

THE DEMENTIAS

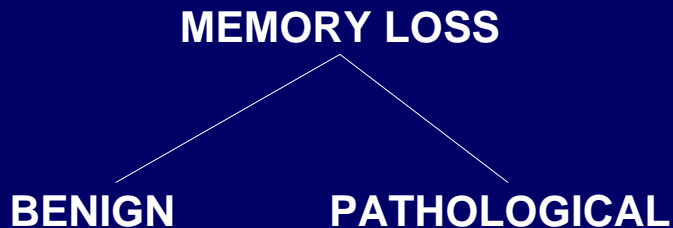
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2007

[//adfoap.med.unsw.edu.au](http://adfoap.med.unsw.edu.au)

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ASSESSMENT: STEP 1



EARLY DEMENTIA -VS- AGEING

Suspect early dementia if:

- Progressively worse
- Difficulty learning even with effort
- Events, not just details, forgotten
- Interferes with normal function
e.g. hobbies, social life, shopping
- Other cognitive difficulties
 - hard to understand a story/follow movie
 - difficulty finding words
 - can't do calculations
 - more disorganised

Mild Cognitive Impairment



'MCI refers to the state of cognition and functional ability between normal aging and very mild AD'

(Petersen, 2001)

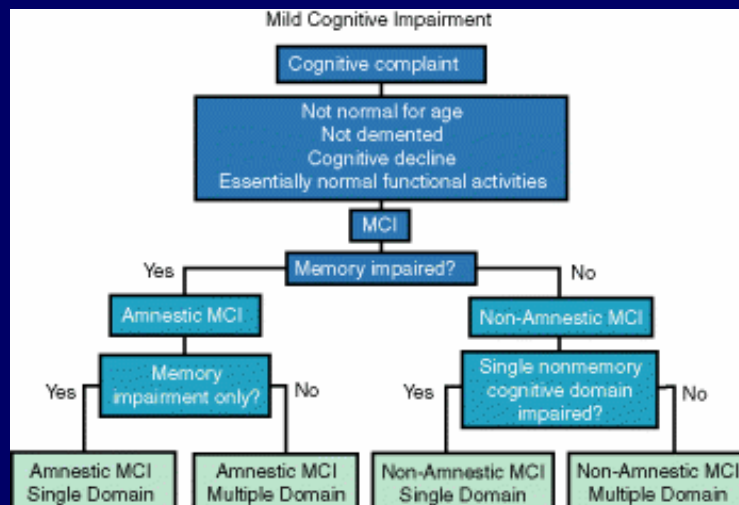
Revised Petersen Criteria (2004)

4 subsets of MCI now included:

- 1. aMCI (single domain)**
- 2. aMCI (multiple domains)**
- 3. Non-amnestic MCI (single domain)**
- 4. Non-amnestic MCI (multiple domains)**

Petersen RC (2004) Journal of Internal Medicine 256 (3), 183-194

Revised Petersen Criteria (2004)



Petersen RC (2004) *Journal of Internal Medicine* 256 (3), 183-194

Amnestic MCI (Petersen, 1995)

1. Cognitive complaint, usually memory, by subject (preferably) or informant
2. Cognitive screening test in normal range for age (eg MMSE>24)
3. 1.5 SDs below age-appropriate norms on memory tests or memory component of other cognitive tests - *clinician judgement*
4. ADLs not “significantly” affected
5. Not meeting DSM dementia criteria



**But there are problems
with each of these
criteria**

MCI 1: cognitive complaint

- **Who complains?**
 - Patient or family member
- **Complaint about memory or other cognition?**
- **Does the person complain**
 - Spontaneously? or
 - In response to interviewer asking about memory problems?
- **Does the person seek assessment/treatment or is s/he recruited from community survey?**

MCI 2: general cognition normal for age

- Usual to base this on a MMSE score above certain threshold, eg >24
- Does not make allowance for effects of intelligence, education, language, culture
- Person of low intelligence is more susceptible to MMSE decline (than person with high IQ)

MCI 3: objective memory impairment

- What is impairment? What memory tests? What cut-offs?
- Define ?1 or ?1.5 SD below population norms corrected for age, education
- By statistical definition \cong 7% of population will be at least -1.5 SDs on any test
- More tests \rightarrow more chance of impairment
- Ultimately memory impairment is based on clinician judgement
 - But this can *not* be operationalised

MCI 4: Problem with intact ADLs

- Intact ADLs can be as simple as still being able to dress, wash
- Or, intact IADLs e.g. driving car, managing housework, catching public transport
- What if IADLs impaired because of physical handicap?
- Does not include subtle impairments?
 - eg ability to weigh up competing investment portfolios and make decisions about finance

MCI 5: not dementia

- If only one cognitive domain and functional abilities are 100% preserved: decision easy.
- But how to distinguish
 - **Multiple domain amnesic MCI** (with subtle impairment in function) *from*
 - **Mild Alzheimer's disease?**

Rates of conversion

- Vary between 0 and 34% p.a.
- Depends on
 - Sample source, *clinic vs community vs population*
 - Age of sample, *higher if older*
 - Criteria for defining sample
 - Exclusion criteria

Instability of MCI syndromes?

