New Concepts in Alzheimer’s Disease and Dementia

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Nov.23, 2010
Disclosures

• Funding for study of cognitive disorders from:
  – Alberta Heritage Foundation for Medical Research.
  – Canadian Institutes for Health Research
  – U.S. National Institutes of Health
  – Canadian Stroke Network
  – Heart and Stroke Foundation of Canada.
Prevalence of Cognitive Impairment in Canada

http://www.alzheimer.ca/english/rising_tide/rising_tide_summary.htm
The New York Times

OP-ED CONTRIBUTORS
The Age of Alzheimer’s
By SANDRA DAY O’CONNOR, STANLEY PRUSINER and KEN DYCHTWALD
Published: October 27, 2010

OUR government is ignoring what is likely to become the single greatest threat to the health of Americans: Alzheimer’s disease, an illness that is 100 percent incurable and 100 percent fatal. It attacks rich and poor, white-collar and blue, and women and men, without regard to party. A degenerative disease, it steadily robs its victims of memory, judgment and dignity, leaves them unable to care for themselves and destroys their brain and their identity — often depleting their caregivers and families both emotionally and financially.
In Spinal-Fluid Test, an Early Warning on Alzheimer’s

By GINA KOLATA
Published: August 9, 2010

Researchers report that a spinal fluid test in identifying a signature level of abnormal tau protein in people who went on to develop Alzheimer’s disease is further evidence that early detection could be a real possibility. The test, which is currently available in only a handful of research centers, involves the examination of spinal fluid for the presence of a protein that is characteristic of Alzheimer’s disease.

Emerging Alzheimer's tests raise ethical debate

By PAULINE TAM, POSTMEDIA NEWS
October 12, 2010

EDITORIAL

Early Detection of Alzheimer’s

Published: August 10, 2010

GUIDELINES SEEK EARLY DETECTION OF ALZHEIMER’S

By GINA KOLATA
Published: July 14, 2010

For the first time in 25 years, medical experts are proposing a major change in the criteria for Alzheimer’s disease, part of a new movement to diagnose and, eventually, treat the disease earlier.
Outline

• Alzheimer’s disease (AD) basics.
• Earlier detection.
• AD and the aging brain.
• Prevention and treatment.
Alois Alzheimer

Cerebral Amyloid Angiopathy (CAA)

Neurofibrillary Tangles (NFT)

β-Amyloid Plaques
Abeta and Plaque Formation

Cleavage by β- and γ-secretase

Soluble Aβ monomers

Oligomeric Aβ

Aggregation

Amyloid formation

Senile plaque with β-amyloid

Cleavage by α-secretase

Non-amyloidogenic fragments

No amyloid

Proteolysis

CAA

Cross Blood-brain barrier

APP → Aβ40 → Aβ42

Amyloid Plaque

Perivascular Drainage
Neurofibrillary Tangles

Healthy Neuron

Stabilizing Tau Molecules

Microtubules

Diseased Neuron

Disintegrating Microtubules

Disintegrating Microtubules Fall Apart

Microtubule Subunits

Tangled Clumps of Tau Proteins
Amyloid Hypothesis

• Posits that beta-amyloid formation is a necessary early step in AD.

• Supported by finding that all rare monogenic forms of AD are caused by mutations in APP or the enzyme activities that cleave it to form abeta.
Diagnosis

Dementia

Moderate to High Alzheimer Pathology
Distribution of Alzheimer’s Pathology

Typical Alzheimer’s History

- Early: difficulty with memory retrieval (hippocampal dysfunction).
- Middle: increasing difficulty with visuospatial function (parietal), praxis and executive function (parietal and frontal association cortices), anomia (perisylvian).
- Late: Global impairment, parkinsonism, myoclonus.
Montreal Cognitive Assessment Tool
Mild Cognitive Impairment

- Dementia: cognitive impairment in memory plus at least one other domain with a decrease from previous social or occupational function.

- Mild cognitive impairment: cognitive symptoms with objective evidence of impairment (score <1.0 to 1.5 SD below age-adjusted mean, or <26 on MoCA) but no significant impairment in social or occupational function.
Pathology of Mild Cognitive Impairment

• Patients are at risk for future dementia: 10-20% will convert to dementia per year.

