Biomarkers in the Diagnosis of Dementia

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8TH MEDICINE REVIEW COURSE
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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>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
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<tbody>
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<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
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<td>With three levels of evidence of AD pathophysiological process</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
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<td>High but does not rule out second etiology</td>
<td>Positive</td>
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<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
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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 prevalence 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

• 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/language 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

- 67-year-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
Case 2

- CSF biochemistry normal, CSF culture and VDRL: negative
- CSF amyloid β42 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