MCI

- Petersen 10-12%pa → dementia
- Ritchie (2001):
 - After 1 year, 25/27 improved (93%); No dementia
- Wahlund (2003):
 - After 3 years, 5/43 improved (11%)

Conversion from MCI to AD- Consistently reported

- ↑ age¹⁻³
- Apoe4 genotype³⁻⁶
- ↓ general cognition^{1-3,7}
- ↓ memory^{1,2,5,8-11}
- ↓ function^{5,10-12}
- Lower education¹³
- ↓ Recall and ↓ executive function

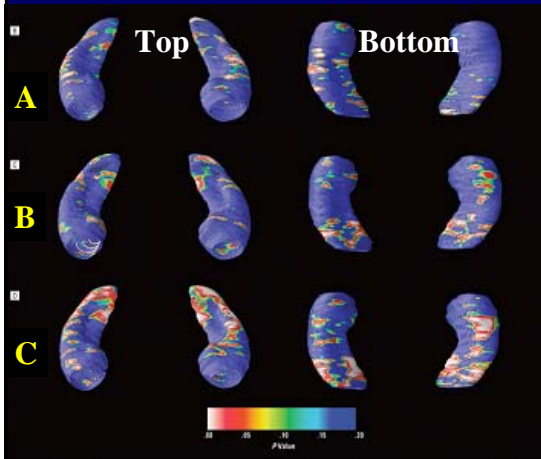
¹Visser et al, 2000; ²Devanand et al, 1997; ³Petersen et al, 1995; ⁴Petersen et al, 1996;
⁵Morris et al, 2001; ⁶Tierney et al, 1996; ⁷Devanand et al, 2000; ⁸Flicker et al, 1991;
⁹Marquis et al, 2002; ¹⁰Wentzel et al, 2001; ¹¹Hanninen et al, 1995; ¹²Artero et al, 2001;
¹³Tervo et al, 2004

Conversion of MCI to AD Predicted by Hippocampal Atrophy Maps Apostolova et al. 2006

- Smaller hippocampi are associated with increased risk for conversion
- MCI patients who improved over 3 years tended to have larger hippocampal volumes & relative preservation of the subiculum and CA1 than patients who converted or remained stable

Apostolova, L. G. et al. Arch Neurol 2006;63:693-699.

Hippocampal Maps



Hippocampal radial atrophy between:

A: MCI pts that converted to AD (MCI-c) and those with stable MCI (MCI-nc)

B: MCI-nc pts & MCI pts who improved (MCI-i)

C: MCI-c and MCI-i pts

$= p < .05$ $= p < .01$ Apostolova, L. G. et al. Arch Neurol 2006;63:693-699.



ASSESSMENT: STEP 2

Organic vs functional

PATHOLOGICAL MEMORY LOSS

Functional

- depression
- mania
- anxiety
- schizophrenia
- hysteria
- malingering

Organic

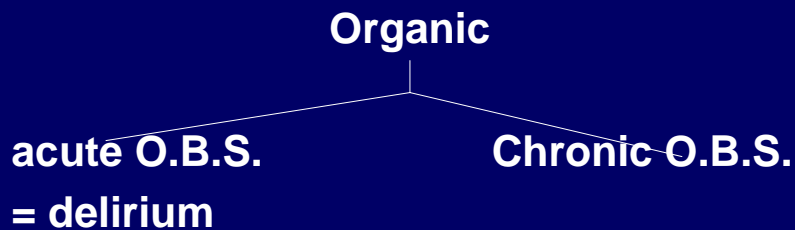
	Depressive pseudo-dementia	Alzheimer's
Onset	Quick = weeks to months	Insidious, slow - yrs
Course	Quicker descent, plateau	Slow, progressive decline
Family History	± Affective disorder	± Dementia
Pt's Sx	<ul style="list-style-type: none"> ± Emphasise disability ± Highlight failure ± Distress 	<ul style="list-style-type: none"> ± Cover up ± Delight in accomplishment ± Lack of concern

	Depressive pseudo-dementia AD	
Affect	Pervasive depression	If depression, labile, shallow
Social skills	out of proportion to cognition	Retained
D.M.V.	± a.m. worse	± p.m. worse
Memory loss	Inconsistent, variable ↓	Consistent, recent > long-term

Diagnostic trap:

dementia *plus* depression

STEP 3: Acute vs Chronic Organic Brain Syndrome



TRAP = DEMENTIA PLUS DELIRIUM

NOTE: delirium *not* delErium

History	Dementia	Delirium
- onset	Insidious	Sudden
- duration	Months - years	Hours - days
- course	Constant	Fluctuating
Sleep	Normal (early)	Reverse sleep-wake cycle
Motor activity	Normal (early)	Agitation
Hallucinations	Occur later, not prominent	Often florid
Mood/affect	Apathy, disinhibition	Fear

Mental state	Dementia	Delirium
Consciousness	Normal	Clouded
Attention	Normal (early)	Clouded
Registration	Normal	Impaired
S/T memory	Impaired	Impaired
General knowledge	Gradual decline	Normal
System review	Normal	Systemic illness, toxin
EEG	Normal, mildly slow	Diffuse slowing

STEP 4: GLOBAL -VS- FOCAL

Chronic

Focal

- dysmnestic syndrome
- parietal lobe syndrome
- frontal lobe syndrome

“Global” (i.e. > 1 lobe)

= dementia

Frontal Lobe Syndromes: medial

- apathy, lack of spontaneity
- lack of initiative, drive
- dullness
- slowness

Frontal Lobe Syndromes: orbito-basal

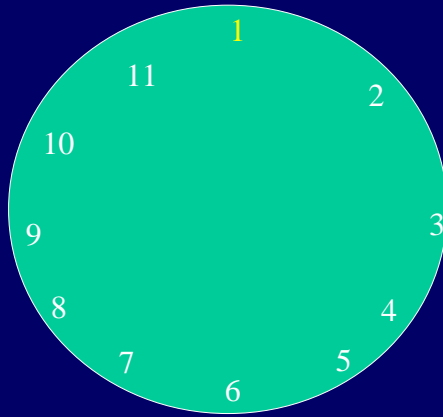
- disinhibition
- fatuous jocularity
- lack of control

