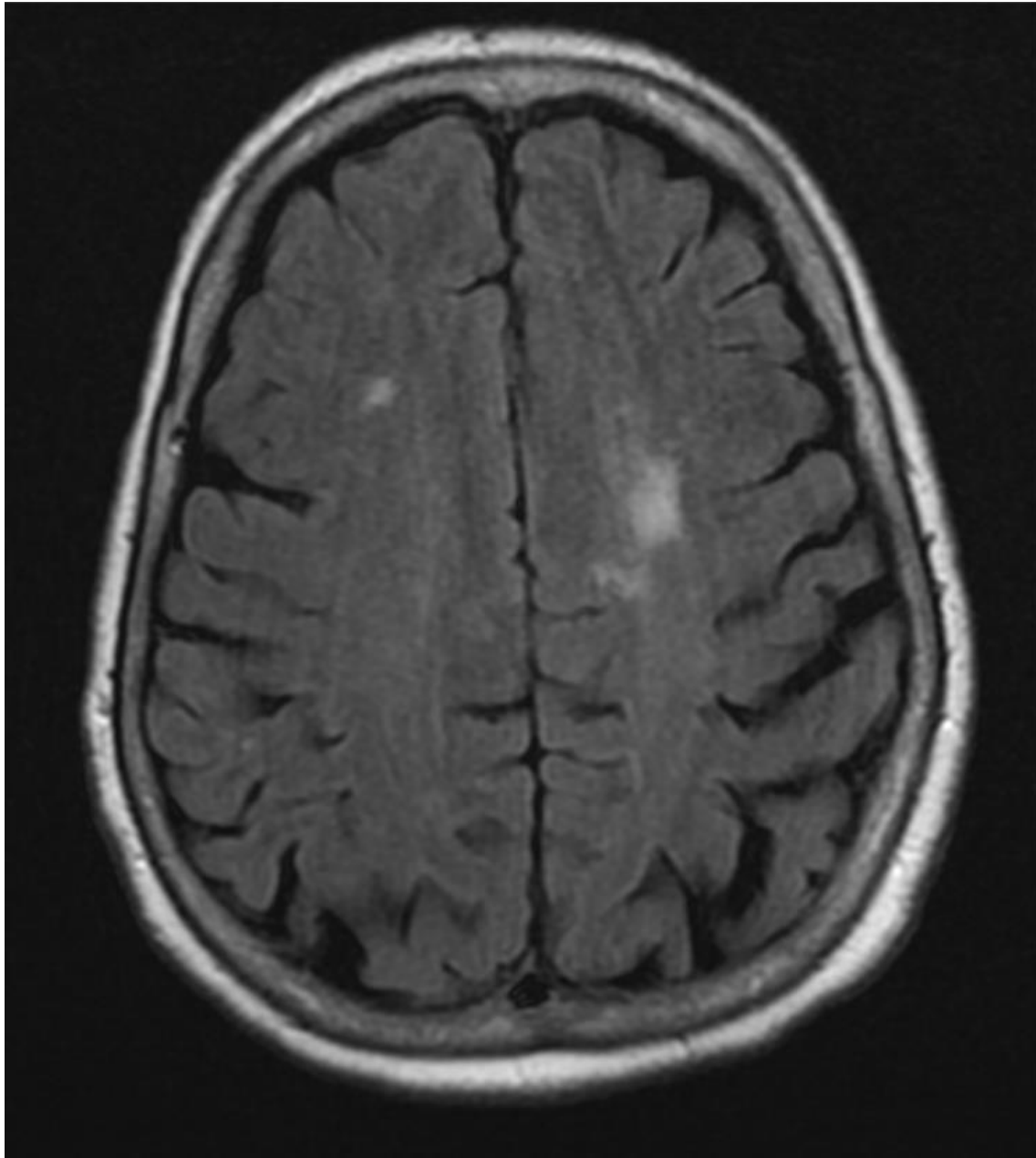
VASCULAR DEMENTIA

- Dementia associated with a clinical stroke
- Strokes on CT or MRI
- Abnormal neurological exam
- (Presence of vascular disease risk factors)

