Mixed Dementia: Emerging Concepts and Implications for Treatment and Research

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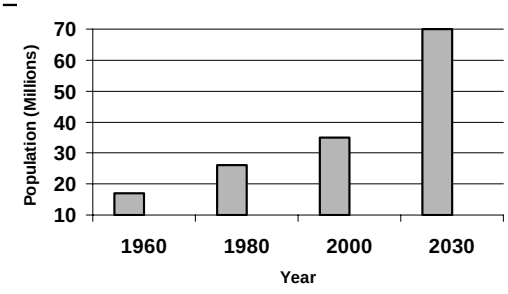
Overview

- Mixed Dementia: The Brain – Heart – Vessel Connection
- Implications for Treatment of Dementia
- Implications for Research on Dementia
  - Studying dementia in the "real world"
  - The Health and Retirement Study
  - The Aging, Demographics, and Memory Study
  - Conceptual model for studying longitudinal cognitive decline
  - Hypotheses derived from some early results

"Demographic Imperative"

Population Age 65 + in the US



Source: Dept. of Health and Human Services, *A Profile of Older Americans: 2001*.

Definitions: Dementia (DSM-IV)

- Impairment in short and long-term memory, as well as at least one of the following cognitive disturbances: aphasia; apraxia; agnosia; disturbance in executive function; AND
- The cognitive deficits cause significant impairment in social or occupational functioning, AND represent a significant decline from a previous level of functioning

**Clinical diagnosis NOT straightforward--different classification systems make for very different prevalences

Definitions: Alzheimer's Disease (AD)

- DSM-IV
  - Dementia with course characterized by gradual onset and continuing cognitive decline
  - Cognitive deficits not due to other CNS conditions (e.g., cerebrovascular dz, Parkinson's) or medical conditions (e.g., hypothyroidism, B12 deficiency)
- NINCDS-ADRDA criteria
  - Define: "Probable," "Possible," and "Definite" AD

Source: McKhann et al, Neurology, 1984.

Definitions: Vascular Dementia (VaD)

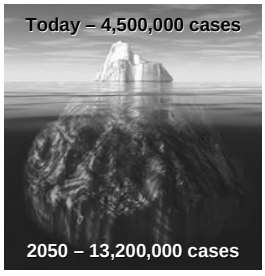
- DSM-IV
  - Dementia accompanied by evidence of cerebrovascular disease (e.g., focal neuro. signs and symptoms, and/or brain imaging) that is judged to be etiologically related to the dementia
  - "Onset is typically abrupt, followed by a stepwise and fluctuating course"
- NINDS-AIREN criteria
  - Define: "Probable," "Possible," and "Definite" VaD

Source: Roman et al, Neurology, 1993.

Definitions: Mixed Dementia

- No current consensus on appropriate clinical or neuropathologocal criteria and terminology
- "AD with cerebrovascular disease" is the preferred term in the NINDS-AIREN framework
- Hachinski Ischemic Score, ICD-10, DSM-IV have mixed dementia categories, although specific criteria differ across systems

Epidemiology of Alzheimer's Disease



- Alzheimer's disease mainly affects individuals older than age 65 [1]
- Affects ~ 10% of people > 65 years old [1]
- Affects ~ 50% of people > 85 years old [1]
- If current trends continue, the prevalence of AD could triple over the next 50 years [2,3]

1. Evans et al, Milbank Q, 1990.
2. Brookmeyer et al, AJPH, 1998.
3. Hebert et al, Arch Neurol, 2003.

Dementia in the Clinic vs. the 'Real World'?

- Co-existing AD and VaD in clinical samples ~ 25%
- Co-existing AD and VaD in population-based samples ~ 50%
- Reasons for difference?
  - Referral bias (older patients with co-morbidities less likely to be referred to academic centers)
  - Study inclusion criteria (criteria may be designed to select "pure AD" and "pure VaD")

Sources: Massoud et al, Arch Neuro, 1990; Gearing et al Neuro, 1995; Lim et al, JAGS, 1999; MRC/CFAS, Lancet, 2001.

Overlap / Interaction of AD and CV disease

- Risk Factors
  - Hypertension, Hypercholesterolemia, Diabetes, Metabolic Syndrome, Physical inactivity, Smoking, Alcohol (protective), Apolipoprotein E e4 genotype, Inflammation
- Clinical
  - For a given level of AD pathology in the brain, the greater the number of cerebrovascular lesions, the greater the likelihood of clinically significant cognitive impairment / dementia

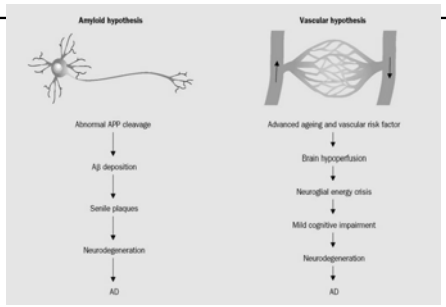
Sources: Snowdon et al, JAMA, 1997; Riekse et al, JAGS, 2004.