Frontal Lobe Syndromes: lateral convexity

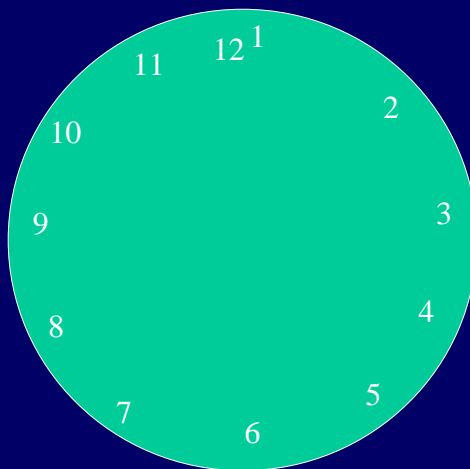
Impaired:

- planning
- executive functions
- organisation
- abstract conceptualisation

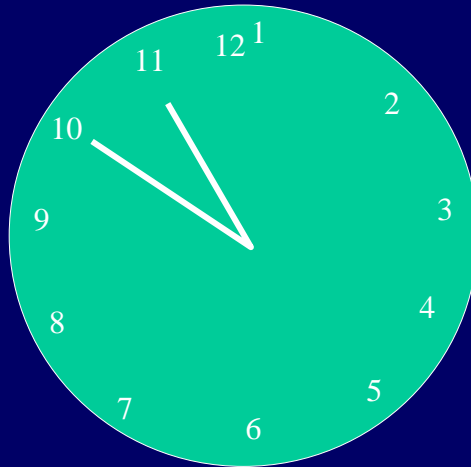
Draw a circle and put in all the numbers to represent the hours of a clock



...and realises that the 12 is missing



**Draw in the hands to show 10
past 11 o'clock or 11.10**



Tapping task

- When I tap once I want you to tap twice
- When I tap twice I want you to tap once
- Got it?

Tapping task – conceptual shift

- When I tap once I want you to tap once
- When I tap twice I want you *not* to tap
- Got it?

Luria three stage command

1. Slap (Palm)
2. Fist
3. Cut (Side)

Word fluency

- **Semantic**
 - 18 ± 6 animals in one minute
- **Phonemic**
 - 15 ± 5 words beginning with (F, A or S) within one minute

Step 5: Cause of the dementia (Irreversible vs Potentially Reversible)

- pseudo-dementia
- thyroid deficiency (or excess)
- B12 deficiency
- folate deficiency
- calcium excess (or deficiency)
- normal pressure hydrocephalus
- infection e.g. with syphilis
- toxins e.g. alcohol.
- Treatment, when late, may only be able to halt but not reverse further deterioration

DD of dementia

- Onset – acute v subacute v gradual
 - Stepwise v gradual
- Cognitive – cortical v subcortical
- Behavioural – frontal involvement
 - FTD, VaD, CJD, DLB
- Neurological – movement disorder
 - Gait disorder

	Cortical	Sub-cortical
Psychomotor speed	Normal	Slow
Complex attention	Normal	Abnormal
Information management	N - AbN	AbN
Executive function	N - AbN	AbN

	Cortical	Sub-cortical
Verbal output	Normal to decreased	Decreased
Language	Aphasic	Normal – xpt ↓verbal fluency
Speech	Normal	AbN – (mute hypophonic, dysarthric)

	Cortical	Sub-cortical
Memory	Learning deficit (amnesia)	Retrieval deficit
Cognition	AbN – acalculia, ↓judgement, ↓abstraction	AbN - ↓executive fntn
Visuo-spatial	AbN	AbN
Affect	Unconcerned, disinhibited	Apathetic , depressed

	Cortical (xpt in late stage)	Sub-cortical
Posture	Normal	AbN - stooped
Tone	Normal	Increased
Movements	Normal	AbN – tremor, chorea, dystonia asterixis
Gait	Normal	Abnormal

Cortical dementias

- AD
- FTD
- Asymmetrical cortical atrophies

Frontal- subcortical

- DLB
- PD
- HD
- PSNP
- VaD
- CJD
- HIV
- Neuro\$
- NPH

Neurological signs

Movement disorders

- CJD
- PD
- Wilson's
- HD
- CBD
- Vasculitides
- Hashimoto's
- SSPE

Gait disorders

- NPH
- LBD
- PD
- PSNP
- Hereditary ataxias

Step 6: What deficits does the dementia cause?

- Personality change: exaggerated or flattening of premorbid traits
- dysphasia and dyspraxia
- problem behaviours commonly emerge as dementia progresses, e.g. of continual questioning, aggressiveness.

Step 7: What else is treatable? (Other pathology)

- Coexisting physical disease (e.g. chronic urinary infection)
- Sensory impairment
- Psychological disorder which may magnify cognitive impairment.

Step 8: What's right about the patient? (Assets)

- Assets or healthy parts of patient may influence management as can knowledge of previous interests, hobbies and friendships.

Step 9: What are the effects on the family?

- Dementia is not just one person's illness - it affects the whole family
- Carers suffer psychological, social, physical and financial consequences
- If carers break down through physical or psychological ill health, then home care often breaks down.

Effects on carers/caregivers

- High rates of depression, burden, low morale
- Predictors of CG stress can be identified
- Chronic physical conditions worsen eg Hi BP
- High levels of cortisol and ↓ immune response, correlates with degree of stress
- Financial hardship

Assessment - The Practice

- **History: crucial, especially from an informant**
- **Onset: sudden (e.g. vascular), insidious (e.g. AD)**
- **Progression: step-wise (e.g. multi-infarct dementia), gradual (e.g. AD).**

Assessment - level and nature of current difficulties

- **Abstract, complex skills e.g. following a plan, learning language**
- **Instrumental activities of daily living (IADL), eg finances, 'phone, transport**
- **Basic activities of daily living (ADL), e.g. dressing, washing, toileting**

Assessment (cont'd)

- Mental state examination - check cognitive functions of all lobes
- Physical examination including neurological, cardiovascular, endocrine

