National Neuroscience Institute
SingHealth

Biomarkers in the Diagnosis of Dementia

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8TH MEDICINE REVIEW COURSE
23 – 24 JULY 2016
AUDITORIUM, THE ACADEMIA

Outline

- Review on diagnostic criteria for Alzheimer's disease (AD)
- Current biomarkers on AD
- Case scenarios

Alzheimer's Disease Diagnostic Criteria

- The diagnosis of dementia due to AD: Recommendations from the National Institute of Aging – Alzheimer's Association workgroups on diagnostic guidelines for AD
  - Alzheimer's & Dementia: The journal of the Alzheimer's association 2011;7(3):263-269

Alzheimer's Disease Diagnostic Criteria

- Core clinical criteria
  - Interfere with the ability to function at work or at usual activities; and
  - Represent a decline from previous levels of functioning and performing; and
  - Are not explained by delirium or major psychiatric disorder;
  - Cognitive impairment is detected and diagnosed through a combination of (1) **history**-taking from the patient and a knowledgeable informant and (2) an objective cognitive **assessment**, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
  - The cognitive or behavioral impairment involves a minimum of two of the following domains:
    - Impaired ability to acquire and remember new information
    - Impaired reasoning and handling of complex tasks, poor judgment
    - Impaired visuospatial abilities
    - Impaired language functions (speaking, reading, writing)
    - Changes in personality, behavior, or comportment

Alzheimer's Disease Diagnostic Criteria

- Probable AD dementia
- Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics: A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
  B. Clear-cut history of worsening of cognition by report or observation; and
  C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
  - Amnestic presentation
  - Non-Amnestic presentation
- The diagnosis of probable AD dementia should not be applied when there is evidence of :
  - concomitant cerebrovascular disease
  - Core features of DLB
  - FTD
  - PPA
  - Others

Alzheimer's Disease Diagnostic Criteria

- Probable AD dementia with evidence of the AD pathophysiological process
  - Biomarkers of brain **amyloid-beta** (Ab) protein deposition are low CSF Ab42 and positive PET amyloid imaging
  - Biomarkers of downstream neuronal degeneration or injury
    - elevated CSF **tau**, both total tau and phosphorylated tau (p-tau)
    - decreased 18fluorodeoxyglucose (**FDG**) uptake on **PET** in temporo– parietal cortex
    - disproportionate atrophy on **structural magnetic resonance** imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex

Table 1
AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

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Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence	Intermediate	Unavailable or indeterminate	Positive
of AD pathophysiological	Intermediate	Positive	Unavailable or indeterminate
process	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

CSF

- beta-amyloid – soluble abeta42 monomer
  - The beginning of the preclinical state, likely the first positive marker
    - Jack et al. Neurology 2013
- Tau: down stream of neuronal injury
  - Phosphorylated and total tau: non-specific, more meaningful and correlated to AD if amyloid +ve
- Presence of both significant increases the specificity of diagnosis of AD, both clinical and asymptomatic
    - Dubois et al. 2016

Amyloid PET

- High specificity for AD plaques
- CSF amyloid VS PET amyloid?
  - Meta-analysis did not find significant discrepancies in estimation of prevalance of amyloid positivity across the lifespan
    - Jansen et al JAMA 2015
  - Reasonable to conclude amyloid positivity can be established using either one
    - Dubois et al. 2016

