Atypical presentation of Alzheimer’s disease

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Appropriate Use Criteria for Amyloid PET

(1) Patients with persistent or progressive unexplained mild cognitive impairment (MCI);

(2) Patients satisfying core clinical criteria for possible AD, because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation;

(3) Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age).

Impact on diagnosis

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carswell, et al</td>
<td>0.313</td>
<td>0.228</td>
<td>0.412</td>
<td>-3.581</td>
<td>0.000</td>
<td>8.00</td>
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<tr>
<td>Ceccaldi, et al</td>
<td>0.668</td>
<td>0.601</td>
<td>0.729</td>
<td>4.722</td>
<td>0.000</td>
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<tr>
<td>Weidman, et al</td>
<td>0.688</td>
<td>0.433</td>
<td>0.864</td>
<td>1.462</td>
<td>0.144</td>
<td>6.23</td>
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<tr>
<td>Zwan, et al</td>
<td>0.194</td>
<td>0.146</td>
<td>0.253</td>
<td>-8.174</td>
<td>0.000</td>
<td>8.18</td>
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<tr>
<td>Apostolova, et al</td>
<td>0.308</td>
<td>0.198</td>
<td>0.445</td>
<td>-2.699</td>
<td>0.007</td>
<td>7.63</td>
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<tr>
<td>Bensaidane, et al</td>
<td>0.643</td>
<td>0.454</td>
<td>0.786</td>
<td>1.490</td>
<td>0.136</td>
<td>7.11</td>
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<tr>
<td>Boccadi, et al</td>
<td>0.272</td>
<td>0.218</td>
<td>0.333</td>
<td>-6.617</td>
<td>0.000</td>
<td>8.26</td>
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<tr>
<td>Grundman, et al</td>
<td>0.546</td>
<td>0.481</td>
<td>0.609</td>
<td>1.386</td>
<td>0.166</td>
<td>8.31</td>
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<tr>
<td>Shea, et al</td>
<td>0.442</td>
<td>0.302</td>
<td>0.591</td>
<td>-0.761</td>
<td>0.447</td>
<td>7.59</td>
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<tr>
<td>Mitsis, et al</td>
<td>0.333</td>
<td>0.190</td>
<td>0.516</td>
<td>-1.790</td>
<td>0.074</td>
<td>7.15</td>
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<tr>
<td>Sanchez-Juan, et al</td>
<td>0.093</td>
<td>0.055</td>
<td>0.153</td>
<td>-7.827</td>
<td>0.000</td>
<td>7.68</td>
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<tr>
<td>Ossenkopolle, et al</td>
<td>0.188</td>
<td>0.134</td>
<td>0.258</td>
<td>-7.088</td>
<td>0.000</td>
<td>8.06</td>
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<tr>
<td>Frederiksen, et al</td>
<td>0.228</td>
<td>0.137</td>
<td>0.354</td>
<td>-3.862</td>
<td>0.000</td>
<td>7.55</td>
</tr>
</tbody>
</table>

Impact on management

Data on the usage of amyloid imaging in QMH memory clinic

- We reviewed 102 subjects with dementia who received PET with or without (11)C-PIB between January 2007 and December 2014.

- Diagnosis was subsequently changed in 36.3% of subjects following PET with or without (11)C-PIB.

- If counting only those with (11)C-PIB, 25.4% of subjects changed diagnosis.

- The agreement between the initial and final post-imaging dementia subtype diagnosis was only fair, with a Cohen's kappa of 0.25 (95% confidence interval, 0.05-0.45).

History

- M/61
- Social drinker, non-smoker.
- Married with no children.
- University level of education.
- Need to drive car.
- Occupation: accountant, worked as a treasurer of an international organization before he retired 7 years ago (~54 years old).
Family History

• **Mother:** Parkinson’s disease diagnosed in her 80s.
• **Father:** Died of ischemic heart disease.
• 7 siblings.
  • No family history of neurodegenerative disease.
  • No family history of psychiatric illness.

• Referred from TWH clinic because of *deterioration in reading and writing.*
History of present illness

• Informant: wife.

• **7 years ago** (around the time of retirement).
  – Difficulty in writing Chinese (including his name) and reading Chinese.

• **5-7 years ago.**
  – Difficulties in reading newspaper and emails.
  – Problem in spelling names in English.
  – Speak slowly but fluently.
History of present illness

- **Significant impairment in recognition**
  - Failure to recognize “water” but able to describe that is transparent.
  - Unable to recognize the fork (need the wife to give him the fork).
  - Unable to recognize faces (causing some social embarrassment).
  - Unable to recognize bank notes.
  - Unable to name colors (while buying clothes).
History of present illness

• **2 years ago (memory impairment):**
  – Repeated questioning.
  – Misplacement of important items (e.g. wallets).
  – Missed appointments.
  – Forget to turn off the gas stove.

• No confabulation.

• **Judgment problem.**
  – Engagement in high risk investment in Mainland China.
History of present illness

- **Change in personality.**
  - Verbally aggressive and physically aggressive to his wife even for trivial matters.
  - Marital conflict.

