Common Non-AD dementias – How to recognize and treat them

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Dr. Schmolck has no relevant conflicts with commercial interests to disclose.

Outline

- Introductory remarks
- Cortical dementias
  1. Alzheimers Disease
  2. Fronto-temporal Dementias
- Subcortical dementias
- Mixed dementias
  1. Lewy Body Disease
  2. Vascular Disease
- Treatment principles

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- You HAVE to know Alzheimer's Disease to differentiate it from other cognitive disorders.
- So I must talk about Alzheimer's Disease as well

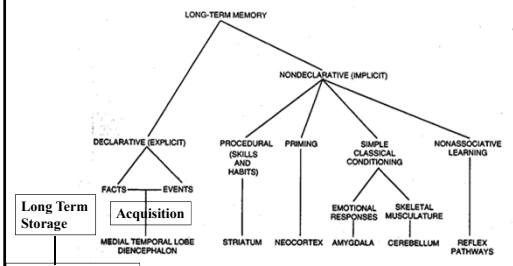
Henry Molaison

February 26, 1926 – December 2, 2008






Taxonomy of Memory



Long Term Storage

Acquisition

Neocortex (temporal/parietal?)

The file and the file clerk problem

- The file problem – the "AD/MTL" memory problem
- The file clerk problem – the most common memory problem and the most non-specific memory problem. Poor encoding due to attentional lapses; Memory inefficiency

The Big Players

- Alzheimer's Disease
- Lewy Body Disease
- Fronto-temporal Dementia
- Vascular Dementia
- PS – Dementia is not a disease

How do we differentiate dementing diseases

- Abnormal protein → predilection to particular brain area → disturbance in function of particular area/cell death → behavioral syndrome/focal atrophy/hypometabolism → diagnosis
- "Tracks in the snow"
- This is most true for CORTICAL dementias

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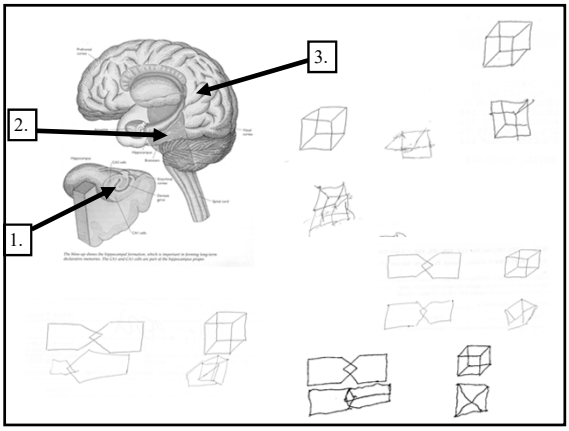
Cortical dementias

- FOCAL deficit
- Pattern makes diagnosis - “footprint”
- AD, FTD
- LBD and VD usually combination of cortical and subcortical pattern.

The Alzheimer’s Pattern

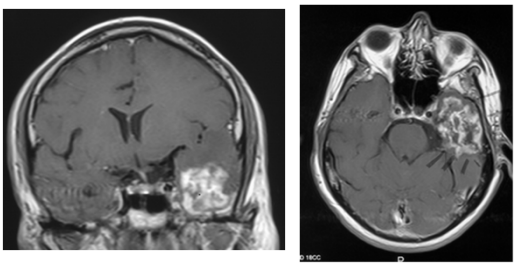
- Medial Temporal Lobe: Impairment in making NEW memories = rapid forgetting = short memory span = “file” memory problem
- NO problem recalling old memories
- Lateral temporal lobe: Language, Naming, facts/lexical information
- Parietal Lobe: Visuo-spatial processing



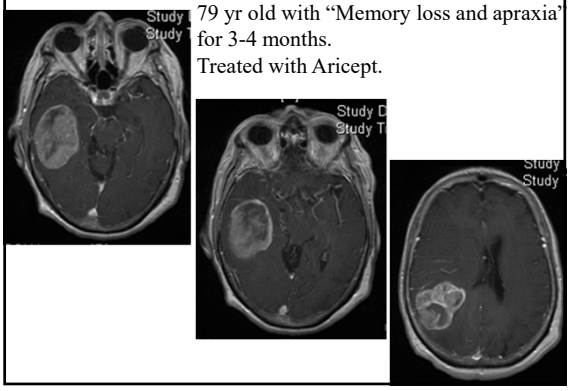
"Atypical AD"

- Language variant – Anomic (logopenic) primary progressive aphasia
- Visuospatial variant – Posterior cortical atrophy (PCA)
- Frontal variant – prominent early executive dysfunction

