Young onset dementia: the challenge of making an earlier diagnosis

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DSIDC Annual Conference Dublin Castle November 20th 2014
## Arguments for & against making an early diagnosis in young-onset patients

**For**
- Identifies treatable and reversible causes
- Provides clarity for patient & family
- Facilitates advance planning
- Allows treatment to be introduced
- Potential genetic testing for at-risk relatives

**Against**
- Nothing can be done
- No effective treatments
- No dedicated services
- Low prevalence & not a priority from a population health point of view
- High investigation costs better used to fund care
Interventions - what works for people with dementia?

- **Exercise** programmes improve cognitive and functional outcomes for people with dementia
- **Cognitive stimulation** improves cognition and quality of life in people with mild to moderate dementia
- Integrating **functional movement** and **mindful body awareness** may improve dementia patients physical and cognitive functions (and decrease caregiver burden)
- Goal oriented **cognitive rehabilitation** may work in early stage dementia
Mercer’s Memory & Brain Health Clinic

- National referral base
- 500 assessments per year
- Approximately 1/3 of these assessments are in people under 65
- Memory and behaviour focus rather than neurology/movement disorders
- Complex cases of decline in individuals with long standing functional [mood/psychotic] illness
Mercer’s Memory Clinic Assessment

- History and physical (neurological)
- Collateral history
- Blood screen
- Neuropsychological testing
- Neuroimaging
- CSF analysis
- Multidisciplinary consensus
- Disclosure & advice

No case management or follow-up once diagnosis disclosed
Memory Clinic: all patients seen 2013 (n=500)
Memory Clinic: comparison of young & late onset patients 2013

Less AD, less mixed, less MCI, more FTD, SMC, functional & unsure diagnoses in young onset
Unsure cases were mix of FTD phenocopies, possible MND/FTD, alcohol, epilepsy, possible TEA
Relatively more treatable or reversible causes

• ~10% may have treatable or reversible aspects
  - Transient epileptic amnesia (TEA)
  - Obstructive sleep apnoea (OSA)
  - Autoimmune/paraneoplastic dementia
  - CNS vascular disease

• Functional disorders & worried well constitute a significant number of referrals
Delay & difficulty in making a diagnosis compared to older subjects

- Time from first symptoms to dementia ~2.2-4.4 years compared to 1 year for late-onset cases*
- Multiple reasons:
  - Poor clinical pathways
  - Atypical and complex presentations
  - Misdiagnosis as functional illness
  - Neurodegeneration not considered as too young
  - Delay in accessing assessment and investigations

It's harder to make a diagnosis in younger patients. Needs a systematic approach & specialised assessment

Villiet et al. 2014*
Young-onset dementia presentations are more complex

• Alzheimer’s disease can present in an atypical fashion more often in younger people

• Fronto-temporal dementia is more common as a cause of young onset dementia with language, motor and in addition to behavioural presentations & can be difficult to distinguish from atypical AD

• Behavioural phenocopies of bvFTD or slowly progressive FTLD can make for a ‘tricky’ diagnosis
Young-onset Alzheimer’s disease

• 1/3 young onset AD have non-memory presentations compared to 5% of late-onset AD

• Non-memory presentations can include posterior cortical atrophy (visual variant) [gets an eye exam], primary progressive aphasia [is it a stroke?], dysexecutive features [must be psychiatric]
FTD

• Depression, emotional & personality changes can occur as early features of FTD but functional disorders can also mimic FTD

• bvFTD phenocopy syndrome: is it related to mood disorder or autistic spectrum disorder or really a very slow burn FTLD?
How to improve accuracy of clinical diagnosis in young-onset cases?

- Systematic approach
- Multidisciplinary and specialised assessment clinic
- Biomarkers use
## Systematic stepped up approach to assessment

### Step 1
- History, collateral, physical & neurological
- Routine dementia blood tests
- Neuropsychological testing
- Neuroimaging (CT or MRI) to exclude space occupying lesion, assess focal atrophy, vascular disease
- Connective tissue screen if CNS vasculitis suspected

### Step 2
- More detailed neuropsychological testing
- DAT scan if DLB suspected
- Genetic testing if indicated
- Autoantibody screen if autoimmune disorders (limbic or Hashomoto’s)
- CSF for protein, cells, autoimmune/paraneoplastic antibody screen for RPD or if limbic encephalitis suspected

### Step 3
- PET-FDG if diagnosis unclear
- CSF for AD biomarkers
- Amyloid PET if available
Use of CSF (spinal fluid) biomarkers in making an earlier and more accurate diagnosis
Molecular biomarkers in spinal fluid
CSF $\text{A}\beta_{42}$ and tau as diagnostic biomarkers for Alzheimer's disease.