Aetiology of dementia



- Over 100 causes
- AD up to 50%
- VaD or multi-infarct dementia (MID) about 15-20%
- Mixed AD/VaD about 15%
- Lewy body (up to 20%)
- Fronto-temporal (5%+)
- Alcohol
- Head injury

Clinical features

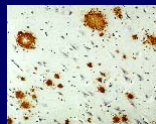
- Alzheimer's disease
- Vascular dementia
- Lewy body dementia
- Fronto-temporal dementia
- Cortical versus subcortical
- Rarer syndromes

AD: a progressive CNS disorder with characteristic pathology

Brain atrophy



Senile plaques

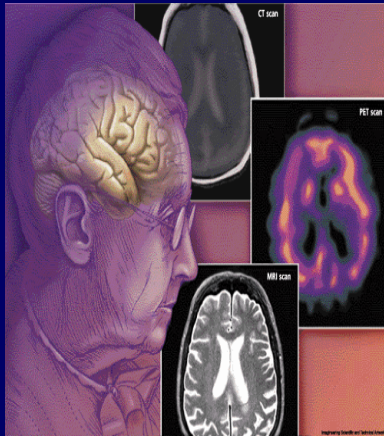


Neurofibrillary tangles



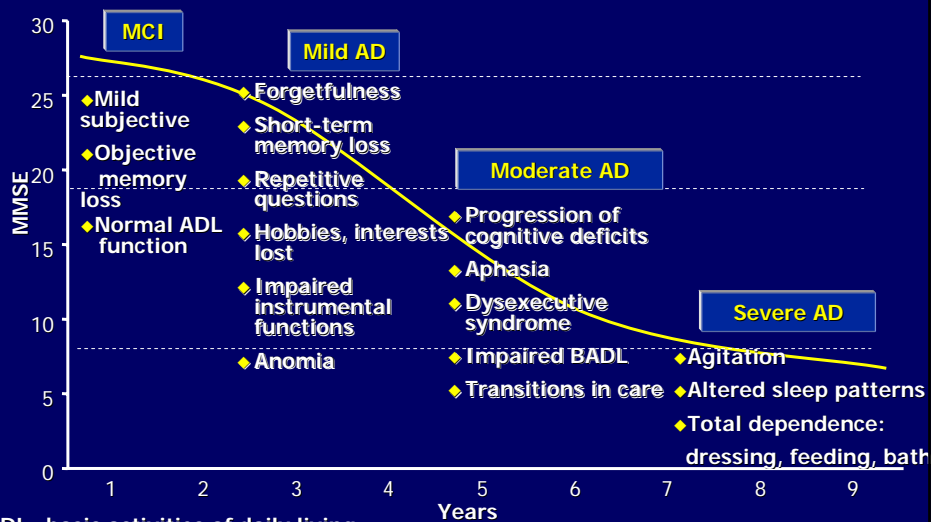
Katzman, 1986; Cummings and Khachaturian, 1996

Clinical features of dementia



- AD is the prototype of dementia
- Insidious onset with gradual decline
- Women affected slightly > men
- Death usually with 10 years (1- 20+ years)
- Some familial clustering
- Three stages: mild, moderate & severe

Symptom Progression in AD



BADL=basic activities of daily living.

Modified from Feldman et al. *Clinical Diagnosis and Management of Alzheimer's Disease*. 1st ed. 1998.

Early Stage of AD (1-3y)

- **memory** - new learning impaired
- remote relatively but not totally spared
- **visuo-spatial** - topographic disorientation,
- poor construction
- **language** - poor word-list generation,
anomia
- **personality** - irritability, sadness, apathy
caricaturing previous traits
- **normal** - motor system, EEG and CT

Middle Stage of AD (2-10y)

- **memory** - S/T and L/T memory more severely impaired
- **visuo-spatial** - poor construction, spatial disorientation
- **language** - fluent aphasia
- **frontal** - comprehension impaired
- perseveration
- **parietal** - acalculia, ideomotor apraxia

Middle Stage of AD (continued)

- **personality** - indifference, apathy
- **psychiatric** - hallucination, delusions
- behavioural disturbances
- **motor system** - restlessness
- **EEG** - background rhythm slower
- **CT** - normal or enlarged sulci
and dilated ventricles.

Late Stage of AD (3-12y)

- **intellectual** - severe deterioration
- **language** - echolalia, palilalia,
- logoclonia, dysarthria, mutism
- **motor** - limb rigidity, flexion posture
- **sphincters** - urinary and faecal incontinence
- **EEG** - diffuse slowing
- **CT** - enlarged sulci, dilated
ventricles

VaD -v- AD

- Earlier onset than AD and M>F
- Sudden onset, stepwise deterioration
- History of hypertension
- History of strokes
- Evidence associated arteriosclerosis
- Focal neurological symptoms
- Focal neurological signs
- Focal pathology on brain imaging

Vascular dementias*

- Infarct
 - Multi-infarct (thrombo-embolic)
 - Single strategic stroke – thalamus. Caudate nucleus, ant cingulate/basal forebrain, genu of internal capsule, L angular gyrus
 - Lacunar state – deep penetrating arterioles
- Non-infarct ischaemia
 - Binswanger's, deep penetrating arterioles

*Mendez MF, Cummings JL. *Dementia. A Clinical Approach.* Butterworth/Heinemann. 3rd Ed 2003

Vascular dementias

- **Post-ischaemic - ↓ perfusion**
- **Haemorrhagic – malignant hypertension, amyloid angiopathy**
- **Genetic – CADASIL, Fabry's**
- **Mixed – AD/VaD**
- **Vasculitides**

Criteria for VaD (NINDS-AIREN)

- **Dementia**
- **Memory + 2 cognitive domains**
- **CVD – focal signs, evidence on imaging**
- **Relationship between CVD and dementia – within 3 months of stroke OR acute deterioration OR fluctuating cognitive function**
- **Clinical features consistent with VaD – gait, falls, incontinence, pseudobulbar palsy, mood/ personality changes**