Imaging

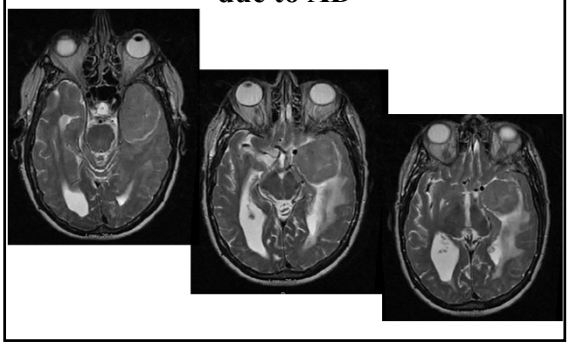


Schmolck (2003) Radiation necrosis in the temporal pole and lateral temporal cortex, presenting with a deficit of semantic memory. Baylor Webcase #73. http://www.bcm.tmc.edu/neurol/challeng/pat73/summary.html



79 yr old with “Memory loss and apraxia” for 3-4 months.
Treated with Aricept.

Clinically mild cognitive impairment due to AD



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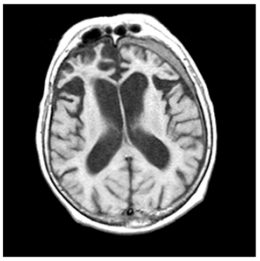
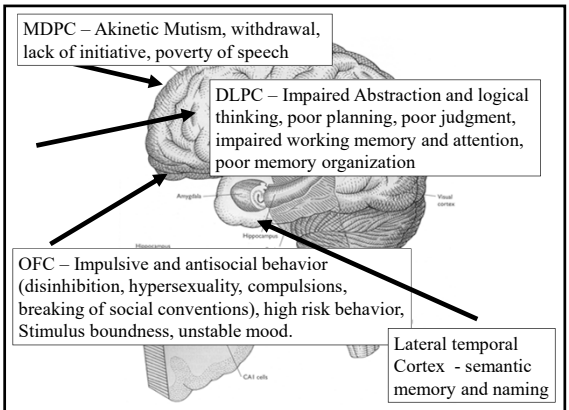
Treatment principles

FTD

- Many syndromes, many pathologies…



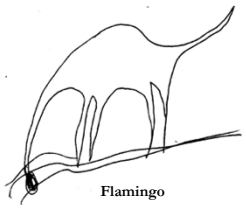


FTD subtypes

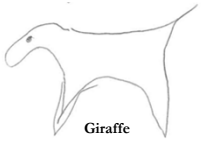
- Behavioral variant bvFTD = frontal variant FTD
- Nonfluent primary progressive aphasia
- Temporal variant FTD = semantic dementia = fluent primary progressive aphasia

Semantic Dementia

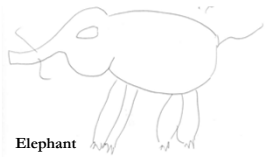
Owl



Flamingo

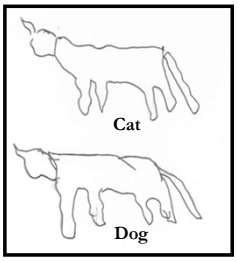


Giraffe



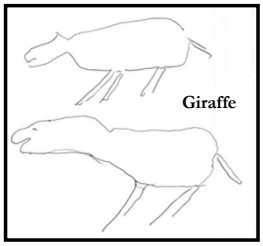
Elephant

Regression towards the Category Exemplar



Cat

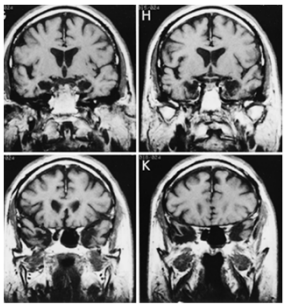
Dog



Giraffe

Patient H.M.

He is a bird. He hoots a lot and is in a tree. He guards an area, if anything comes around he can hoot to let the other animals know. They use them now for clocks, they come out on the hour and make timing.