Combination of Amyloid-$\beta$ 42 and Tau in diagnosing Alzheimer's disease:

- Sensitivity: 93.5%
- Specificity: 82.7%

Published $\text{A}\beta_{42}$:
- Sensitivity: 70-100%
- Specificity: 40-90%

Published Tau:
- Sensitivity: 40-85%
- Specificity: 65-85%

*Clinical Chemistry* 2010 Feb;56(2):248-5
CSF levels $\text{A}\beta_{42}$ are fully changed 5 to 10 years before the onset of ‘symptomatic’ AD. Tau levels increase in clinical [pre-dementia] phase.
Recent changes NIA/AA diagnostic criteria dementia **due to AD**

There are 4 levels of certainty for dementia due to AD based on biomarkers

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Likelihood of AD</th>
<th>Biomarker Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>High likelihood</td>
<td>(+) amyloid-β biomarker <strong>AND</strong> (+) neuronal injury biomarker*</td>
</tr>
<tr>
<td>Dementia</td>
<td>Intermediate likelihood</td>
<td>(+) amyloid-β biomarker <strong>OR</strong> (+) neuronal injury biomarker*</td>
</tr>
<tr>
<td>Dementia</td>
<td>Uninformative situation</td>
<td>Biomarkers fall in ambiguous ranges, conflict, have not been obtained</td>
</tr>
<tr>
<td>Dementia</td>
<td>Unlikely due to AD</td>
<td>Demonstrated absence of AD-type molecular marker and possible presence of marker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>suggestive of non-AD disorder</td>
</tr>
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Dubois et al., Lancet Neurol., 2007
Recent changes NIA/AA diagnostic criteria MCI due to AD

2 types of MCI criteria:
• clinical settings – very similar to Petersen (modified) criteria
• research purposes MCI criteria plus biomarkers.

There are 4 levels of certainty for MCI due to AD based on biomarkers

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Clinical indications for use of CSF biomarkers

- Early onset neurodegeneration/dementia cases with clinical uncertainty
- Atypical presentation of neurodegeneration [PPA/PCA/dysexecutive]/dementia cases with clinical uncertainty
- Persistent, progressive or unexplained Mild Cognitive Impairment
- Informed by patient preference
Providing accurate and realistic pre-testing patient information

- Biomarkers may help improve confidence of diagnosis but also may be uninformative.
- CSF biomarker testing is not absolutely diagnostic on its own & must be considered together with clinical, neuropsychological & neuroimaging data.
Biomarkers in neurodegeneration in Ireland

- Growing awareness of the utility of biomarkers to support diagnosis

- Different centres have varied access to MRI / FDG-PET / CSF

- Varying attitudes [clinicians] to their utility

- Varying attitudes [patients & clinicians] to lumbar puncture procedure

- Lack of national standardised practice/guidelines – acquisition / interpretation and disclosure
Is FDG PET informative in diagnosis of memory clinic patients?