Overlap / Interaction of AD and CV disease (cont'd)

- "Silent" Strokes and Dementia
  - Even strokes that are not clinically apparent increase the risk of dementia
- Subcortical ischemic lesions ("white matter lesions")
  - Can cause executive dysfunction, cognitive decline, and dementia even in the absence of stroke
  - Strongly correlated with cardiovascular risk factors and likely due to cerebral ischemia

Sources: Vermeer et al, NEJM, 2003; O'Brien et al, Lancet Neuro, 2003; Kuo and Lipsitz, J of Geron, 2004.

Pathophysiology of AD (?)



Source: de la Torre. Lancet Neuro, 2004.

Is AD Really a Vascular Disease?

- de la Torre, 2004
  - "There is now substantial and growing evidence from studies of epidemiology, pharmacology, neuroimaging, clinical medicine, microscopic anatomy, and cellular-molecular biology to suggest that…AD is a vascular disorder caused by impaired cerebral perfusion."
- Casserly and Topol, 2004
  - "The recognition that atherosclerosis and AD are independent but convergent disease processes represents a *paradigm shift* in our thinking about their pathogenesis."

Sources: de la Torre, Lancet Neurology, 2004; Casserly and Topol, Lancet, 2004.

Summary of AD – VaD Overlap

- Especially in older patients, AD and VaD brain lesions often co-exist (~ 50% in population-based studies)
- Clinically significant dementia is more likely when AD is accompanied by strokes
- AD and VaD share many risk factors, and (perhaps) pathophysiology
- Difficult to disentangle cause for cognitive decline in older patients ('Occam's Razor' not operative)

Implications of AD – VaD Overlap for Treatment

- Aggressive identification and treatment of CV risk factors in middle-age and older adults may prevent AD and VaD, as well as slow cognitive decline among those with these conditions

Implications of AD – VaD Overlap for Treatment

- Antihypertensive therapy
  - both observational and RCT evidence show benefit
- Statin therapy
  - observational evidence mixed; RCT evidence not supportive so far
- Physical activity
  - both observational and RCT evidence show benefit

Source: Langa, Foster, Larson, JAMA, 2004.

Implications of AD – VaD Overlap for Treatment

- Cholinesterase Inhibitors and Memantine
  - Similar efficacy in mixed dementia as in AD
  - Are their benefits worth the cost?
    - Important topic for another day

Source: Langa, Foster, Larson, JAMA, 2004.

Implications of AD – VaD Overlap for Future Research

- "Population-based studies that can provide more generalizable information on real-world patients—including better identification of the risk factors, prevalence, trajectory of cognitive decline, and survival in patients with mixed dementia—will be important for informing clinicians, patients, and families."

Source: Langa, Foster, Larson, JAMA, 2004.

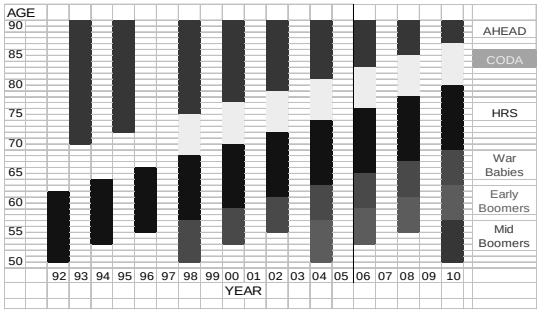
Health and Retirement Study (HRS)

- Ongoing, nationally representative, longitudinal, biennial survey of 22,000 Americans aged $\geq$ 50
- Performed at the Institute for Social Research at the University of Michigan (PI: Robert Willis)
- Funded by the NIH / NIA since 1990
- Collects data on health, economic, cognitive, work, and family status of respondents and their spouses

HRS Survey Content

- **Demographic characteristics**
- **Physical and functional health**
- **Performance-based cognitive testing**
- **Family structure and transfers**
- **Employment status, job history, and disability**
- **Retirement plans and perspectives**
- **Assets, income, and net worth**
- **Housing and services use**
- **Health insurance and pension plans**
- **Out-of-pocket costs**
- **Links to data from employers, Medicare, NDI, and SSA**

HRS Longitudinal Sample Design



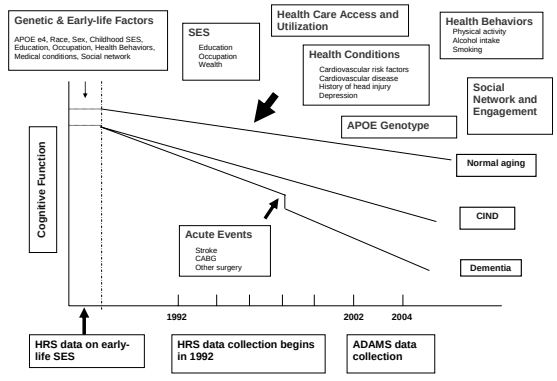
Aging, Demographics, and Memory Study (ADAMS)

- Supplemental study to the HRS funded by NIA
- First national, population-based study of dementia to include subjects from all regions of the country
- Field period: 2001 - 2005