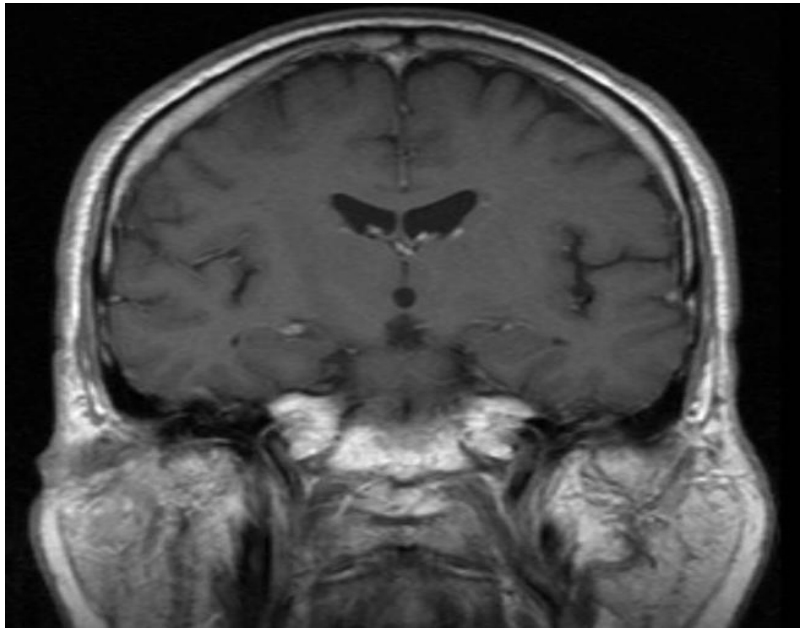
Other imaging modalities

- FDG-PET Brain
  - sensitivity, specificity, and diagnostic accuracy of bilateral temporo-parietal hypometabolism being associated with AD were 93%, 63%, and 82%, respectively
    - » Hoffman et al. J Nucl Med. 2000 Nov;41(11):1920-8
- Functional MRI brain – connectivity markers
  - Defaulted mode network (DMN) resting state, task-induced deactivation

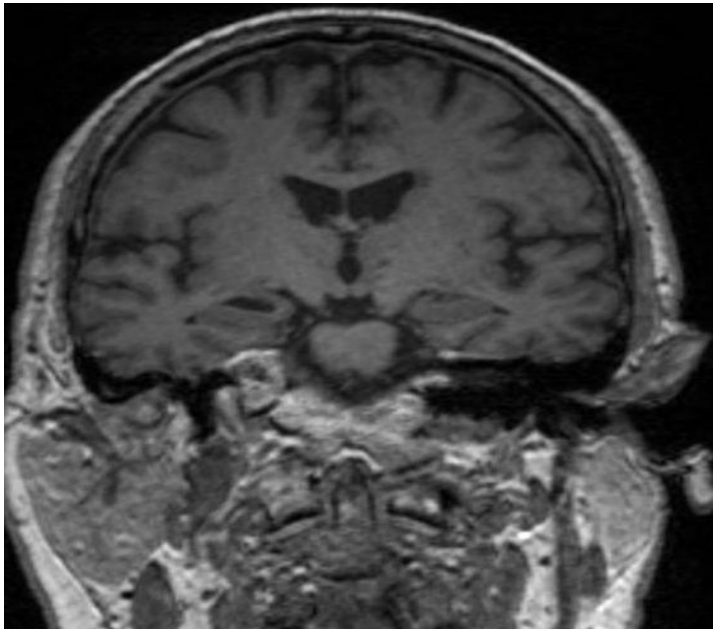
Case 1

- 72 years man, right handed, multilingual, secondary education
- Started complaining forgetful since age 60 years old
- Most forgetful related to distractibility and attention to begin with
- Gradually unable to keep track on work, forget recent event details, and losing less dominant dialects/langauge at age 70
- Repeated assessment done since presentation