<table>
<thead>
<tr>
<th>Pre PET diagnosis</th>
<th>PET diagnosis</th>
<th>Post PET Diagnosis</th>
<th>Informative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI aetiology uncertain</td>
<td>No neurodegeneration</td>
<td>CI aetiology uncertain</td>
<td>N</td>
</tr>
<tr>
<td>PPA-AD</td>
<td>AD</td>
<td>PCA AD</td>
<td>Y</td>
</tr>
<tr>
<td>Atypical AD</td>
<td>No neurodegeneration</td>
<td>Possible AD</td>
<td>N</td>
</tr>
<tr>
<td>MCI ?AD</td>
<td>No neurodegeneration</td>
<td>MCI ? AD</td>
<td>N</td>
</tr>
<tr>
<td>AD</td>
<td>No neurodegeneration</td>
<td>Unclear</td>
<td>N</td>
</tr>
<tr>
<td>AD</td>
<td>Possible AD</td>
<td>MCI aetiology unceratin</td>
<td>N</td>
</tr>
<tr>
<td>FTD V atypical AD</td>
<td>Inconclusive</td>
<td>FTD V atypical AD</td>
<td>N</td>
</tr>
<tr>
<td>PPA-AD</td>
<td>Mild AD</td>
<td>Possible AD</td>
<td>Y</td>
</tr>
<tr>
<td>Query Neurodegenerative</td>
<td>No significant abnormality</td>
<td>MCI cause unspecified</td>
<td>Y</td>
</tr>
<tr>
<td>AD</td>
<td>Possible AD</td>
<td>MCI possible AD</td>
<td>Y</td>
</tr>
<tr>
<td>PPA-AD</td>
<td>AD</td>
<td>PPA AD</td>
<td>Y</td>
</tr>
<tr>
<td>PPA ?AD</td>
<td>No neurodegeneration</td>
<td>PPA ?AD</td>
<td>N</td>
</tr>
<tr>
<td>? Neurodegenerative</td>
<td>AD</td>
<td>naMCI</td>
<td>N</td>
</tr>
<tr>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>PPA-AD</td>
<td>AD</td>
<td>AD</td>
<td>Y</td>
</tr>
<tr>
<td>Atypical AD</td>
<td>AD</td>
<td>AD</td>
<td>Y</td>
</tr>
<tr>
<td>MCI PPA ?AD</td>
<td>FTD</td>
<td>Logopenic PPA; Possible AD</td>
<td>N</td>
</tr>
<tr>
<td>AD</td>
<td>FTD</td>
<td>AD</td>
<td>N</td>
</tr>
<tr>
<td>MCI ?AD</td>
<td>Possible AD</td>
<td>MCI ?AD</td>
<td>Y</td>
</tr>
<tr>
<td>?Neurodegenerative</td>
<td>AD</td>
<td>Probable AD</td>
<td>Y</td>
</tr>
</tbody>
</table>
## Biomarker testing informative in selected Memory Clinic patients

<table>
<thead>
<tr>
<th>Pre-test</th>
<th>Post-test</th>
<th>Informative Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>MCI due to AD-intermediate</td>
<td>Y</td>
</tr>
<tr>
<td>Probable AD</td>
<td>AD</td>
<td>Y</td>
</tr>
<tr>
<td>Non-amnestic MCI</td>
<td>MCI</td>
<td>Y</td>
</tr>
<tr>
<td>PPA</td>
<td>MCI</td>
<td>N</td>
</tr>
<tr>
<td>AD</td>
<td>AD</td>
<td>Y</td>
</tr>
<tr>
<td>Non-amnestic MCI</td>
<td>Non-amnestic MCI</td>
<td>Y</td>
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<tr>
<td>Possible AD</td>
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<td>Y</td>
</tr>
<tr>
<td>Atypical AD</td>
<td>Atypical AD</td>
<td>N</td>
</tr>
<tr>
<td>MCI</td>
<td>Atypical AD</td>
<td>Y</td>
</tr>
<tr>
<td>FTD/Atypical AD</td>
<td>FTD</td>
<td>Y</td>
</tr>
<tr>
<td>MCI/non AD pattern</td>
<td>AD</td>
<td>Y</td>
</tr>
<tr>
<td>MCI</td>
<td>MCI due to AD</td>
<td>Y</td>
</tr>
<tr>
<td>MCI ? AD</td>
<td>MCI</td>
<td>N</td>
</tr>
<tr>
<td>MCI ? AD</td>
<td>MCI</td>
<td>N</td>
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<tr>
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<tr>
<td>CBS</td>
<td>AD</td>
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Lumbar puncture in young onset patients

American Academy of Neurology & European Federation of Neurological Sciences recommend lumbar puncture in younger patients (<55 years) and rapidly progressive dementia.

Consensus that lumbar puncture for AD CSF biomarker analysis be considered as a routine clinical test in patients with early-onset dementia, at the prodromal stage or with atypical AD.

Ideal assessment and treatment service

- Regional Multidisciplinary Assessment Clinics involving psychiatrist, neurologist, geriatrician, nurse practitioner, neuropsychologist, social worker
- Access to neuropsychology, neuroimaging & CSF biomarkers for selected cases
- Case register with case management model
- Identification and access to age appropriate day care, respite and continuing care beds
- Create intervention programmes around life style modification, exercise, CR for people with MCI & early AD