VaD Clinical features

- Sudden onset, step-wise deterioration
- CVD risk factors
- Focal neurological Sx & Sg
- Subcortical or mixed cortical & subcortical impairment
- Imaging

Stroke and dementia

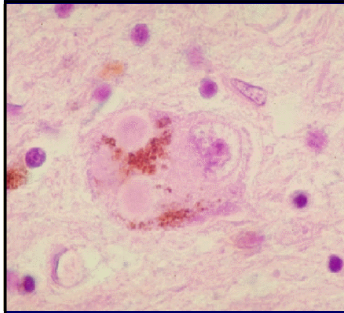
- 1/3 pts admitted for stroke have dementia within one year (Sydney Stroke Study)
- Age, DWMH, interval CVA

Parkinsonian ~~A~~s with dementia

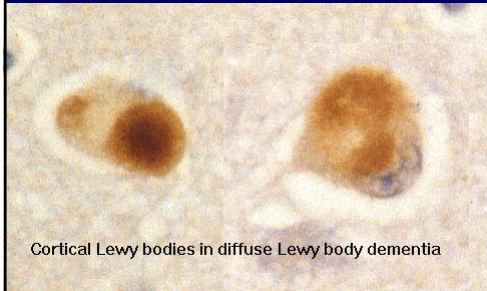
- Dementia with Lewy Bodies (DLB)
- PD with dementia
- Progressive Supra-nuclear palsy (Steele-Richardson Syndrome)
- Cortico-basal degeneration
- Heredo-degenerative eg ICBG (Fahr's)
- Secondary parkinsonism
 - Post-encephalitic
 - Vascular
 - Drugs

DLB

- 3rd most common dementia
- M > F; usu. >65 yo
- Survival shorter than AD, mean 7yrs



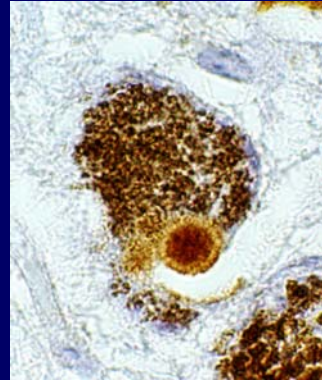
Cortical Lewy bodies



Cortical Lewy bodies in diffuse Lewy body dementia

Lewy body disease

Synuclein +



Dementia with Lewy Bodies

- **Progressive cognitive decline sufficient to interfere with normal social and occupational function**
 - Attention, visuo-spatial, frontal-subcortical
 - Memory ↓ usu. evident with time
- **CORE (2 for Dx = probable; 1 = possible):**
 - Fluctuating cognition
 - Recurrent visual hallucinations (40-75%)
 - Spontaneous features of parkinsonism

LBD supportive features

- Repeated falls
- Syncope or transient loss of consciousness
- Neuroleptic sensitivity
- Systematised delusions
- Hallucinations in other modalities
- REM Sleep behaviour disorder
- Depression

LBD & PD & AD

- disease dementia (PDD)
- If motor symptoms (> 1 year B4 cognitive symptoms → PDD diagnosis)
- In PD, usually 10 years B4 cognitive Sx
 - esp. if older, bradykinetic, akinetic-rigid, bilateral onset of PD, depression, early visual hallucinations, ↓response to L-DOPA
- In AD, parkinsonism develops late in course

Progressive Supranuclear Palsy

- Uncommon
- M > F, median onset 63yo; duration 6 yrs
- Supranuclear gaze palsy – can't look down, doll's eye reflex
- Axial rigidity, pseudobulbar palsy
- Postural instability, falls, gait abN
- Parkinson Sx not responsive to L-DOPA
- Frontal release signs
- High BP (adrenergic nuclei)

PSP

- Dementia common
- Subcortical pattern – slowing, apathy, forgetfulness and prominent frontal executive dysfunction
- DD – PD posture hyper-erect, little tremor; Vascular parkinsonism
- Tau pathology

Cortico-basal degeneration

- Rare, parkinsonism+ syndrome
- Specific motor features
 - Lateralised motor signs
 - Asymmetrical Parkinsonism, tremor
 - Dystonia, myoclonus, limb dyspraxia
 - Pseudobulbar palsy, dysarthria
 - Frontal release signs, pyramidal tract signs

CBD

- Specific cognitive features
 - Alien limb phenomenon
 - Ideomotor dyspraxia
 - Slow, learning↓
 - Frontal dysexecutive syndrome

Multiple System Atrophy

- **Striato-nigral degeneration (SND)**
 - Predom pyramidal dysfunction
- **Olivo-ponto-cerebellar atrophy (OPCA) – ataxia prominent**
- **Shy-Drager Syndrome (SDS) – dysautonomia (dementia - rare)**
- **Cell loss in basal ganglia (putamen)**

Multiple System Atrophy

- **Parkinsonism – severe, abrupt onset, poor response to L-DOPA**
- **Pyramidal, cerebellar and autonomic dysfunction (esp. orthostatic hypotension)**
- **Cognitive: Frontal executive and attentional set-shifting**

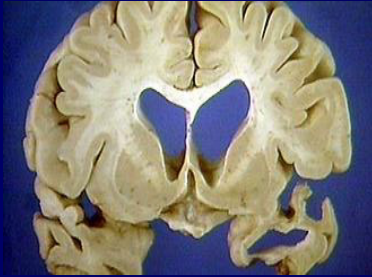
Other motor disorders with dementia

- Huntington's
- Wilson's
- Hallervorden-Spatz (iron deposition)
- ALS PD complex
- MND with dementia
- Hereditary spino-cerebellar ataxias

Fronto-temporal dementias (Pick syndrome/ complex)