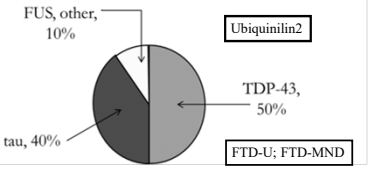


FTD overlaps with

- CBGD – cortico-basal-ganglionic degeneration
- PSP – progressive supranuclear palsy
- "multi system tauopathy"

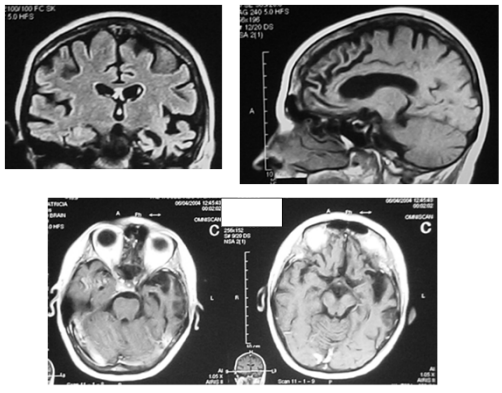
- ALS/Lou Gehrig's Disease/Motor Neuron Disease = FTD-MND

Percentage of FTD cases relatable to an identified protein



Progressive Supranuclear Palsy
Corticobasal Syndrome
FTD-Parkinsonism
Nonfluent Primary Progressive Aphasia

Fluent Primary Progressive Aphasia
= Semantic Dementia
ALS
FTD-MND



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Treatment principles

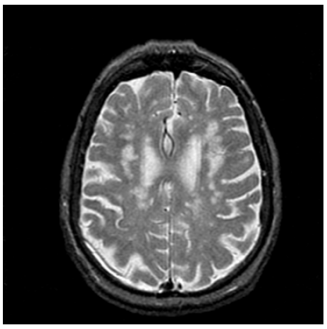
Subcortical dementias

- GLOBAL deficit, inefficiency of processing
- Psychomotor slowing
- Poor attention and concentration, distractible, problems with multitasking
- "file clerk" memory problem

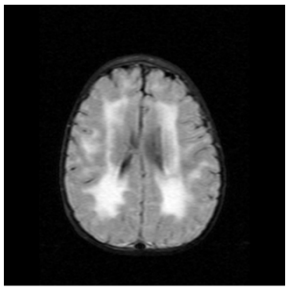
Subcortical dementia

- The cognitive profile of all these dementias is very similar!
- Diseases of white matter and basal ganglia = diseases of CONNECTIONS
- Multiple Sclerosis, Normal Pressure Hydrocephalus, severe small vessel disease (Binswanger's Disease)
- Parkinson's disease (and "Parkinson's plus"), Huntington's disease

MS



Extensive subcortical white matter disease



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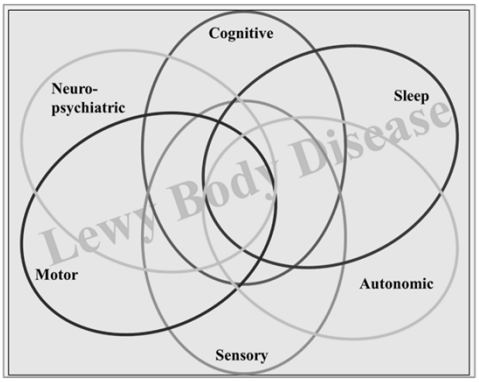

Thanks to Dr. Boeve, Mayo Clinic Rochester

Lewy Body Disease (LBD) (20-25% of dementias)

- CENTRAL FEATURES: Frontal/subcortical deficit - dysexecutive syndrome (difficulty planning, attention and concentration problems predominate). Also common are visuospatial problems. Memory difficulties later and usually not so severe.
- CORE FEATURES:

1. Visual hallucinations (well formed),
2. Fluctuating cognition with pronounced variations in attention and alertness
3. Parkinsonism. Cognitive symptoms precede motor symptoms or come on within one year of motor symptoms.

Lewy Body Disease (LBD)

- SUGGESTIVE FEATURES:
  - REM sleep behavior disorder
  - neuroleptic sensitivity
- SUPPORTIVE FEATURES:
  - Restless legs syndrome
  - Unexplained transient unresponsiveness, falls, syncope
  - Autonomic problems – temperature regulation, bowel/bladder/sexual dysfunction, orthostatic hypotension
  - other hallucinations, delusions, mood instability, anxiety, depression

And the difference to Parkinson's Disease is what?

- Well…. Nothing?

