Early Onset Dementia

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Dementing disorders

- Major public health concern
- Incidence increasing in tandem with the ageing population
  - 2001 = 24.3 millions ⇒ 2040 = 80 millions
  - 71% in developing countries

- Disease of older people +++

What about Early Onset Dementia?
Cognitive and functional impairment in individuals <65 years of age

• Further classification
  – Early Onset Dementia <65 years of age
  – Young Onset Dementia <45 years of age

Rossor et al 2010

From Schofield « Genetic contributions to Young Onset Dementia »
More than 100 years ago...

• 1907: Aloïs ALZHEIMER gave a lecture on the 1st case
Augusta D 51 years

⇒ Presenile dementia

• Neuritic Plaques & Neurofibrillary Tangles

In February 1871, the great naturalist Charles Darwin received a letter from Dr. James-Crichton Browne, who was serving as Director of the largest lunatic asylum in England. Darwin had been introduced to Crichton-Browne 2 years earlier by Henry Maudsley, who believed that the young psychiatrist could provide Darwin with clinical examples of extreme emotional expression, to aid him in preparing to write *Expression of the Emotions in Man and Animals* (1872). This particular letter from Crichton-Browne contained the first and only reference to “premature dotage” or “senile decay” found anywhere in Darwin’s entire corpus of correspondence, which amounted to more than 80,000 pages of handwritten letters to nearly 2,000 individuals throughout his lifetime. Moreover, this letter from Crichton-Browne, received by Darwin 36 years before the first case report of senile dementia by Professor Alois Alzheimer, explicitly noted that such premature dotage is the result of “brain wasting.” Crichton-Browne believed that senile dementia was the result of a central nervous system disease, with the emotional lability observed in his patients linked inextricably to the disease process. This early hypothesis, of interest to Darwin in 1871, anticipated the groundbreaking neurohistopathologic research and case description by Alzheimer 36 years later, and has been confirmed by all clinical research in this field since 1907. This concordance between psychological
Important medical and social problem

Not uncommon even if few studies that have addressed the prevalence are available \( \approx \frac{50}{100,000} \)  

Harvey 2003

Often misdiagnosed (more varied differential diagnosis than late-onset dementia)

Specific and timely diagnosis = crucial
Epidemiology of EOD

• Not uncommon

• Diagnosed in up to 1/3 of patients with dementia

• Prevalence estimation

  • 54 / 100,000H in UK
    
    J Harvey et al 2003

  • 42.3 /100,000 in Japan

    Ikejima C et al
EOD: Recent Gain of interest

Young-Onset Dementia
Demographic and Etiologic Characteristics of 235 Patients
Brendan J. Kelley, MD; Bradley F. Boeve, MD; Keith A. Josephs, MST, MD

Incidences and subtypes of early-onset dementia in a geographically defined general population

Early Onset Dementia
Characteristics in a Large Cohort From Academic Memory Clinics
Candice Picard, MD,* Florence Pasquier, MD, PhD,† Olivier Martinaud, MD,‡ Didier Hannequin, MD, PhD,‡ and Olivier Godefroy, MD, PhD*
Tunisian Cohort

To identify demographic characteristics and etiologic causes of dementias in younger patients

- Observational retrospective study
- 10 years (August 2002 - August 2012)
- Inclusion: Onset before 65 years
- Clinical, laboratory and imaging data
Pavillon Alzheimer
Service de Neurologie
للمرضى
Results: Tunisian Cohort

- 415 cases of EOD among 1505 demented patients
  \[ \Rightarrow 27.57 \% \text{ of all dementias cases} \]
- 375 patients included
- 40 excluded (lack of investigations)
- Sex ratio = 1.15

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Mean age at onset (years)</td>
<td>55.2</td>
</tr>
<tr>
<td>Mean age at 1\textsuperscript{st} presentation (years)</td>
<td>58.9</td>
</tr>
<tr>
<td>Mean time for diagnosis</td>
<td>3.5 years</td>
</tr>
<tr>
<td>Education Level</td>
<td>Percentage</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>High-school</td>
<td>10.9%</td>
</tr>
<tr>
<td>Secondary</td>
<td>19.4%</td>
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<tr>
<td>Primary</td>
<td>25.8%</td>
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<tr>
<td>Illiterate</td>
<td>43.7%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Professional Status</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Active</td>
<td>29.25%</td>
</tr>
<tr>
<td>Inactive</td>
<td>70.74%</td>
</tr>
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### Signs at onset