- 2-5% of all dementing disease
- In <65 yo^s = AD
- Clinico-path studies
- Pick bodies in 20-25%
- Accompanying:
 - MND in 10%
 - Early parkinsonism in 3-4%
 - CBD – smaller %

FRONTO-TEMPORAL DEMENTIAS (PICK SYNDROME)



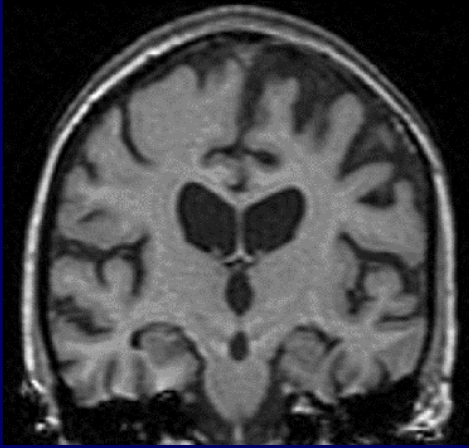
Pathology

- *Pick's disease: Pick bodies on microscopy*
- *Fronto-temporal degeneration lacking distinctive histopathology*
- *MND-inclusion dementia*

FTD – protein inclusions

- *Tau pathology in 1/3*
 - *10% have tau gene mutation*
- *Ubiquitin +ve and tau negative (non-argorphylic)*

FTD - Macroscopic/brain scan



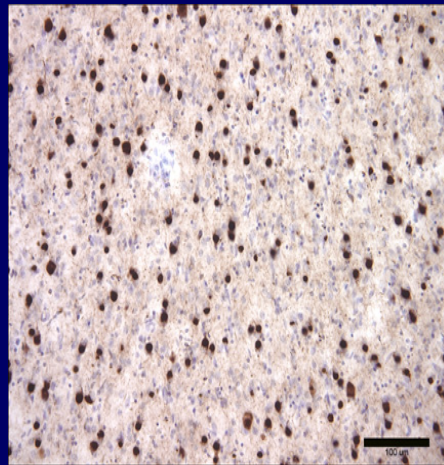
Atrophy only
frontal and
temporal areas
(until late
disease)

Often
asymmetrical

FRONTO-TEMPORAL DEMENTIAS (PICK SYNDROME)

Pathology

- *Pick's disease:*
Pick bodies on
microscopy



FTD

- Onset usually 50-60y.o. (20-80 y. range)
- Women affected more than men
- Positive FH in 1/3 – 1/2
- Cases w autosomal dom^{nt} inheritance
- Death occurs within 2-15 years (6-12 y)
- Rare type - chromosome-17 mutation
 - → tauopathy
 - presents with FTD *and*
 - parkinsonian symptoms

FTD

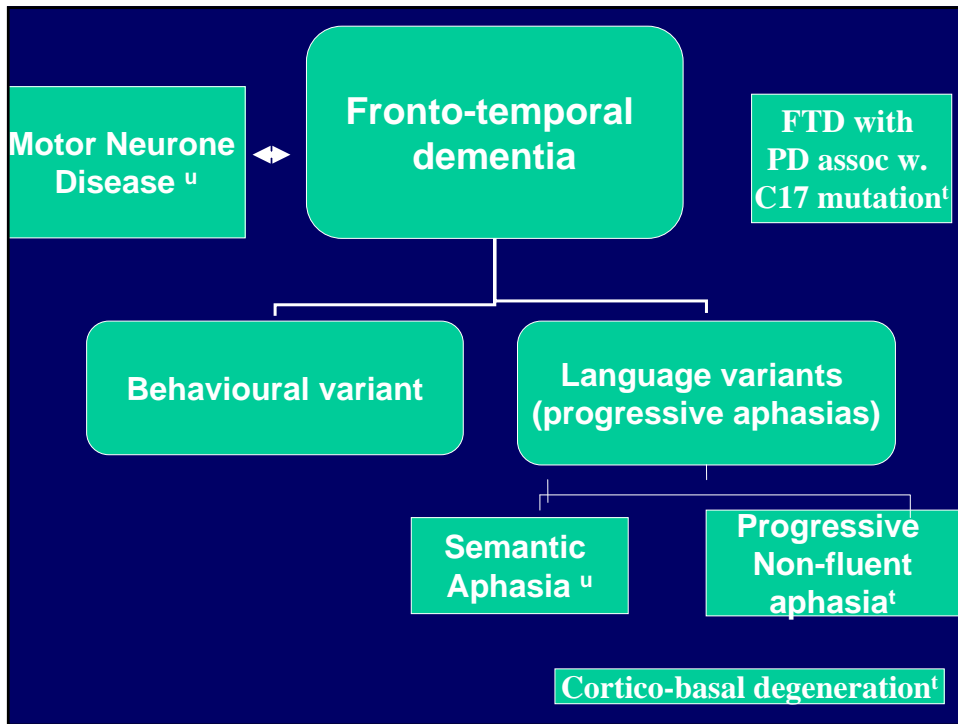
- Preservation of memory until late
- Early, prominent personality changes
- Apathy
- Irritability
- Jocularly and euphoria
- Loss of tact and concern
- Impaired judgement and insight
- Word finding difficulties; repetitive
- Hyperorality, hypersexuality

FTD – clinical features

- Compulsive behaviours
 - Repetitive acts, verbal or motor stereotypies
 - Collecting, hoarding
 - Rituals, superstitious acts

Fronto-temporal dementias (Pick syndrome/complex)

- *Language* abnormalities, including word finding difficulties, circumlocution, tendency to repeat anecdotes monotonously (Gramophone syndrome)
- Features of the *Kluver-Bucy* syndrome (emotional blunting, hyperorality, hypersexuality, etc.)



