Alzheimer’s disease mimics and human brain aging

Pete Nelson
Change in Number of Deaths Between 2000 and 2008

- Breast Cancer: +66%
- Prostate Cancer: -3%
- Heart Disease: -8%
- Stroke: -13%
- HIV: -20%
- Alzheimer’s Disease: -29%

Thanks to the Alzheimer’s Association

Based on preliminary 2008 mortality data
Recent years have seen dramatic advancements. A central role for ADRCs and UCI90+.
Better data → more valid conclusions
ADRCs and related series: a new standard

- Improved study designs
- Improved clinical, biomarker, & neurocognitive evaluation
  - Improved pathological evaluation (new diseases!)
  - More variables, more quantitative correlation
- Far better comprehension of the complexity involved
ADRCs and related series: *a new standard*

- Improved study designs

Allow us to start leaving behind studies with:

- Overly interpreted under-evaluated patients
- Fewer variables, over-dichotomization
- “The Anecdote”
ADRCs and related series: a new standard

• Improved study designs

Allow us to start leaving behind studies with:
• Overly interpreted under-evaluated patients
• Fewer variables, over-dichotomization
• “The Anecdote”

Prior era unsubstantiated “myths” still remain!
Myth Roundup

1. There is just one dementia-causing brain disease
2. AD is just “brain aging”, and vice versa
3. A 95-year old is just like a 75-year old, only more so

NON-ALZHEIMER BRAIN DISEASES (AD “mimics”)
DATA
Clinical-pathological studies: rich resources with both antemortem data and thorough autopsy information
Myth #1

There is only one disease that causes cognitive impairment in the elderly
Meta-analysis of clinical (no-autopsy) studies: positive association between diabetes and "Alzheimer’s disease"
Studies with brain autopsies show the opposite result

<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
<th>In diabetics, versus nondiabetics</th>
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<tbody>
<tr>
<td></td>
<td>$N$</td>
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<td>Risk of AD pathology</td>
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Diabetes is associated with increased cerebrovascular disease, not AD pathology (N>1,600)

Studies with brain autopsies show the opposite result

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Acta Neuropathologica, 2011
Much of the impact of diabetes on cognition is mis-diagnosed during life as Alzheimer’s disease.
I'll be the first to admit, the results of your autopsy were very surprising.
“There was a discrepancy rate of 26% between premortem clinical diagnoses and postmortem findings in cancer patients…” (26% had major missed diagnoses)

- 54% of autopsies revealed a new diagnosis with potential adverse impact on survival

Changes in rates of autopsy-detected diagnostic errors over time: a systematic review.
Shojania KG, Burton EC, McDonald KM, Goldman L.

(based on systematic review of autopsy series)

“A contemporary US institution could observe a major error (clinically MISSED diagnoses involving a ‘primary cause of death’) rate from 8.4% to 24.4%”
Generalizable key point:

In advanced old age, it is the norm for human brains to exhibit impactful non-Alzheimer’s pathology.
Group I: No cortical LBs, AGD, HS, infarcts, or FTD (n=134)
Group II: One subtype of non-AD pathology (n=180)
Group II: Two subtypes of non-AD pathology (n=71)
Group II: >2 subtypes of non-AD pathology (n=5)

~2/3rd of UK ADC cohort have important non-AD pathology by age 80; after that, the proportion increases further

Nelson PT et al, JNEN 2007
There should be greater appreciation of diversity of diseases in human brain aging. What then exactly is Alzheimer’s disease?
What is Alzheimer’s disease?
“A”: Aβ PLAQUES

“C” (CERAD): NEURITIC AMYLOID PLAQUE

“B” (BRAAK): NEURO-FIBRILLARY TANGLE

AD neuropathologic hallmarks
Myth 2.

Myth #2

Myth 2. Alzheimer’s disease is just “brain aging”, and vice versa

Testable via

Genetics
Epidemiology
Biochemical pathways
Progerias, or progeroid syndromes, are human diseases with “accelerated aging”:

**Some features:**

Premature “aging” appearance
Wrinkled skin
Hair loss (premature graying)
Loss of fat tissues/atrophy
Atherosclerosis
General weakening/lack of elasticity
Progerias, or progeroid syndromes, are human diseases with “accelerated aging”:

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<td>Hutchinson-Gilford progeria syndrome</td>
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<td>Cockayne syndrome</td>
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<td>Trichothiodystrophy</td>
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Progerias, human diseases with “accelerated aging”: Any increase in AD pathology?