- No delusion or hallucination.
- No features of depression.
- No over-eating.
- No evidence of obsession or compulsion or stereotyped behavior.
- No evidence of social dis-inhibition.
History of present illness

• No developmental language impairment.
• No history of encephalitis.
• No family history of early onset dementia.
• No history of usage of illicit drugs.
• Wife as the only sexual partner.
• No evidence of increase in sexual desire.
Physical examination

- BP 126/72 mmHg, P 73 bpm.
- Right handed.
- No obvious hearing impairment.
- Visual acuity both eyes of 20/70 (eyeglasses on).
- Confrontation test: (Rt) homonymous hemianopia.
- Fundoscopy – normal.
- No parkinsonism signs.
- No focal neurological deficit
- No primitive reflex
- Cardiovascular, respiratory and abdominal examination – normal.
Visual field perimetry testing

Left eye

Right eye
Mini-Mental State Examinations (MMSE) = 29/30
# Neuropsychological profile

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Score of our patient</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cognitive Functioning (CDRS)</td>
<td>135/144</td>
<td>Abnormal if ≤112</td>
</tr>
<tr>
<td>Attention (CDRS)</td>
<td>35/37</td>
<td>Abnormal if ≤ 29</td>
</tr>
<tr>
<td>Memory (CDRS)</td>
<td>22/25</td>
<td>Abnormal if ≤ 18</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>Moderately to severely impaired</td>
<td>--</td>
</tr>
</tbody>
</table>
| Category fluency                            | **Animal (13 in one min)**  
Transportation (14 in one min) | Normal > 15  
Normal ≥ 10                           |
| Visual Perception and construction (CDRS)   | 5/6                  | Abnormal if ≤ 3                  |
| Executive function (CDRS)                   | 36/39                | Abnormal if ≤ 28                 |

CDRS = Chinese Dementia Rating Scale

Test performed on 25/04/2011 by Dr. Wilson Tsui, Clinical psychologist, QMH
Investigations

- Normal complete blood picture.
- Normal liver and renal biochemistries.
- Vitamin B12 and folate – normal.
- Thyroid function test – normal.
- Venereal Disease Research Laboratory: non-reactive.
Magnetic Resonance Imaging (MRI)

More prominent left parietal lobe atrophy
Two major diagnostic categories

• Frontotemporal dementia
  – Primary progressive aphasia (PPA).
    – Semantic dementia.

• Atypical presentation of Alzheimer’s disease.
  – Posterior cortical atrophy (PCA).
FDG-PET brain of our patient

Bilateral hypometabolism over the temporoparietal lobe

PiB imaging of our patient
Progress of our patient

• Diagnosed to have posterior cortical atrophy (PCA) – Alzheimer’s pathology.

• **Treatment:**
  – Cholinesterase inhibitor: Rivastigmine patch.
  – Memantine.

• Advised against driving.
Latest progress of the patient

• Currently 68 years old.

• Now on Crenezumab clinical trial.

• Abbreviated Mental Test score remained at 10.

• Main problem still with visual agnosia and language:
  – Mixing up the male/ female toilet logo.
  – Deterioration in writing own Chinese name.
  – Further impairment in Chinese and English reading or comprehension.
Atypical AD

Progressive Aphasia (56%)*
Mimicking Frontotemporal dementia (6%)*
Mimicking corticobasal degeneration (18%)*
Posterior cortical atrophy (20.6%)*

PNFA
Logopenic aphasia
Semantic dementia

1. Occipitotemporal syndrome
   • Alexia (inability to read).
   • Visual agnosia.
   • Prosopagnosia (problem with facial perception).

2. Biparietal variants
3. Visual variants

* (% total number = 34 patients with atypical AD

Another patient with PCA

- 68/F with history of hypertension.
- Education up to F.2 level.
- CC= prosopagnosia (for 3 years) and anterograde episodic memory impairment (1 year).
- BPSD – dysphoria, disinhibition, agitation, irritability, visual hallucination.
- P/E: blindness (cannot count fingers or detect hand movement).
- Differentials = PCA vs. FTD
F18-Flutametamol scan
Symptoms of posterior cortical atrophy

Is it neurodegenerative?
1. Insidious onset
2. Gradual progression
3. No other cause (e.g. tumor, vascular disease)

Is it preferentially posterior?
Fulfills PCA core clinical/cognitive features
+/- supportive evidence of predominant occipital, parietal and/or occipitotemporal atrophy/dysfunction on brain imaging

Classification Level 1:

Does the patient also meet core criteria for another neurodegenerative syndrome?

Classification Level 2:

Are biomarkers available and conclusive?
[solid ovals: existing biomarkers; dashed ovals: biomarkers pending]

Classification Level 3:

PCA-AD  PCA-LBD  PCA-CBD  PCA-Prion  Other classifiers tbc

Learning points

• Patients with Alzheimer’s disease can present atypically with visual symptoms.

• Appropriate usage of amyloid imaging can help to diagnose atypical Alzheimer’s disease.