Case 1

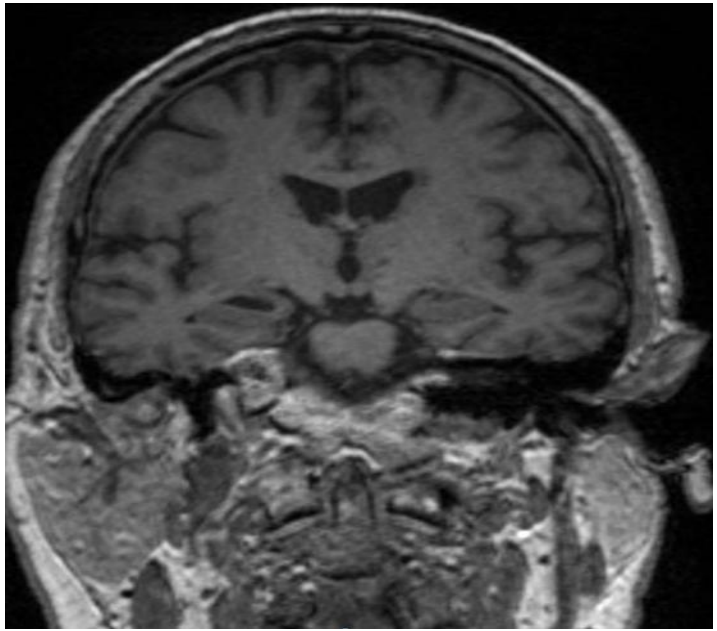


Age 60

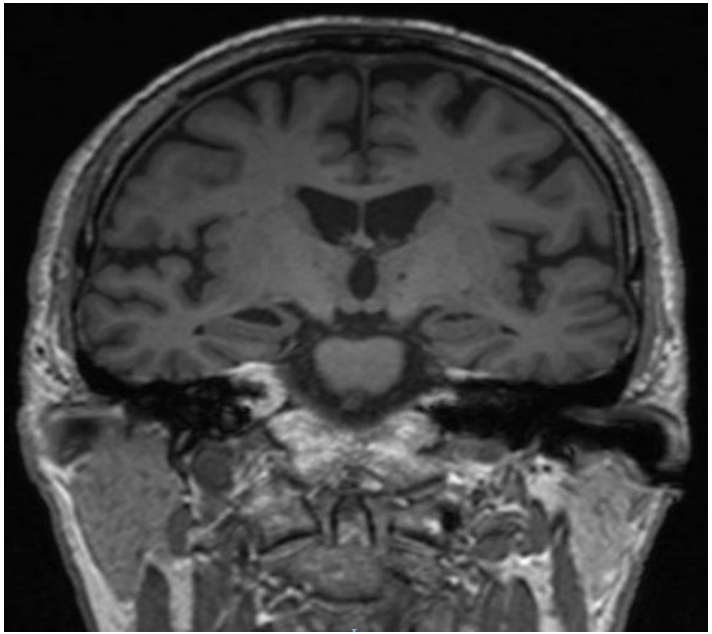


Age 66

Case 1



Age 66



Age 70

Case 1

- Diagnosis: Alzheimer’s disease
- Biomarker: neuronal injury – structural MRI evidence of hippocampal atrophy

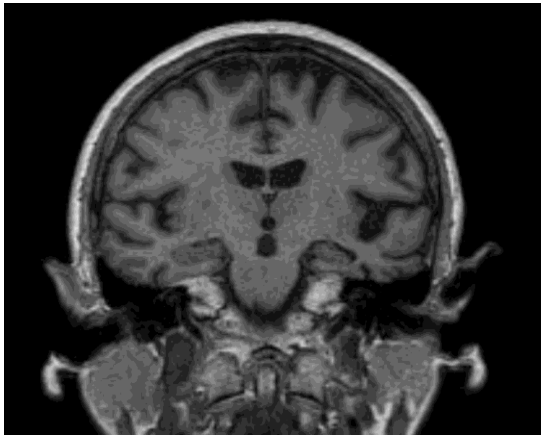
Case 2

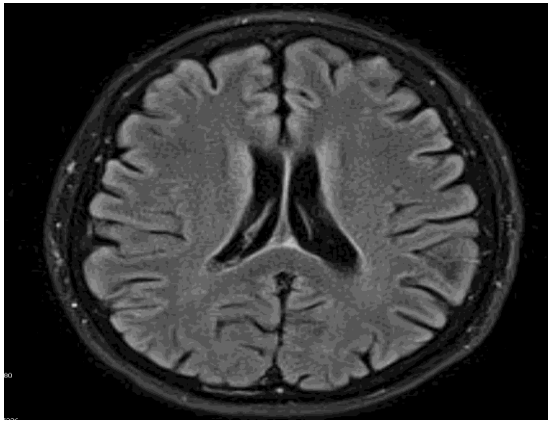
- 67year old lady
- Bilingual, mostly in mandarin
- First seen 3 years ago
- Word finding difficulty for 2 years
- Progressive decline in her ability to express herself and mild forgetfulness over the past few years
- Has difficulties elaborating on details during a conversation and display word finding difficulties.
- Very occasional lapses of memory such as forget to add in certain ingredients during cooking, forgetting certain recipes, misplacing her personal belongings