- The TIMING is the only difference
- LBD has early widespread damage, PD starts more focal and then spreads.
- If cognitive symptoms occur within one year of motor symptoms or before motor sx = LBD

RSBD

- 90% develop PD or LBD within 10 years

- No paralysis during REM sleep – motor acting out of dream content
- Can be detected during sleep study as muscle activity is recorded

Capgras Delusion

- Around 15% of LBD patients. The most common etiology of Capgras Delusion is LBD

- Disconnect between recognition and emotion = spouse (or other family member) can thus not be spouse but must be an imposter/a double/a replacement "you look like my husband but your really aren't my husband"

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Vascular Dementia

- May be cortical or subcortical
- May be independent entity
- May be found with AD, FTD or LBD
- May be associated with mutation in NOTCH 3 (CADASIL)

Vascular Dementia

- Two main types:
- Multi-infarct Dementia: Deficits are a sum of the cortical strokes a patient has had, that is a mosaic of deficits, and there is usually clear step-wise progression
- Diffuse white matter disease, subcortical leucoencephalopathy, Binswanger disease: A subcortical dementia with diffuse global impairment, chronic progressive, sometimes in conjunction with lacunar strokes. Hallmark is attention and concentration deficit with psychomotor slowing

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Try and modify disease process

- **STRONG evidence for EXERCISE EXERCISE EXERCISE**
- This is true for both Alzheimer's Disease and Parkinson's Disease, so can be assumed to be true for Lewy Body Disease
- Effect in AD disregarding severity is seen with 30 min of walking 4x a week.
- Treat vascular risk factors if a vascular contribution is identified.

Try and modify disease process

- Cholinesterase Inhibitors show **modest** disease modifying effect in AD.
- Historically, AD progresses by 3 points on the MMSE per year.
- This is rare in treated patients.
- Paucity of studies for the other diseases does not allow firm conclusions.

Use CHEIs

- Improve outcome, improve quality of life, don't prolong life, lower caregiver burden, prolong time to nursing home admission, lower number of ED/urgent care visits
- Can help symptoms, especially concentration/attention/focus/efficiency/speed of processing (thus not the cardinal symptom of AD, memory – but the most common symptom in PD, LBD, FTD, Vascular Dementia)
- Can use interchangeably, depending on tolerability
- GI side effects: Rivastigmine > Donepezil > Galantamine> Rivastigmine Patch
- Give in am, they can disturb sleep, cause vivid dreams

Use CHEIs

- In LBD, first line therapy for hallucinations and Capgras Delusion. Frequently also improves motor symptoms.
- If patient has a an amazing improvement with CHEI, they likely have LBD
- Can push up to highest tolerated dose
- Careful in severe anxiety, agitation

Memantine

- Approved for moderate to severe AD (NMDA receptor (a glutamate receptor) leak current blocker)
- Supposed to (in vitro) decrease excito-toxicity and regulate receptor function (reduces "noise" in synaptic transmission)
- Paucity of data for MCI and mild AD, and other diseases. No convincing evidence for Monotherapy.
- Dual therapy better than CHEI Monotherapy
- Can help symptomatically with mood and behavior

Treatment of Dementia

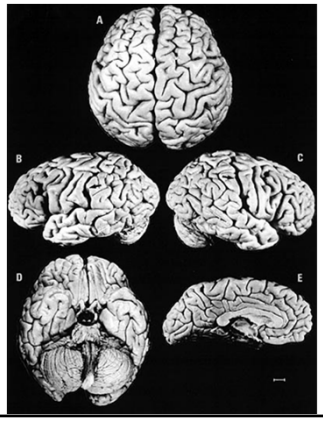
- SSRIs/SSNRIs as needed for anxiety, depression, irritability
- Mood stabilizers as needed (Depakote, Lamictal)
- Atypical antipsychotics if unavoidable . Quetiapine preferred. Nuplazid for PD Psychosis. Others have high rate of parkinsonism in the elderly. NO typicals
- No need to treat all hallucinations. Educate.
- Melatonin (up to 15mg), Clonazepam for RSBD
- Stimulants

Non-pharmacological treatment for AD

- STRONG evidence for disease modifying effect of EXERCISE! Goal is 30 min of brisk walking 4 times a week (or exercise biking, other aerobic exercise)
- Weak evidence for disease modifying effect of good nutrition (Mediterranean diet, more fish, more fruits and vegetables, whole grains); epidemiological evidence for prevention
- Theoretical disease modifying effect of sufficient SLEEP (Beta Amyloid is cleared in animal models during the second half of the night); epidemiological evidence for prevention – and strong evidence that sleep deprivation acutely worsens cognition
- Theoretical disease modifying effect of meaningful social interactions, cognitive engagement, sense of purpose; epidemiological evidence for prevention

Vascular Dementia/mixed Dementia

- Control vascular risk factors
  - Tight control of blood sugar, blood pressure
  - ASA 81mg (or other antiplatelet)
  - Statin
  - Usually benefit from Cholinesterase-Inhibitors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