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Lack of a “progeria”-AD link is circumstantial evidence against Alzheimer’s disease being an outcome of “aging”-type biological mechanisms.
Myth #2

AD is just “brain aging”, and vice versa (everyone gets AD if they live long enough)
Epidemiology

Neuropathology
An important and topical issue!!

Source: U. S. Census Bureau
# Alive per 100,000 population, U.S.

Source: 2007 Actuarial Tables

- ~1% alive at age 101

<table>
<thead>
<tr>
<th>Age</th>
<th># Alive per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100,000</td>
</tr>
<tr>
<td>21</td>
<td>60,000</td>
</tr>
<tr>
<td>41</td>
<td>40,000</td>
</tr>
<tr>
<td>61</td>
<td>20,000</td>
</tr>
<tr>
<td>81</td>
<td>10,000</td>
</tr>
<tr>
<td>101</td>
<td>~1%</td>
</tr>
</tbody>
</table>

- Men
- Women
Centenarians
Mean Age at death:
102.2 +/- 2.5 yrs
N=52

CERAD Plaque Densities
- No
- Possible
- Probable
- Definite
Centenarians

Mean Age at death:
102.2 +/- 2.5yrs
N=52

Not everyone gets AD
Other large datasets agree:

It is by no means inevitable for centenarians to get AD

Braak H, et al,
J Neuropathol Exp Neurol. 2011
Studies of epidemiologic scope indicate that Alzheimer’s disease (unlike many other aging features) is not inevitable even in the “oldest-old”
Specific Pathway(s) → AD
The disease of plaques and tangles (AD) begins at young age among individuals with high genetic risk.
5-month old with Down Syndrome
(thanks to Dr. Elizabeth Head and UCI colleagues)

The disease of plaques and tangles (AD) begins at young age among individuals with high genetic risk

Specific (non-Aging!) Pathway(s)
According to genetics, epidemiology, and biochemical pathways, Alzheimer’s disease isn’t necessarily best attributed to “aging” mechanisms.
Myth #3

A 95-year old is just like a 75-year old, only more so
Study of advanced old age...
(individuals beyond 85 years old)
1. ...some cognitive impairment is usual;
2. ...Non-AD pathologies occur with prevalence that approximates AD prevalence.
3. ...HOWEVER, advanced AD pathology (neocortical plaques+tangles), as assessed quantitatively, still always correlates with cognitive impairment.
Two common AD mimics:

Hippocampal sclerosis of aging (HS-Aging)

Cerebrovascular disease (vascular brain injury)
Two common AD mimics:

- Hippocampal sclerosis of aging (HS-Aging)
- Cerebrovascular disease (vascular brain injury)
HIPPOCAMPAL SCLEROSIS (HS-AGING)

- Cell loss/gliosis in hippocampus
- NOT Alzheimer’s
- Usually: TDP-43 pathology
  
  (Neumann et al, 2006)
  (Amador-Ortiz et al, 2007)

Normal aged person’s hippocampus

HS-Aging
**HS-Aging: common, high-morbidity disease**

- HS-Aging pathology is strongly associated with impaired cognitive status
  
  *Nelson PT et al, Brain Pathol 2010*

- A cognitive test-based algorithm (WLD/VF) differentiates HS-Aging from AD at group level
  
  *Nelson PT et al, Brain 2011*
  *Brenowitz W et al, JAD 2014*

- HS-Aging is typically misdiagnosed during life as AD
  
  *Brenowitz W et al, JAD 2014*
2 Key Points:
1. AD pathology levels off in oldest-old
2. HS-Aging pathology increases dramatically in oldest-old

Nun Study: “population-based” cohort of women followed longitudinally for decades, from relatively young age, to autopsy
To elucidate disease mechanisms for therapeutic targets, we asked: what are the genetic risk factors of HS-Aging?
BIG DISTINCTION VS. ALZHEIMER’S DISEASE:

THERE IS NO ASSOCIATION BETWEEN APOE GENOTYPE AND HS-AGING PATHOLOGY

Troncoso JC et al, Neurosci Lett. 1996
Leverenz JB et al, Arch Neurol. 2002
Nelson PT et al, Brain. 2011
Pao WC et al, Alzheimer Dis Assoc Disord. 2011
Brenowitz W et al, JAD. 2013
Recently there been progress in the field identifying putative HS-Aging risk factor genes:

1. GRN
2. TMEM106B
3. ABCC9
4. KCNMB2
Recently there been progress in the field identifying putative HS-Aging risk factor genes:

1. GRN
2. TMEM106B
3. \( \rightarrow \) ABCC9
4. KCNMB2
ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology

Peter T. Nelson · Steven Estus · Erin L. Abner · Ishita Parikh · Manasi Malik · Janna H. Neltner · Eseosa Ighodaro · Wang-Xia Wang · Bernard R. Wilfred · Li-San Wang · Walter A. Kukull · Kannabiran Nandakumar · Mark L. Farman · Wayne W. Poon · Maria M. Corrada · Claudia H. Kawas · David H. Cribbs · David A. Bennett · Julie A. Schneider · Eric B. Larson · Paul K. Crane · Otto Valladares · Frederick A. Schmitt · Richard J. Kryscio · Gregory A. Jicha · Charles D. Smith · Stephen W. Scheff · Joshua A. Sonnen · Jonathan L. Haines · Margaret A. Pericak-Vance · Richard Mayeux · Lindsay A. Farrer · Linda J. Van Eldik · Craig Horbinski · Robert C. Green · Marla Gearing · Leonard W. Poon · Patricia L. Kramer · Randall L. Woltjer · Thomas J. Montine · Amanda B. Partch · Alexander J. Rajic · KatieRose Richmire · Sarah E. Monsell · Alzheimer’ Disease Genetic Consortium · Gerard D. Schellenberg · David W. Fardo
Table 1  Research subjects (n = 2,666 research subjects total) and the five autopsy cohorts analyzed in the current study

<table>
<thead>
<tr>
<th>Autopsy cohort</th>
<th>Pathologic phenotype evaluated</th>
<th>HS cases</th>
<th>Avg age (years ± st dev)</th>
<th>Non-HS controls</th>
<th>Avg age (years ± st dev)</th>
<th>Total</th>
<th>Role in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADGC</td>
<td>HS pathology</td>
<td>186</td>
<td>84.1 ± 8.2</td>
<td>1,450</td>
<td>81.5 ± 8.7</td>
<td>1,636</td>
<td>Stage I (GWAS)</td>
</tr>
<tr>
<td>ROS-MAP</td>
<td>HS pathology</td>
<td>29</td>
<td>93.3 ± 5.4</td>
<td>398</td>
<td>90.8 ± 4.1</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>ACT</td>
<td>HS pathology</td>
<td>26</td>
<td>87.6 ± 4.2</td>
<td>150</td>
<td>88.4 ± 2.2</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>UK-ADC</td>
<td>Hippocampal TDP-43 pathology</td>
<td>94</td>
<td>92.3 ± 6.9</td>
<td>161</td>
<td>93.3 ± 6.4</td>
<td>255</td>
<td>Stage II #1</td>
</tr>
<tr>
<td>UCI90+</td>
<td>HS pathology</td>
<td>28</td>
<td>94.1 ± 2.3</td>
<td>144</td>
<td>92.3 ± 4.5</td>
<td>172</td>
<td>Stage II #2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>363</td>
<td>94.1 ± 2.3</td>
<td>2,303</td>
<td>92.3 ± 4.5</td>
<td>2,666</td>
<td></td>
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GWAS was performed on the three Stage I datasets, from Alzheimer’s Disease Genetics Consortium (ADGC, which are based mostly on dementia research clinics), Rush Religious Order Study and Memory and Aging Project (ROS-MAP, which is an epidemiologic cohort), and Adult Changes in Thought (ACT, which is a community-based autopsy cohort). First Stage II was performed at University of Kentucky Alzheimer’s Disease Center (UK-ADC), and second Stage II at the University of California Irvine 90+ Study (UCI90+). None of the cases used in the assessment of HS-Aging overlapped between cohorts.