<table>
<thead>
<tr>
<th>Sign</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Loss of memory</td>
<td>67.1%</td>
</tr>
<tr>
<td>Behavioral disorder</td>
<td>29.2%</td>
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<tr>
<td>Speech disturbance</td>
<td>6.6%</td>
</tr>
<tr>
<td>Mood disturbance</td>
<td>6.4%</td>
</tr>
<tr>
<td>Delirium</td>
<td>3.2%</td>
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</table>

**Mean MMSE score at 1\textsuperscript{st} presentation**: 14
Etiologies of EOD

- Neurodegenerative causes: 64.27%
  - Alzheimer Disease = most frequent (44%)
- 11 patients (2.93%): unknown etiology at last follow-up
## Tunisian Cohort: Etiologies of EOD Versus LOD

<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>FREQUENCY IN LOD</th>
<th>FREQUENCY IN EOD</th>
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</thead>
<tbody>
<tr>
<td>Neurodegenerative dementia</td>
<td>71.72%</td>
<td>64.27%</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>16.93%</td>
<td>16%</td>
</tr>
<tr>
<td>Metabolic</td>
<td>0.27%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>0.27%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Other</td>
<td>4.7%</td>
<td>12%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.65%</td>
<td>2.93%</td>
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## Comparative data: Monocentric Studies

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</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td>112</td>
<td>141</td>
<td>34</td>
<td>278</td>
<td>185</td>
<td>93</td>
<td>375</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>NS</td>
<td>51</td>
<td>NS</td>
<td>51.5</td>
<td>NS</td>
<td>56.5</td>
<td>55.2</td>
</tr>
<tr>
<td><strong>Etiologies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AD</td>
<td>29 (25.9%)</td>
<td>30 (21.3%)</td>
<td><strong>38.2%</strong></td>
<td>48 (17.3%)</td>
<td>31 (33%)</td>
<td>165 (44%)</td>
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</tr>
<tr>
<td>FDT</td>
<td>43 (38.4%)</td>
<td>14.7%</td>
<td>2.9%</td>
<td>7 (2.5%)</td>
<td>25 (27%)</td>
<td>35 (9.3%)</td>
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</tr>
<tr>
<td>LBD</td>
<td>1 (0.9%)</td>
<td>NS</td>
<td>23.5%</td>
<td>NS</td>
<td>NS</td>
<td>60 (16%)</td>
<td></td>
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<tr>
<td>Vas.D</td>
<td>7 (6.3%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>17 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>1 (0.9%)</td>
<td>7 (5.0%)</td>
<td>NS</td>
<td>4 (1.4%)</td>
<td>NS</td>
<td>2 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>12 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>6 (5.4%)</td>
<td>NS</td>
<td>7 (5.0%)</td>
<td>15 (5.4%)</td>
<td>NS</td>
<td>2 (0.5%)</td>
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</tr>
<tr>
<td>Alcohol-related dementia</td>
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*NS* indicates non-significant differences.
# Comparative data: Multicentric studies

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</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td>185</td>
<td>54</td>
<td>617</td>
<td>144</td>
<td>811</td>
<td>375</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>53.3</td>
<td>NS</td>
<td>53.4</td>
<td>58.1</td>
<td>55.9</td>
<td>55.2</td>
</tr>
<tr>
<td><strong>Etiologies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AD</td>
<td>62 (33.5%)</td>
<td>19</td>
<td>25.6%</td>
<td>61 (42.4%)</td>
<td>181 (22.3%)</td>
<td>165 (44%)</td>
</tr>
<tr>
<td>FDT</td>
<td>23 (12.4%)</td>
<td>16</td>
<td>2.8%</td>
<td>14 (9.7%)</td>
<td>79 (9.7%)</td>
<td>35 (9.3%)</td>
</tr>
<tr>
<td>LBD</td>
<td>12 (6.5%)</td>
<td>3</td>
<td>6.2%</td>
<td>20 (13.8%)</td>
<td>21 (2.6%)</td>
<td>14 (3.7%)</td>
</tr>
<tr>
<td>Vas.D</td>
<td>34 (18.4%)</td>
<td>NS</td>
<td>42.5%</td>
<td>129 (15.9%)</td>
<td>129 (15.9%)</td>
<td>60 (16%)</td>
</tr>
<tr>
<td>HD</td>
<td>9 (4.9%)</td>
<td>NS</td>
<td></td>
<td>3</td>
<td>24 (3%)</td>
<td>17 (4.5%)</td>
</tr>
<tr>
<td>MS</td>
<td>8 (4.3%)</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Metabolic Alcohol-related dementia</td>
<td>19 (10.3%)</td>
<td>NS</td>
<td></td>
<td>5</td>
<td>76 (9.4%)</td>
<td></td>
</tr>
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Etiologies