• Pathology studies show about half have moderate to severe AD.
Surrogate Markers of AD

- Structural MRI.
- SPECT.
- FDG-PET.

For the most part, testing is done to rule out other causes of dementia, not rule in AD.
MRI
FDG-PET
Emerging Highly Specific Markers

• CSF amyloid and tau protein ratios.
• PET ligands for beta-amyloid.
CSF Markers

- Reduced abeta 1-42.
- High CSF tau and phosphorylated tau.
- Ratio of CSF tau:abeta 1-42.

Limitations:
- Lack of standardization across analysis platforms.
- Mostly validated in case control studies.
- Marginal predictive value frequently not studied.
- Requires CSF sampling.
- Don’t predict rate of decline except in milder stages.
- Detect presymptomatic changes.

PET Molecular Imaging

- PET ligand Pittsburgh Compound B (PIB) binds fibrillar beta-amyloid deposits.
- PIB +ve mild cognitive impairment has higher rate of conversion to MCI (as high as 50% per year vs. 10% per year).


PIB-PET in Normal vs. AD

Courtesy Keith Johnson, Massachusetts General Hospital
PIB Positive “Normals”

• 20-30% of “normal” >70 year olds show PIB retention.

• Similarly, senile plaques frequently seen at autopsy in asymptomatic elderly.

• Outcome in these patients uncertain (longitudinal studies ongoing).


Aizenstein HJ, Nebes RD, Saxton JA et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol. 2008;65:1509-1517
Time Course of AD

- Neuritic Plaques
- PIB-PET
- Hippocampal Atrophy
- NFTs
- Whole-brain atrophy
- Decreased glucose metabolism

Normal
“Normal” Asymptomatic at-risk state
MCI
Dementia
Revising the definition of Alzheimer’s disease: a new lexicon


• Diagnostic categories:
  – AD dementia.
  – Prodromal AD: amnestic MCI + biomarkers.
  – Asymptomatic at-risk state for AD: normal cognition + biomarkers.
  – Presymptomatic AD: monogenic carrier of AD mutation that will develop AD.
  – Mixed AD: AD with other diseases.
A PANEL of medical experts from the National Institute on Aging and the Alzheimer’s Association last week proposed changes in the way doctors diagnose Alzheimer’s disease — including the use of so-called biomarkers, tests like PET brain scans and analyses of spinal fluids to promote early detection of the disease. Although these recommendations are well intentioned, evidence suggests that it would be a mistake to adopt them at this time. To understand why, it’s important to recognize what these tests mean, in what context the information will be used and what experience has shown us.
Time Course of AD

Global Cognitive Performance

- Neuritic Plaques
- PIB-PET
- Hippocampal Atrophy
- NFTs

- Whole-brain atrophy
- Decreased glucose metabolism

Normal
“Normal” Asymptomatic at-risk state
MCI
Dementia
Cognitive Reserve

• Factors that allow some brains to accommodate larger amounts of AD pathology without symptoms.
  • Absence of other brain pathologies.
  • Presence of protective factors (e.g. education).
AD and the Aging Brain
Mixed Dementia is Most Common

Main Pathologies of Dementia

Alzheimer’s disease

Cerebrovascular disease
Small Subcortical Infarcts Independently Contribute to Risk of Dementia


Figure. Probability of clinically diagnosed dementia proximate to death as a function of level of the Alzheimer disease (AD) pathology (summary measure) in persons with cerebral infarction (solid line) and persons without cerebral infarctions (dashed line).
Risk Factors for Dementia

- Age
- APOE e4 allele
- Education
- Mid-life hypertension
- Mid-life hypercholesterolemia
- Diabetes mellitus
- Homocysteine
- Obesity
- Smoking
MRI Markers of Cerebral Small Vessel Disease

- Lacunes: 20-25% (90% “silent”)
- Intracerebral hemorrhage: 2-12% (90% “asymptomatic microbleeds”)
- White matter T2 hyperintensity: 95%
- Cerebral microinfarction: ?