HS Hippocampal sclerosis

363 HS-Aging cases

2303 Controls

NEUROPATHOLOGY-based GWAS
**Strengths**

- Multiple population-based autopsy series (ROS-MAP, ACT, UCI90+ [THANK YOU!])
- Many of the best neuropathologists in the USA
- Tailored methodology to task at hand

**Weaknesses**

- Unimpressive sample size by GWAS standards (only tested for large effect size risk allele[s])
- Non-uniform case/control operationalizations
- Evolution over time
- Differences between centers
- Certainly many false-negative HS-Aging cases (e.g. low awareness, sampling ½ of brain)
ABCC9

ATP-binding cassette, sub-family C member 9 also known as sulfonylurea receptor 2 (SUR2)
**ABCC9** gene changes (SNPs) linked to HS-Aging pathology:

- Comprise multiple intronic SNPs in LD (spanning over 10 exons)
- Appear to be local eQTLs for **ABCC9** (polymorphism correlates with mRNA levels)
ABCC9/HS-Aging association: interesting on multiple levels...

A functional role of the C-terminal 42 amino acids of SUI and SUR2B in the physiology and pharmacology of cardio; ATP-sensitive K⁺ channels

Mitsuhiro Yamada, Yoshifusa Kurachi
... including the possibility to accomplish one of the great un(der)achieved goals of genomics studies: clinical relevance ...
...because ABCC9 is a "druggable" target.
Sulfonylureas (SUR) – popular oral antidiabetes drugs – **inhibit** ABCC9(SUR2) function

<table>
<thead>
<tr>
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<th>Sulfonylurea Use (N=36)</th>
<th>No Sulfonylurea Use (N=588)</th>
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<tr>
<td></td>
<td>HS-Aging Pathology (n=11)</td>
<td>HS-Aging Pathology (n=97)</td>
</tr>
<tr>
<td></td>
<td>No HS-Aging Pathology (n=25)</td>
<td>HS-Aging Pathology (n=491)</td>
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NACC data (n=624):
>85 y.o. people with well-documented drug history
NOT a population-based cohort
Sulfonylureas – popular antidiabetes drugs – inhibit ABCC9 function

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Documented sulfonylurea exposure is associated with *increased* risk for HS-Aging pathology (p = 0.03)

Not a non-specific association with (a/w) diabetes

--Diabetes is not a/w HS-Aging pathology

--other diabetes drug classes do not a/w HS-Aging
Where it didn’t “work”

(null hypothesis about SUR/HS-Aging association NOT disproven)

• NACC cohort, among individuals <85 years at death
Where it didn’t “work”

(null hypothesis about SUR/HS-Aging association NOT disproven)

• NACC cohort, among individuals <85 years at death
• ACT cohort (n=424, ~1/2 were <85 years at death)
Proportion with HS-Aging pathology, by documented years on SUR (n=67)

SUR/HS-Aging pathology correlation is stronger with chronic use of SUR drug
SUR/HS- Aging pathology correlation is stronger with chronic use of SUR drug

Proportion with HS-Aging pathology, by documented years on SUR (n=67)

Average age, by documented years on SUR (n=67)
Conclusions on HS-Aging

- HS-Aging pathology:
  - Common, high-morbidity AD mimic
  - Associated with heritable mutations
  - Associated with ABCC9-inhibiting drug
    - Working now on ABCC9 agonist

- Underscores importance of pathology-based phenotypes
Two common AD mimics:

- Hippocampal sclerosis of aging (HS-Aging)

- Cerebrovascular disease (vascular brain injury)
Blood vessels in the brain are extremely complex and vulnerable.
Cerebrovascular brain disease/VBI: Practically universal in aged individuals!!

% Cases with Cerebrovascular Pathology
(NACC data, N=4,423 cases)
Specific key point:

It is the norm for people in advanced old age to have both Alzheimer’s and cerebrovascular diseases.
Is there ANY HOPE?!?!
Advice

Virtually guaranteed to make it so that if you live to be 95, you will have better cognition than if you did NOT take this advice (all other things being equal)
Blood vessels in the brain:

Vascular brain disease risk is modifiable by environmental factors
Blood vessels in the brain:

What are they vulnerable to
Blood vessels in the brain: What are they vulnerable to?

- High blood sugar
- High blood pressure
- High cholesterol
- Smoking
Blood vessels in the brain: What makes them happy?