- Broad variety of etiologies
- Few patients having a potentially treatable disorder
- Neurodegenerative causes (AD ++)
  - Frequent, but
  - Considerably less common than LOD
- Exhaustive exploration
Standard Diagnostic Steps

• Clinical and Neuropsychological evaluation
  - Dementia subtype (cortical, subcortical...)
  - Amnestic syndrome subtype (hippocampal, dysexecutive...),
  - Behavioral disturbance?
  - Altered cognitive functions Vs Conserved

• Familial history? If yes: Mode of Inheritance

• Cerebral MRI: FLAIR, T2, T2* and Diffusion

• Biology

• +/- EEG, PET scan

Hannequin et al 2010
Etiology
Preliminary work up

Biology

• CBC & CRP
• Ca/P
• TSH
• HIV; TPHA/VDRL
• Vitamin B12 & folate
Etiology

Expanded work up

• EEG
• Brain Pet scan
• Antibody screen
• Ceruloplasmin / copper
• Iron studies
• Heavy metal screen
• Homocysteine
• Genetic testing
• ...
Discussion: Etiologic diagnosis

- Variable etiologies / age
  - The more the age is younger
    - Less degenerative disorders
    - More secondary causes
  - Young Onset Dementia < 45 years
    - AD : 1.7%
    - Inflammatory causes: 23.3%
    - Metabolic: 10.6%

Need for exhaustive screening

Brendan J. Kelley, 2008
Undetermined etiology

- 2.93%: dementia of undetermined etiology
- Kelly et al: Study including 235 patients with age at onset of younger than 45 years, 44 (18.7%) had unknown etiology
  
  Kelly & al, 2008

- Anatomopathological studies: non conclusive cerebral biopsies in 43% of cases
  
  Warren et al. 2005

→ Difficulties to establish etiology in Early Onset Dementia
Management of Early Onset Dementia

- Agents that increase cholinergic activity:
  - modest but variable benefit in AD, Vascular and Parkinson’s disease dementias
  - Risk of worsening in FTLD

- Treatment of manifestations: symptoms of depression, aggression, sleep disturbance, seizures and hallucinations: managed on an individual basis

- Physical and occupational therapy: help manage activities of daily living

- Eventually: assisted living/nursing home care;
Early Onset Dementia: Burden

Devastating effects on patients and family members

- Children and spouse burden: Patients in the age range common to those raising children,
- Working patients: mistakes and loss of ability to perform their jobs competently $\Rightarrow$ forced into early retirement and may not have access to the full range of benefits
- Loss of ability to take care of their own needs, such as money management
Dementia burden & cost

- Social rejection
- Forensic Behaviour/Acts → Homicide

- Caregivers
  - Deal with changes in a loved one’s personality
  - Provide constant attention for years

→ Absenteism
→ Productivity loss
→ Vulnerable to physical and emotional stress
Economic Impact

- Direct costs for the care of patients in 1991 were calculated at US $20.6 billion.
- Total cost was calculated to be $76.3 billion.
- Most direct costs of care for patients with AD are absorbed by the expense of nursing home care, approximately $47,000/patient/year.
Consequences of the disease’s onset delay on dementia’s prevalence (Estimation USA)

And when the Onset is earlier???


**Conclusion: Early Onset Dementia**

- Frequent
- Broad variety of etiologies / age of onset
- Few patients: potentially treatable disorder
- Neurodegenerative causes (AD): frequent but considerably less common than in elderly people
- Management more challenging than older patients
- Important predictor of overall dementia’s prevalence
Conclusion

• Devastating consequences

• Financial loss: patient's family as well as society,

⇒ Importance of developing strategies for diagnosis and management of younger patients