Progressive non-fluent aphasia (PNA or PPRA)

- Verbal expression ↓, anomia, shortened phrase length
- Speech, reading, repetition are hesitant, broken, dysarthric and effortful
- Phonemic paraphasia, esp on repetition
- Memory, behaviour = normal initially
- Atrophy left frontotemporal lobe, asymmetric

Semantic dementia

- Naming↓; comprehension ↓
- Fluent, empty speech
- Semantic paraphasia
- Read, repeat, write – normal
- Semantic knowledge ↓
- Episodic memory – normal or slightly ↓
- Bilateral atrophy of anterior temporal neocortex, esp. inferior and middle temporal gyri
- Ubiquitin +ve, tau -ve inclusions in some

Posterior Cortical Atrophy

- Insidious progressive visuo-cognitive syndrome associated with atrophy of occipital and occipito-parietal regions
- Complex visual disturbances including Balint's syndrome, visual agnosia, constructional disturbances
- Memory, language maintained till later

Infectious agents and dementia

- HIV
- Syphilis
- CJD
- Herpes
- SSPE
- Tuberculosis
- Fungal

Creutzfeldt-Jakob Disease

- 1/million/year; rapid subcortical dem.
- Bovine spongiform encephalopathy
- Iatrogenic CJD – corneal grafts, HCG, depth e-
- Onset 60s/70s; death <1 year
- 15% familial CJD, auto dom, C20, earlier onset
- Periodic EEG, myoclonic jerks
- 14-3-3 protein in CSF

Investigations

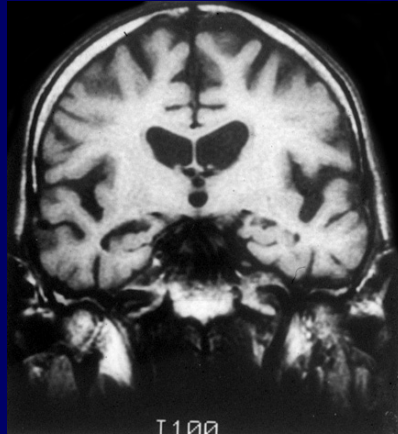
- Routine
- Specific for AD

Assessment: Routine investigations

- FBC, ESR
- Clinical chemistry *including calcium*
- Thyroid function tests
- B12, folate
- CT scan of brain (*without contrast*)
- Fasting BSL, Lipids, Homocysteine

Assessment: Elective Ix

- ECG
- CXR
- EEG
- micro-urine
- fasting glucose
- serology for β , AIDS
- neuropsychological assessment
- MRI
- PET scan



Biomarkers for early detection and Rx monitoring of AD¹

- The CSF is in direct contact with the extra-cellular space of the brain and reflects biochemical changes in the brain
- CSF biomarkers in AD²
 - Total Tau protein \uparrow
 - Phosphorylated Tau protein \uparrow
 - β amyloid (42 amino acid form) \downarrow

1. Blennow K, Neurodegenerative Diseases Discussion group 30/01/06
2. Sunderland T et al, JAMA 2003

Biomarkers for early detection and Rx monitoring of AD cont.¹

- The concentration of tau protein in the CSF reflects the intensity of neuronal degeneration in chronic neurodegenerative diseases
- Decreased CSF β amyloid protein may be due to deposition of β amyloid in plaques

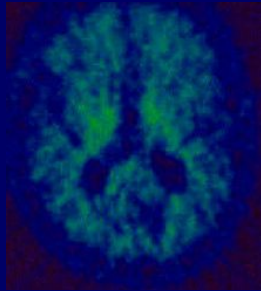
1. Blennow K, Hampel H, Lancet Neurology 2004

Biomarkers for AD

- CSF concentration of phosphorylated tau protein reflects the phosphorylated state of tau and thus the formation of tangles in AD
- Blood levels of β amyloid not reliable, though ratio of β 40 to β 42 better

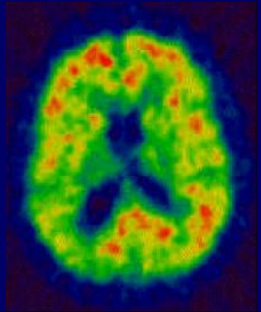
Neuroimaging biomarkers

Normal
PET



- PET imaging of amyloid plaques (PIB)

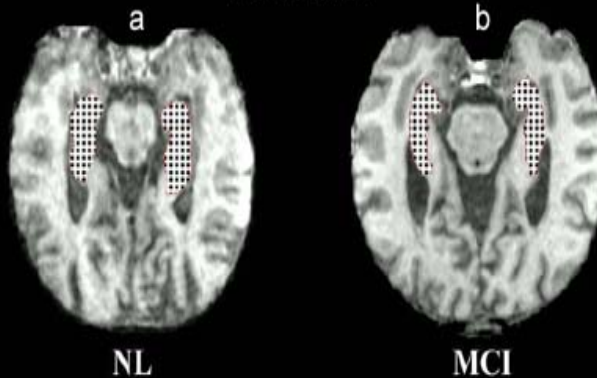
PET
in AD



Neuroimaging biomarkers Hippocampal atrophy (serial MRIs)

Hippocampal Atrophy

75 Years



M.J. de Leon, et. al. Neurobiology of Aging 1997, 18, 1-11

Use of biomarkers in AD^{1,2}

- To predict which MCI pts will progress to AD¹
- To monitor progress of MCI → AD (w. MRI/PET)¹
- To monitor biochemical effects of new AD drugs
- In differential diagnosis of type of dementia, esp. phosphorylated tau ¹
- To differentiate incipient AD, depression and alcohol related cognitive dysfunction ¹
- Use in discriminating normal elderly from those with MCI has not yet been studied ²