- Exercise
- Healthy diet
- Good cardiac care
- Moderate alcohol
• High blood sugar
• High blood pressure
• High cholesterol
• Smoking

• Exercise
• Healthy diet
• Good cardiac care
• Moderate alcohol
Alzheimer’s disease

DEMENTIA

Cognition

Time
Alzheimer’s disease

DEMENTIA

Cognition

Time

Cerebrovascular disease/VBI

HS-Aging
Additional pathologies in advanced old age require an overhaul of prior assumptions.
In advanced old age, non-AD diseases underlie much of clinical dementia.

“Classic” clin-path studies addressed much younger cohorts.
AD is not “brain aging”; there are abundant evidences for a specific plaque+tangle disease with strong genetic contribution.

Multiple diseases often coexist in aged human brains.

Both HS-Aging and cerebrovascular brain diseases are common, providing hope for new therapeutic strategies aimed at what a layperson would refer to as Alzheimer’s disease.
Neuropathology (NP) is complicated

Consideration of NP necessary to optimize management of
- patients, clinical trials, biomarkers, animal models, etc

NP has become more, not less, relevant and important
Hickam's dictum is a counterargument to the use of Occam’s Razor, in the medical profession.

The principle is commonly stated: "Patients can have as many diseases as they damn well please."
Obvious fact:
Obvious fact:

We’re not done yet
UK-ADC Neuropathology Core
Thanks to:

Dr. David Fardo

Dr. Steven Estus
Big Team
Thanks to:

- ADGC
- NACC
- ACT
- ROS-MAP
- UCI 90+ Study
- Georgia Centenarians
Thanks

NIH/NIA ADC Neuropathology Core

ADGC Special Analysis Group grant (U01 AG032984)

NIH/NIA NACC (U01 AG016976)
Thanks

Dr. William Markesbery

NIH/NIA
NIH/NINDS
NIH/NINDS
NIH/NIA
NIH/NIA ADC NP Core

Pilot Grant
K08 Grant
R01 Grant
R21 Grant
P30 Grant

Alzheimer’s Association
NIR Grant
Does Occam’s razor apply to research on brain in health and disease?
Occam’s razor, in a nutshell:

Simpler theories are preferable to more complex ones

“Principle of parsimony”
William of Ockham
(c. 1287 – 1347)

“Occam’s [or Ockham’s] razor”
“Anti-Razors“
Gottfried Wilhelm Leibniz
(c. 1646 – 1716)

(Other “Anti-Razors”: Emmanuel Kant, Karl Menger)

• "It is vain to do with fewer what
  requires more."

• Occam’s razor may lead to the
  "science of imaginary solutions"
Does Occam’s razor apply to research on brain in health and disease?
Cerebrovascular disease: Brain disease linked directly to blood supply to the brain
Blood vessels in the brain are incredibly complex and also very vulnerable.
What is Alzheimer’s disease (AD) and why are autopsies important?

Good news: not everyone will get AD

Bad news: other diseases, in addition to AD, afflict aged human brains

What do I recommend that YOU do…?

How about that U. KENTUCKY-ADC?
Logistic regression models were used to determine the probability of AD (CERAD Possible or Probable, Braak stages V or VI at autopsy) and the probability of HS pathology (regardless of laterality) as a function of age at death using SAS/STAT® 9.2 software.

“Definite” AD pathology

Hippocampal sclerosis pathology

Autopsy series with 106 HS cases, 1,004 controls
So why is clinical-pathologic correlation so (apparently) imperfect?
Thought experiment:

Could you detect a clinico-pathological relationship in heart disease if testing the correlation of atherosclerosis and cardiac health?

“Clean sample”
Clean sample – good correlation

Cardiac Function

Amount of atherosclerosis
“Dirty sample”
Clean sample – good correlation

Cardiac Function

Amount of atherosclerosis
Dirty sample – poor correlation

Cardiac Function

Amount of atherosclerosis
YOU HAVE NINE DISEASES?

THAT HAVE NAMES.
A large proportion of MRI-visualized hippocampal atrophy is NOT AD!
A large proportion of MRI-visualized hippocampal atrophy is NOT AD!

Biomarkers’ prediction of cognitive decline not good enough: for therapeutic relevance one needs specific data about disease mechanism(s).
Development of disease-specific therapies are helped by understanding disease mechanism.
Development of disease-specific therapies are helped by understanding disease mechanism.

What mechanism(s) underlie HS-Aging?