Analytical Issues in Alzheimer’s Disease

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CRITICAL FEATURES OF ALZHEIMER’S DISEASE (AD) FOR DESIGN AND ANALYSIS
Features to be discussed

- Common disease with age-dependent onset
- Diagnosis ambiguous: terminology, impairment, and etiology
- Complex relationship to cerebrovascular disease
- Long prodrome with multiple biomarkers
- Cognition is central, but hard to measure
Common disease with age-dependent onset

Semi-log plot of prevalence data from recent population studies


Rise in incidence of AD by age

Common disease with age-dependent onset

Incidence and prevalence exquisitely sensitive to age structure of the population, so comparisons across populations complicated

Protective factors as important as risk factors

Survivors represent a highly selected sample, especially at later ages
Diagnosis ambiguous: Terminology

Classically “Alzheimer’s disease” synonymous with AD dementia, but now often refers to AD pathology

AD pathology common in Mild Cognitive Impairment (MCI), more subtle impairments, and normal elders, particularly at advanced ages

Gold standard autopsy diagnosis of AD is now divorced from symptoms and largely quantitative
Diagnosis ambiguous: Impairment
Thresholds on a continuum

Cognitive Function

Disease Progression

Presymptomatic
Prevention

Preclinical
Early intervention

Clinical Dementia
Treatment

< MCI >
Diagnosis ambiguous: Impairment
Thresholds on a continuum

Dementia threshold based on functional impairment: socially important but of limited reliability

MCI diagnosis much less reliable: 2 unreliable boundaries, more subtle features, and 3 embedded binary decisions:

  No significant functional impairment
  Impaired test performance
  Cognitive concern
Diagnosis ambiguous: Etiology
AD vs. other pathologies

Autopsy gold standard ideal, but limited
Samples are highly selected
Pathology is cumulative and sequence unclear
Differential diagnosis of AD dementia imperfect
Even in tertiary care, PV+ only ~90%
Multiple other neurodegenerative syndromes
Mixed pathology common in AD, particularly vascular
Unclear relationship with Parkinson’s dementia and Lewy Body dementia
Complex relationship to cerebrovascular disease

Picture courtesy of Dr. Eric Smith
Complex relationship to cerebrovascular disease

Two highly prevalent disorders of aging that commonly co-occur: mixed dementia is the rule rather than the exception at advanced ages.

For a given level of AD pathology, the chance of manifesting AD dementia rises with the level of cerebrovascular pathology.

Growing understanding that white matter disease and microhemorrhage, as well as stroke, contribute to vascular cognitive impairment (VCI).

Many shared risk factors: this probably in part reflects vascular contribution to cognitive decline and dementia.
Long prodrome with multiple biomarkers

Slide courtesy of Dr. Reisa Sperling; Figure adapted from Dr. Cliff Jack
Long prodrome with multiple biomarkers

Very long period of silent disease, and additional variable period of unrecognized disease

Some or all of “normal” aging is due to occult AD pathology

Because most measures are sigmoid in distribution, slope depends on starting point, which often varies within samples

Order of biomarkers depends to some extent on biology, but will shift as sensitivity of specific measures
Cognition is central—*but hard to measure*

Spaghetti plots show downward tendency, but considerable noise

*Boyle et al, Frontiers in Neuroscience, 2013*
Cognition central--but hard to measure

Many limitations to neuropsychological tests as an outcome

- Considerable baseline variation in all cognitive measures, even if control for education
- Limited test re-test reliability
- Multiple additional sources of variability in the elderly—sensory and motor issues, intercurrent illness
- Tests with greater sensitivity to early decline often more susceptible to educational and other biases
GWAS of longitudinal cognitive change

Appealing outcome compared to arbitrary unreliable diagnostic categories, but . . . . .

In population data, most people normal, so noise from lifelong cognitive variability swamps signal of early cognitive change

Add to that noise from unreliability of measures (and regression to the mean), practice effects (or potential signal from lack of practice effect)

Distortion of slope from sigmoid measures and left censoring, plus bias from missing data

If focus on AD, real change from non-AD pathologies (and “normal aging”) becomes noise

Very small signal to explain by genes (or other factors, or to modify in a prevention trial)
Potential solutions

Design
Start early in life, or select more homogeneous samples (e.g., for trials)
Repeated/multiple measures at each time point
Develop measures with greater reliability and less susceptibility to education, effort, sensory loss

Analysis
Robust baseline (e.g., mean of 1st two visits)
Mean of multiple time points over several years (single value incorporating repeated measures, decline at entry, lack of practice effect, and additional decline)
Change point models to accommodate non-linear change (but hard to see through the noise)
Additional examples

Design/analysis of a preclinical AD trial: optimize selection to maximize fraction of subjects declining, and outcomes to maximize sensitivity and specificity for real decline (Macklin et al, 2013)

Observed decreased risk of dementia with cognitive activity: impact of definition of normal at baseline and duration of follow up on role of reverse causation (Sajeev et al, submitted)

Prediction of risk of MCI/dementia in normal elders by APOE, age, etc. for a prevention trial: impact of definition of normal, age at baseline, and health on power, expected trajectories, and impact of mixed pathology (Jing et al, in preparation)
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