Current view & future trends - Alzheimer’s disease 2010

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<table>
<thead>
<tr>
<th>Name</th>
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</table>
| Dr. Philip Lee| - Involvement in clinical trials sponsored by Bristol-Meyer Squib, Baxter, Plan, Janssen and Pfizer.
               | - Received honorarium from Pfizer, Novartis, and Janssen – Ortho.                                                                                                                                 |

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Objectives

- To describe the pathophysiology behind Alzheimer’s disease;
- To discuss our knowledge about diagnosis and management of Alzheimer’s disease;
- To describe potential future implications of current research in the field of Alzheimer’s disease

Alzheimer’s disease 2010

Overview
- Where have we been?
- Where are we now?
- Where are we going?

Dementia Detection in Family Practice

- Increasing number of patients presenting with memory complaints
- Family physicians
  - Screen patients
  - Initiate specialized care
  - Diagnose early to facilitate planning
  - Identify subset of patients with treatable disorders causing memory loss

Feldman et al. CMAJ 2008; 178: 825-836
Auguste D:
Clinical and pathological description

- Ideas of jealousy
- Rapid worsening memory
- Couldn’t negotiate around her home
- At times, she felt she was about to be murdered and yelled loudly
- Disoriented to time and place

- Rapid forgetting
- Language errors
- Decreased comprehension
- Normal gait and extremities
3 Key Pathological Findings:
- Atrophy of brain
- Neurons damaged and decreased in number
- Progressive accumulation of abnormal material
  - Amyloid plaques (amyloid core)
  - Neurofibrillary tangles (p-tau)

Diagnosing Alzheimer’s disease
- Diagnosis for AD based on clinical criteria (DSM-IV, NINDS-ADRD criteria)
- Clinical practice guidelines
  - Canadian Consensus Conference Guidelines on Dementia 2006
  - American Academy of Neurology Guidelines 2000
- Proposed new research criteria
  - Clinical and biomarkers and functional imaging

New Proposed Research Criteria
Core Diagnostic Criteria for Prob AD
- Early and significant episodic memory impairment with:
  - Gradual and progressive change in memory over more than 6 months
  - Objective evidence of significantly impaired episodic memory on testing
New Proposed Research Criteria

Supportive Features
- Presence of medial temporal lobe atrophy
- Abnormal CSF biomarker
- Specific pattern on functional neuroimaging with PET
- Proven AD autosomal dominant mutation within the immediate family
- Absence of exclusion criteria

Dubois B et al. Lancet Neurol 2007

Brain Abnormality
- Neuronal Injury
  - CSF
  - FDG PET
- Amyloid imaging
  - CSF AB
- Neurodegeneration
  - MRI

Cognitively Normal  MCI  Dementia

Neuroimaging

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The new guy, Tom, and a new woman are coming. Our kids were all over the place. They're much more composed.
Structural Neuroimaging

- Ventricular enlargement
  - Nestor SM et al. Brain 2008

- Hippocampal atrophy
  - Shi F et al. Hippocampus 2009

PET Imaging with PIB

Price JC et al. J Cerebral Blood Flow & Metabolism, 2005
### Early Detection

- FDG-PET, SPECT and structural MRI
- Meta-analysis, 24 eligible studies, n=1112
- Prediction of conversion to AD in patients with MCI
- PET superior to SPECT and structural MRI


### CSF Biomarkers

- Decreased a-beta 42
- Increased total and phosphorylated tau

Hansson O et al. Lancet Neuro 2006

### CSF Biomarkers

<table>
<thead>
<tr>
<th>Table 1: Association Between CSF Biomarkers and Diagnosis</th>
<th>Group</th>
<th>Total</th>
<th>MC</th>
<th>AD</th>
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<tbody>
<tr>
<td>Biomarker Levels</td>
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<tr>
<td>Alpha-133</td>
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<tr>
<td>Cerebrospinal fluid markers</td>
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<td>Protein levels</td>
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<td>Change in levels</td>
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De Meyer et al. Arch Neuro 2010
Predicting AD – Risk Factor Assessment

- Age
- Female gender
- Family History – especially autosomal dominant pattern
- APOE4

The Dementia Risk Calculator Doubling Rule

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Risk Factor Doubling Rate</th>
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</thead>
<tbody>
<tr>
<td>65 years</td>
<td>1%</td>
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<tr>
<td>66 years</td>
<td>2%</td>
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<tr>
<td>67 years</td>
<td>3%</td>
</tr>
<tr>
<td>68 years</td>
<td>5%</td>
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<tr>
<td>69 years</td>
<td>7%</td>
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<tr>
<td>70 years</td>
<td>9%</td>
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<td>71 years</td>
<td>11%</td>
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<tr>
<td>72 years</td>
<td>13%</td>
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<tr>
<td>73 years</td>
<td>15%</td>
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<td>74 years</td>
<td>17%</td>
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<td>75 years</td>
<td>19%</td>
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<td>76 years</td>
<td>21%</td>
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<td>77 years</td>
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<td>83 years</td>
<td>35%</td>
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<tr>
<td>84 years</td>
<td>37%</td>
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<tr>
<td>85 years</td>
<td>39%</td>
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</tbody>
</table>

Treating Vascular Risk Factors may slow progression of Dementia

- High blood pressure
  - Systolic ≥ 140 or diastolic ≥ 90 mm Hg
- Dyslipidemia
  - Total cholesterol level ≥ 6.2 mmol/l
  - Triglycerides ≥ 2.3 mmol/l
- Diabetes
  - Fasting blood glucose ≥ 7 mmol/l
- Atherosclerotic disease
  - Infarct or lacunes on brain imaging

http://rgps.on.ca/gic/GiC/pdfs/1b%20Dementia%20screening%20overview.pdf, Dalziel et al., accessed Sept 7, 2010