Data from Rotterdam study, Framingham study, Cardiovascular Health Study, and American Heart Association statistics.
Relationship Between PIB-PET and MRI Markers of Small Vessel Disease in MCI

Figure 12. PIB retention in mildly impaired with low and high WMH. PIB retention, similar in degree to that seen in Alzheimer’s disease, in mildly impaired subject from MGH Study of Memory and Aging with low WMH volume (top). Conversely only non-specific PIB retention, similar in degree to that seen in PIB-negative normal controls, is seen in mildly impaired subject with high WMH (bottom). We hypothesize that WMH and PIB retention are independently associated with cognition in mildly impaired subjects.
PURE-MIND Study
800 participants

Goal: Determine risk factors, prevalence and consequences of “covert” brain ischemia in Canada.
Prevention and Treatment

• Vascular risk reduction: attractive but unproven.

• Other approaches (also unproven):  
  – Mental exercise.  
  – Physical exercise (CIHR-funded interventional study led by Marc Poulin).
Abeta Immunotherapy

- Passive or active immunization clears brain neuritic plaques in animal models.
- Phase 2 study in humans with mild dementia suggests biological effect but no detectable effect on cognitive decline (AN1792).
  - Trial stopped early because of meningoencephalitis in 6%.

7/8 immunized cases died of end-stage dementia despite mean amyloid reduction of 60% vs. age-matched AD controls.
Reasons for Lack of Effect

- End-stage.
- Soluble oligomeric forms of abeta.
- Inadequate sample size.
- Beta-amyloid hypothesis is wrong.
Lilly Halts Development of Semagacestat for Alzheimer's Disease Based on Preliminary Results of Phase III Clinical Trials

INDIANAPOLIS, Aug 17, 2010 /PRNewswire via COMTEX News Network/ -- Eli Lilly and Company (NYSE: LLY) will halt development of semagacestat, a gamma secretase inhibitor being studied as a potential treatment for Alzheimer's disease, because preliminary results from two ongoing long-term Phase III studies showed it did not slow disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living.

In two pivotal Phase III trials, semagacestat was compared with placebo in more than 2,600 patients with mild-to-moderate Alzheimer's disease. Lilly has now reviewed data from a pre-planned interim analysis of semagacestat studies. This interim analysis showed that, as expected, cognition and the ability to complete activities of daily living of placebo-treated patients worsened. However, by these same measures, patients treated with semagacestat worsened to a statistically significantly greater degree than those treated with placebo. In addition, data showed semagacestat is associated with an increased risk of skin cancer compared with those who received placebo.
Themes

• Dementia is caused by pathologies that act as quantitative traits, often in combination.

• Pre-symptomatic or asymptomatic brain pathologies are the norm, not the exception, in late life.

• The diagnostic paradigm for dementia must change to accommodate these realities.

• Cerebrovascular disease is a much bigger contributor to dementia than was recognized 10 years ago.

• Translating knowledge to treatments remains challenging.
Diagnostic Report 2020

- Clinical indication: Forgetfulness.
- Technique: Brain MRI-PET.
- Findings:
  - PET: PIB retention 20%, NFT binding: 15%
  - MRI Brain Infarcts: 1 (right thalamus)
  - MRI white matter lesion volume: 0.5% of intracranial volume (interquartile range for age, 0.05-0.45%).
- Calgary Risk Score predicts:
  - Current probability of: MCI—80%; dementia—60%.
  - Future cumulative risk of dementia in 3 years: current normal—40%; current MCI—65%.
- Interpretation: Biomarker evidence suggests moderate AD pathology with a single brain infarct and white matter lesions greater than expected for age. No other possible cause of memory loss identified.
Age-Related Degenerative Disease

• What other disease:
  – Onset in 20s or 30s.
  – Slowly progressive.
  – Ubiquitous (essentially 100% prevalence in late life).
  – Associated with clinical events, but in most people it is silent.
  – Readily detectable by highly specific radiographic markers even in the absence of symptoms.

Atherosclerosis!
Thank you

Alberta Innovates – Health Solutions
Canadian Institutes for Health Research
Canadian Stroke Network
Heart and Stroke Foundation of Canada
U.S. NIH