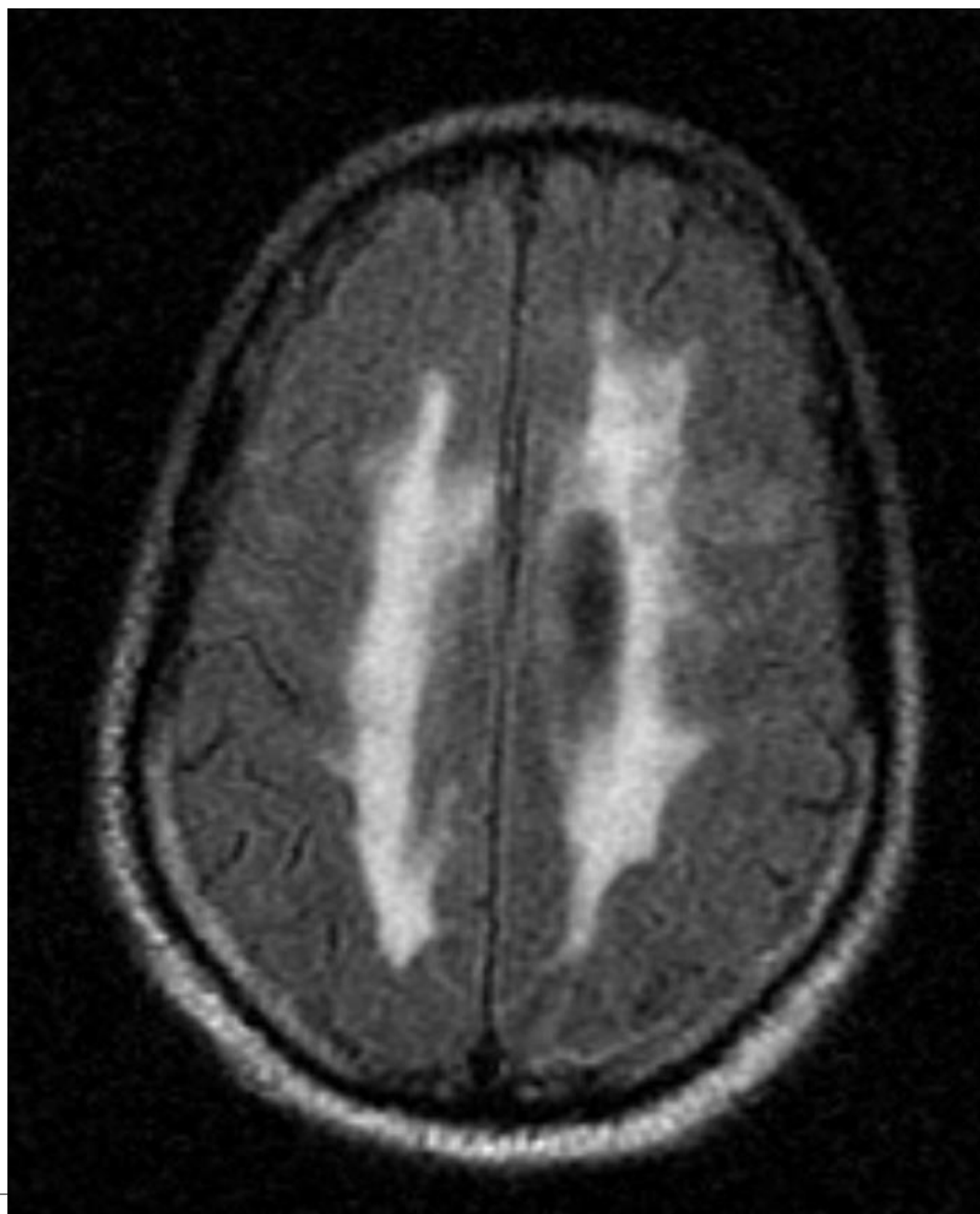
- Strokes seen on CT or MRI

STROKE ON CT





**NON-
SPECIFIC
WHITE
MATTER
CHANGE**



**POSSIBLE
EXCEPTION:
EXTENSIVE
PERIVASCULAR
WHITE MATTER
LESIONS**

WHITE MATTER DISEASE

- Does not prove that a patient is demented
- Does not prove vascular dementia
- Is associated with dementia

VASCULAR DEMENTIA

- Dementia associated with a clinical stroke
- Radiological infarcts
- Stroke risk factors
- Abnormal neurological exam
- **Cannot exclude concomitant Alzheimer's disease**

TREATMENT OF DEMENTIA

- Pharmacological
- Non-pharmacological

TREATMENT

- Non-pharmacological

TREATMENT

- Non-pharmacological
 - Exercise (“If you don’t use it, you lose it!”)
 - Proper nutrition
 - What’s good for the heart is good for the brain.
 - Education of the caregiver

AVAILABLE DRUGS FOR ALZHEIMER'S



TREATMENTS FOR ALZHEIMER'S

- Alter the balance of chemicals in the brain
 - Aricept[®] (donepezil)
 - Razadyne[®] (galantamine)
 - Exelon[®] (rivastigmine)
 - Namenda[®] (memantine)

**NO DRUG HAS BEEN PROVEN TO
SLOW ALZHEIMER'S DISEASE!**



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The available treatments are helpful, but they have not been proven to slow Alzheimer's disease.

Like using a crutch if we
severe leg pain...



SO WHY USE THE DRUGS?

- The average patient functions a little better.
- A few patients do significantly better.

SO WHY USE THE DRUGS?

- They delay the conversion to Alzheimer's disease.
- They help keep the patient out of the nursing home.

COMPLICATIONS OF DEMENTIA

- Agitation
- Depression
- Anxiety
- Disordered sleep
- Psychosis
- Combativeness
- Many others

DRUGS TO TREAT THE COMPLICATIONS

- Anti-agitation
- Anti-depressants
- Anti-anxiety (anxiolytics)
- Anti - no sleep (hypnotics)
- Anti-psychotics
- Anti - caregiver burn-out
- Others

CURRENT TREATMENTS

- Non-pharmacological treatment
- Pharmacological
 - Prescription drugs
 - Medical foods
 - Over-the-counter drugs
 - Drugs to treat the complications of dementia

CURRENT TREATMENTS

- Non-pharmacological treatment
 - What is causing the behavior?
 - Change the environment.
 - How serious is the problem?
 - Don't argue with the patient.
 - Don't try to reason with someone who can't reason.
 - Etc.
 - Etc.

CONFUSION IN THE ELDERLY

Dementia

- Destructive
- Irreversible
- Usually progressive

Delirium

- Functional
- Reversible
- Usually due to a medical condition

DELIRIUM

- Confusion
- Altered level of consciousness
- Prominent inattention
- Acute (or subacute) onset
- Fluctuation
- Usually non-focal neurological exam
- Usually caused by a medical condition

DELIRIUM COMPLICATING DEMENTIA

- Significantly worsened confusion
- Altered level of consciousness
- Prominent inattention
- Acute (or subacute) onset
- Fluctuation
- Usually non-focal neurological exam
- Usually caused by a medical condition

the end



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