Cognitive decline over time (891 patients)

Deschantre et al. Neurology Today; Aug 2007

Exercise and MCI

- N=198 (median age 83) MCI and 1,126 (median age 80) normal
- Questionnaire based
- Moderate exercise -- such as brisk walking, aerobics, yoga, strength training or swimming
- Midlife moderate exercise – 39% reduction in the odds of developing the condition, and late life moderate exercise 32% reduction

Geda et al. Arch Neuro 2010

Exercise and MCI

- Six month, RCT with N=33, 23 assigned to aerobic exercise (45-60 min/day, four days per week); Control performed stretching exercise

Baker et al. Arch Neuro 2010
Mental Exercises

- Novel activities are likely more beneficial
- Some data to support formal programs
  - Commercial products
  - Individualized programs

Mediterranean Diet

- Highest adherence to MeDi associated with lower incidence of MCI (HR 0.72, 95% CI 0.52-1.00; p=0.05)
- Among MCI pts, less risk (HR 0.52, 95% CI 0.30-0.91; p=0.02) of developing AD

Scarmeas et al. Arch Neurol 2009

Treatment for Alzheimer’s disease

Symptomatic treatment – early 1990s
Currently, there are treatments available that focus on symptomatic management
- Cognitive
- Functional
- Behavioural

Research is still ongoing regarding exploring symptomatic treatments
Future treatments – focus on disease modification

Treating Alzheimer’s disease

Timeline of Approved Treatments for AD

- Development of the cholinergic hypothesis
- First Acetylcholinesterase inhibitor: Aricept
- Donepezil, rivastigmine, galantamine
- Approval of Memantine NMDA receptor antagonist

Timeline:
- 1906: Development of the cholinergic hypothesis
- 1974: Identification of other neurotransmitter systems impaired including glutamate and NMDA
- 1982: Approval of Memantine NMDA receptor antagonist
- 1984: First Acetylcholinesterase inhibitor: Aricept
- 1985: Donepezil, rivastigmine, galantamine
Cholinesterase Inhibitor Therapy

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Titratin as Tolerated</th>
<th>Effective Range</th>
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</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>5 mg daily</td>
<td>Increase by 5 mg</td>
<td>5 – 10 mg daily</td>
</tr>
<tr>
<td>Galantamine</td>
<td>8 mg ER daily</td>
<td>Increase by 8 mg</td>
<td>16 – 24 mg daily</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>1.5 mg twice daily</td>
<td>Increase by 1.5 twice daily</td>
<td>6 – 12 mg daily</td>
</tr>
<tr>
<td>Rivastigmine (patch)</td>
<td>1 patch (5 cm²/9mg) daily</td>
<td>Increase to 1 patch (10cm²/18mg) daily</td>
<td>5cm²/9mg – 10cm²/18mg daily</td>
</tr>
</tbody>
</table>

Medication Clinical Trials in MCI

<table>
<thead>
<tr>
<th>Source</th>
<th>Duration</th>
<th>End Point</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersen et al. 2005</td>
<td>3 yrs</td>
<td>AD</td>
<td>Vit E, donepezil</td>
</tr>
<tr>
<td>Thal et al. 2005</td>
<td>3-4 yrs</td>
<td>AD</td>
<td>Rofecoxib</td>
</tr>
<tr>
<td>Feldman et al. 2007</td>
<td>4 yrs</td>
<td>AD</td>
<td>Rivastigmine</td>
</tr>
<tr>
<td>Winblad et al. 2008</td>
<td>2 yrs</td>
<td>CDR 1</td>
<td>Galantamine</td>
</tr>
<tr>
<td>Doody et al. 2009</td>
<td>48 wks</td>
<td>AD</td>
<td>Donepezil</td>
</tr>
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</table>
Currently not recommended…

- Antioxidants, including Vit E (Grade E, Level 1)
- Vitamin B6, B12 or folic acid for AD in those without documented deficiency (Grade D, Level 3)
  - Recent study (PLoS One) re-opens dialogue on B vitamins
- Insufficient evidence for ginkgo biloba (Grade C, Level 1) – (JAMA Dec 2009)
- HMG-CoA reductase inhibitors (Grade D, Level 3)
- Omega 3 PUFA (Prog NeuroPsychoPharmacology and Biological Psychiatry 2008 & Alz Dem 2009)

Future Directions – Disease Modifying Therapy

Figure 1, Patterson et al. CMAJ 2008; 178(5):551
Vaccination with Ab peptide prevents memory deficits in an animal model of Alzheimer's disease (Morgan et al., 2001)

Ab immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease (Janus et al., 2001)
Post Vaccination Meningoencephalitis in 6%


Sample of Research On-going
- Prodromal AD
  - Gamma – secretase inhibitor
- Alzheimer’s disease
  - Bapineuzumab study
  - Intravenous immunoglobulin

Sample of Research On-going
- Alzheimer’s disease
  - Music Therapy
  - Willingness to Pay for Alzheimer’s drug therapy
- Vascular Cognitive Impairment
  - Exercise and Cognition (PROMOTE)
- Mixed Dementia
- Other dementia, FTD
- Knowledge exchange with affected communities in BC
- Alzheimer’s Disease Therapy Initiative (ADTI)