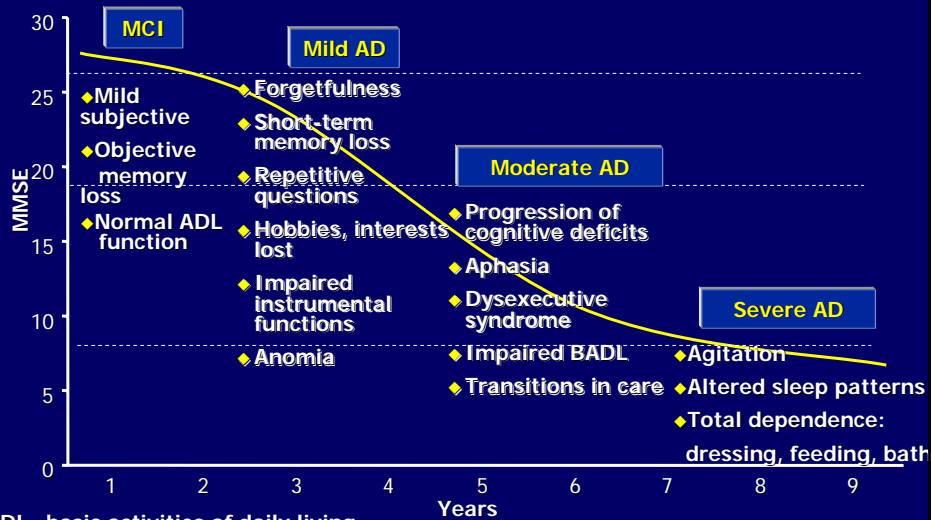
¹ Blennow K, Hampel H, Lancet Neurology 2004

² De Leon M, Neurodegenerative Diseases Discussion group 30/01/06

Natural History/ Prognosis

- From onset of Sx v from diagnosis?
- Mortality depends on age of onset
- 4-10 years quoted
- Brought forward time may be more useful
- AD quicker than VaD??
- FTD, DLB quicker than AD
- Extrapolate – previous rate predicts future?

Symptom Progression in AD



BADL=basic activities of daily living.

Modified from Feldman et al. *Clinical Diagnosis and Management of Alzheimer's Disease*. 1st ed. 1998.

Case History: Mr A

- 67yo M.
- H/O memory disturbance 4-5 yrs, gradually progressive
- Difficulty remembering recent events, difficulty with calculations, reading maps and word finding difficulty.
- Associated gait disturbance/ speech disturbance and sporadic episode of incontinence
- **Write down your diagnostic thoughts**

Past History

- Recent h/o depression & anxiety now treated with citalopram → +ve effects
- No previous psych Hx
- History of tonsillectomy in teens
- History of head injury in MVA in 1968, sustained fractured base of skull, no neurological sequelae.

Family history

- History of AD in father (?) onset in early 40s.
- Grandmother and paternal uncle both committed suicide
- Parents both dead. Sibs OK

Social & Personal History

- Born and raised in Bowral
- Elder of two siblings
- Bachelor Degree in Town Planning
- Senior Public Servant, retired 2002
- Remarried. Three children from 1st m
- Superannuation, financially independent
- Own house, Sydney

Informant Hx (Wife)

- 5 yr h/o stressful events and cognitive decline
- most notable re speech, use of numbers and telling time.
- more withdrawn because of these difficulties
- Significant improvement after Cipramil
- Independent in his ADLs and IADL s.
- No structured routine, hobbies or exercise program

Mental State

- Mood anxious.
- Affect, restricted.
- Delayed reaction time,
- Poverty of content of speech, non-verbal means of communication, word finding difficulties.

Physical Examination

- Pulse: 70 BP: 140/80 Bruits: Nil
CVS, Respiration, GIT: NAD

Neurological Abnormalities:

- Left eye – cataract.
- Tone/Power/Reflexes – normal.
- Sensory system – normal.
- Cerebellum – dysdiadochokinesia, (+) heel knee test?
- Positive palmo-mental reflex

- **MMSE = 21/30**
- **Hamilton Rating Scale for Depression (HRSD-21) = 8/64**

Neuropsychology

- **Speech: word finding difficulties, phonemic and semantic paraphasias.**
- **Fatuous, mildly disinhibited, poor insight into his current level of cognitive function.**
- **Executive dysfunction, slowed information processing and variable attention and working memory capacity**
- **Memory: encoding and retrieval difficulties; storage relatively preserved**

Neuropsychology ^{ctd}

- **Language: deficient naming and poor reading ability of irregular words (eg 'yacht')**
- **Intact ability in areas of basic semantic knowledge, comprehension, repetition and reading of regular words.**
- **General orientation, praxis and right-left orientation intact**
- **In summary, marked executive, attentional and expressive language dysfunction as well as slowed information processing**

Investigations

- **FBC; clinical chemistry; thyroid function; vitamin B12 level; folic acid level; CXR; ECG and MSU all normal.**
- **MRI brain scan (1/6/2006):**
 - **Ventriculomegaly**
 - **Few deep white matter hyperintensities around ventricle**

Differential Dx?

Differential Dx

- NPH
- FTD
- VaD ?
- Atypical AD ??
- Infectious cause ???

NPH

- **Dementia – frontal-subcortical**
- **Ataxia**
- **Incontinence**

- **Ventriculomegaly out of proportion to sulcal atrophy**
- **PH of HI with # base of skull**

Next steps

- **MRI flow studies**
- **CSF tap – temporary improvement**
- **CSF drainage – over 3 days; better at first and then no further improvement or slipped back**

Recommendations

- VDRL/HIV screen
- OT referral
- 2nd opinion by neurosurgeon
- Repeat MRI scan
- Cease driving
- Alzheimer's Australia
- Liaise with your local GP
- An extended family discussion

Questions

- [//adfoap.med.unsw.edu.au](http://adfoap.med.unsw.edu.au)
- www.alzheimers.org.au
- www.alz.co.uk
- h.brodaty@unsw.edu.au
- Mendez MF, Cummings JL
Dementia. A Clinical Approach.
Butterworth/Heinemann. 3rd Ed 2003