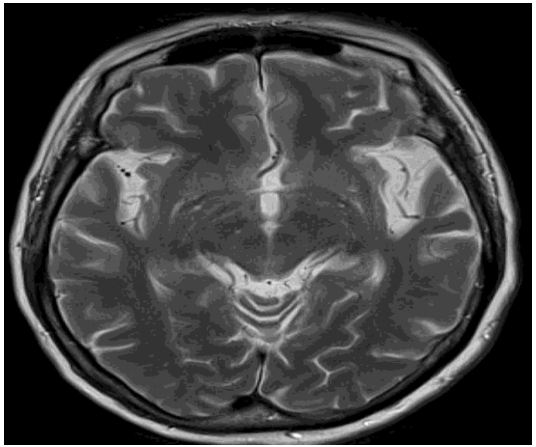
Case 2

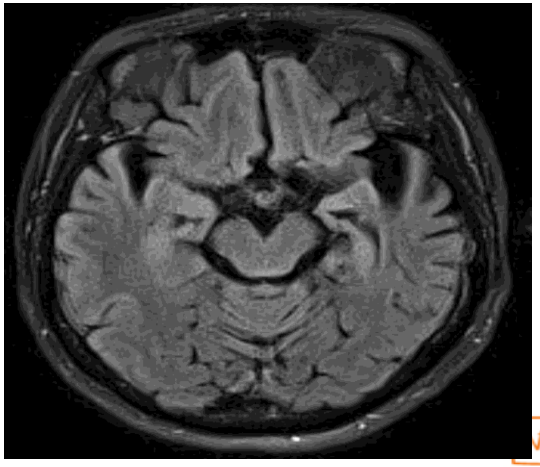
- Mood: not depressed
- No behavioral complaints
- No delusion, no hallucination
- Sleep: not affected, no daytime somnolence
- Otherwise, functionally independent (can manage her appointments and finances)
- Still socializes with friends, cooks, drives and play mahjong during her free time

- MMSE: 26
- B12/folate normal
- VDRL: NR
- T4/TSH: normal
- EEG (14/1/2010)= normal
- MRI (11/11/2009)brain (non contrast): normal









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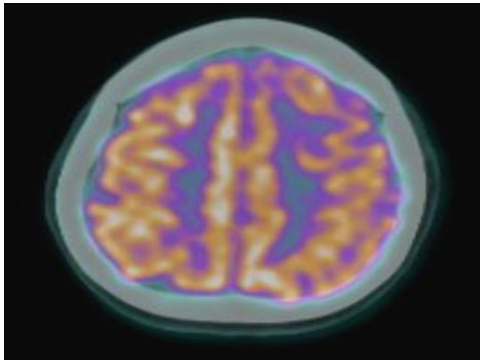
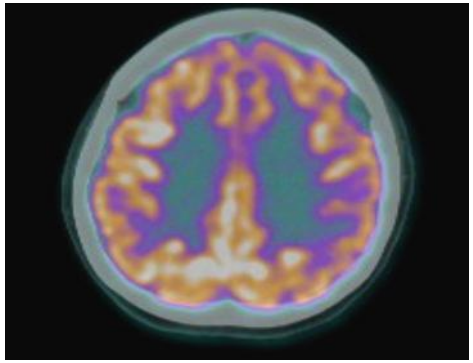
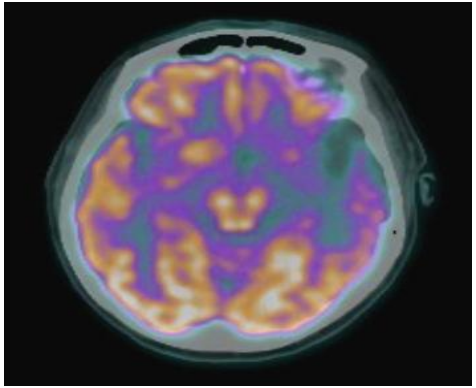
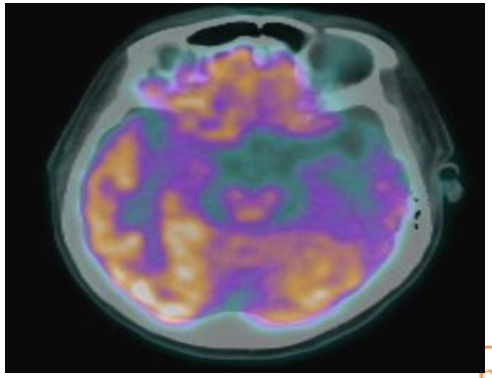
FDG PET