Objectives of the ADAMS

- Select a sub-sample of HRS respondents aged 70+, stratified by level of cognitive impairment on the HRS 2000 and 2002 surveys
- Conduct in-home clinical assessments on about 850 individuals from this sample, including extensive neuropsych. testing, medical history, history of cognitive and functional change, and neuro. exam
- Assign a clinical diagnosis of:
  - **Dementia**
  - **Cognitive Impairment, Not Demented (CIND)**
  - **Normal**

Conceptual Model of Longitudinal Cognitive Decline in the HRS - ADAMS



Characteristics of ADAMS Sample (N=856)

ADAMS Diagnoses (N=856)

Diagnosis	N	(%)
DEMENTIA (n=307, 36%)		
Alzheimer's Disease	228	(27)
Vascular Dementia	48	(6)
Subcortical Dementias	3	(<1)
Other Dementias	25	(3)
CIND (n=242, 28%)		
Mild-ambiguous	94	(11)
Mild Cognitive Impairment	4	(<1)
Cog Imp due to vascular disease	21	(2)
Stroke	34	(4)
Other Neurological conditions	10	(1)
Other Medical conditions	55	(6)
Depression	8	(1)
Psychiatric Disorder	2	(<1)
Low Baseline Intellect	8	(1)
Alcohol Abuse	6	(1)
NORMAL (n=307, 36%)	307	(36)

ADAMS Research Plan

- Use Latent Growth Curve Models and HRS cognitive data from 1992 to 2004 to identify the trajectories of cognitive decline for those diagnosed as Normal, CIND, and Demented in the ADAMS
- Use combined HRS-ADAMS-Medicare data in nested case-control studies to identify medical, behavioral, genetic, economic, and social factors that increase the risk of CIND / dementia (and explore interactions among these factors)

ADAMS Research Questions

- Are high out-of-pocket expenditures for cardiovascular medications a risk factor for CIND / dementia?
- Are women at greater risk for CIND / dementia due to higher rates of poverty and social isolation?

Are there Health Effects of High OOPE?

- After controlling for important patient characteristics, adults who "ended up taking less medication than was prescribed because of the cost" were:
  - More likely to report a decline in health status between 1996 and 1998 (P<.05)
  - More likely to report angina, MI, and Stroke (among those with baseline heart disease) between 1996 and 1998 (P<.05)

Source: Heisler et al, Medical Care, 2004.

Risk of Non-Fatal Stroke or MI Among those with Cardiovascular Disease (n=6105)

	UNADJUSTED			ADJUSTED		
	Restriction due to Cost (%)	No Restriction (%)	Odds Ratio (95%)	Restriction due to Cost (%)	No Restriction (%)	Adjusted Odds Ratio‡ (95% CI)
Angina	21.8	11.7	2.11 (1.58-2.83)	15.9	11.4	1.51 (1.10-2.15)
Cardiovascular event	11.3	7.7	1.54 (1.08-2.18)	10.6	7.4	1.52 (1.06-2.40)

‡ Adjusted for age, ethnicity, annual household income, education, self-reported health status, dementia status, smoking,and other co-morbidities (cardiovascular disease index, chronic lung disease, cancer, psychiatric problems, and arthritis)

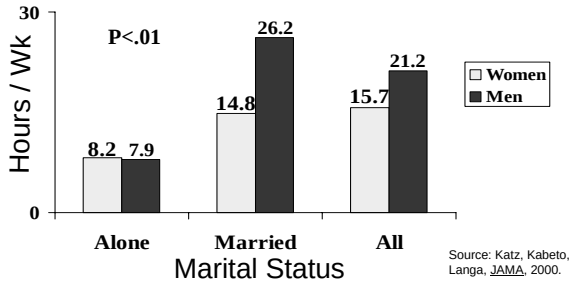
Source: Heisler et al, Medical Care, 2004.

Gender Differences in Social Support

- Older disabled women are:
  - Less likely to be married (28% vs. 74%)
  - More likely to live alone (45% vs. 17%)
  - More likely to have low net worth (24% vs. 11%)
- Even when married, disabled women receive less care from their husbands than disabled men receive from their wives
- Disabled women, therefore, receive significantly fewer hours of informal care than men

Source: Katz, Kabeto, Langa, JAMA, 2000.

Gender Differences in Receipt of Informal Caregiving



Source: Katz, Kabeto, Langa, JAMA, 2000.

Caregiver Burden

Conclusions

- Dementia will be an increasingly important cause of disability as the population ages
- Dementia has a profound and growing impact on individuals, families, and social programs
- Dementia risk is determined by interactions among the brain, the body (esp. heart and vessels), and the physical and social environment in which one lives

Conclusions

- The AD-VaD link suggests that aggressive identification and treatment of CV risk factors may prevent both AD and VaD
- The "true" causes for dementia may differ between clinical and population-based samples
  - population-based longitudinal data will help better identify the causes and consequences of dementia in the "real world"

Conclusions

- A better understanding of the relative importance of medical, behavioral, and SES risks for dementia will help clinicians and policy-makers:
  - target high-risk groups
  - implement interventions to prevent or slow cognitive decline
  - assess the cost-effectiveness of current and future interventions