Case 2

- CSF biochemistry normal, CSF culture and VDRL: negative
- CSF amyloid ß42 tau: low
- CSF phosphorylated tau: increased

Diagnosis

- Primary progressive aphasia
- Biomarker: Alzheimer's Disease pathology, CSF evidence of amyloid and tau

Case 3

- 58 years lady, right handed.
- Started with forgetful and repeated fainting since early 50
- Presented with LOC and ‘funny turn’, with EEG capture non-epileptic event
- Other investigations unremarkable
- Once diagnosed and treated as conversion disorder

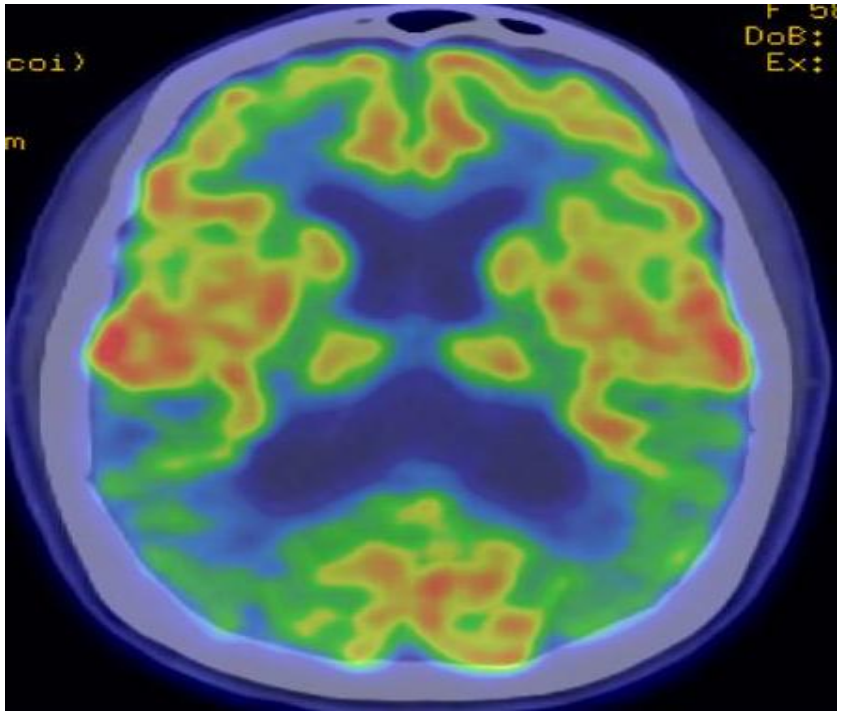
Case 3

- Family noted behavior continued to worsened
- Significant inconsistent history
- Family noted patient is so confused can't perform many things herself, example, she could find the light switch at home.
- Patient quitted job 2 years ago, due to health reason, but claim not because couldn't perform as her role in coordinator for customer service.
- Sister claimed she is so confused, couldn’t do shopping, she has to accompany her for shopping, but patient has her own bank account and still handling herself
- Patient also able to go out herself, able to walk 15min to friend or niece house, but couldn’t go to neighborhood market and perform purchase.
- Neuropsychological test showed profound impaired on all domains, detailed analysis showed significant ‘near missed’ responses suggestive of Ganser phenomenan.
- Combined management with psychiatry colleague for non-specific and ‘dissociative’ symptoms

Case 3

- Family claimed progressively worsened over 2 years duration, however clinic assessment still showed inconsistent behavior
- New investigation ordered.

Case 3



- Profound posterior cingulate cortex and bilateral temporo-parietal hypometabolism, and moderate frontal hypometabolism

Case 3

- Frontal variant Alzheimer's disease
- Biomarker: neuronal injury – FEG-PET brain

Thank you

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PATIENTS. AT THE HEART OF ALL WE DO.