Hippocampal Sclerosis, cognition and dementia in the old and oldest old

The Rush experience in older community-dwelling cohorts

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Hippocampal sclerosis

1. HS and aging; HS in community old and oldest old

2. Relationship with clinical diagnosis and brain pathologies

3. Impact on cognition/dementia

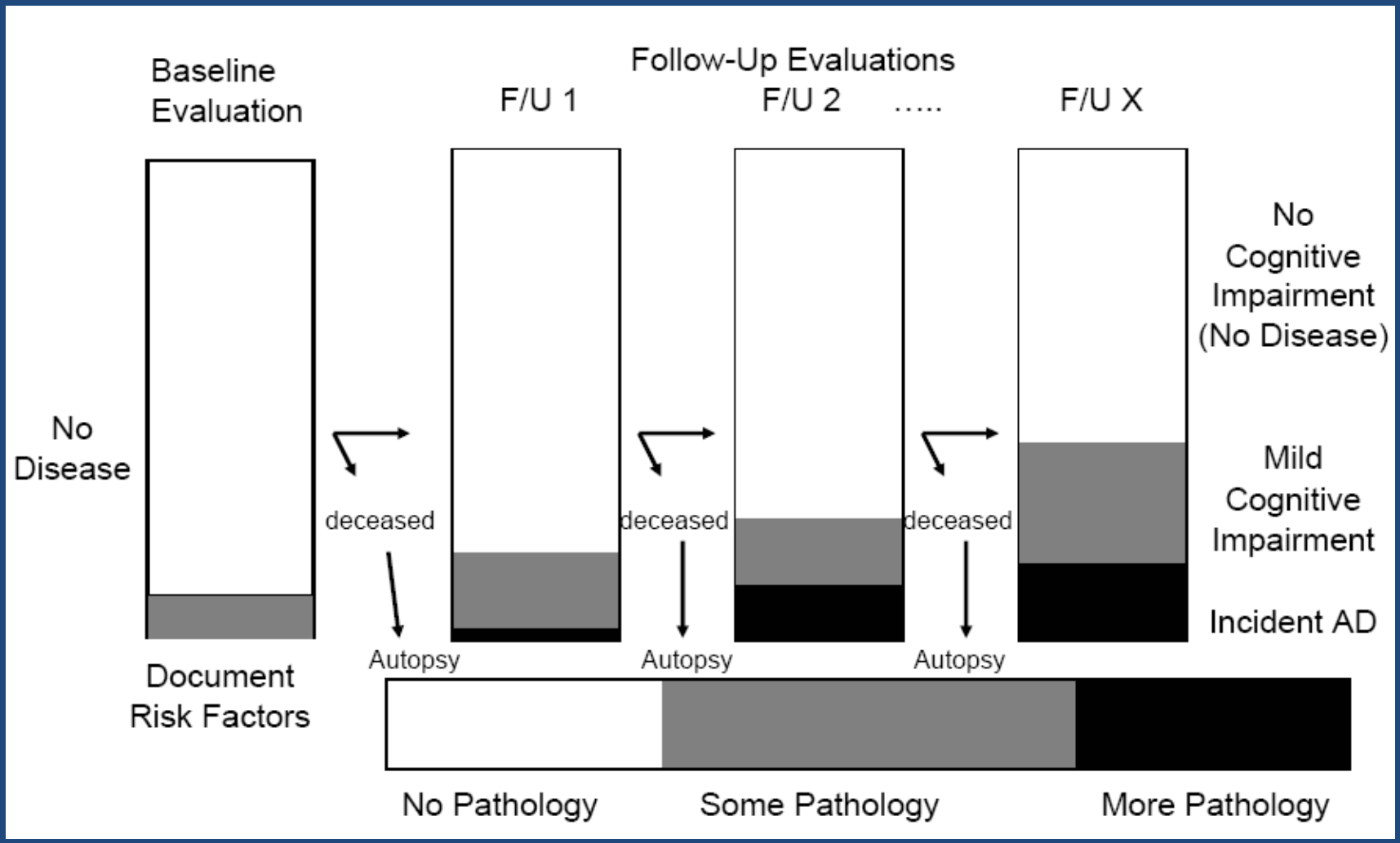
Methods

- Religious Orders Study; started 1993
  - Over 1150 participants; > 550 autopsies;
- Memory and Aging project; started 1997
  - Over 1550 participants; > 450 autopsies

- Longitudinal annual cognitive testing; final diagnoses
  - Enrolled with no dementia
  - Episodic memory, language, working memory, perceptual speed, and visuo-spatial skills
  - Final diagnoses after review of all years/testing/diagnoses by expert neurologist

- All agree to autopsy at end of life
  - ROS - autopsy rate about 94%
  - MAP – autopsy rate about 80%
- Both cohorts have about 6 months interval between last eval and death and average PMI is about 8 hours

The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort

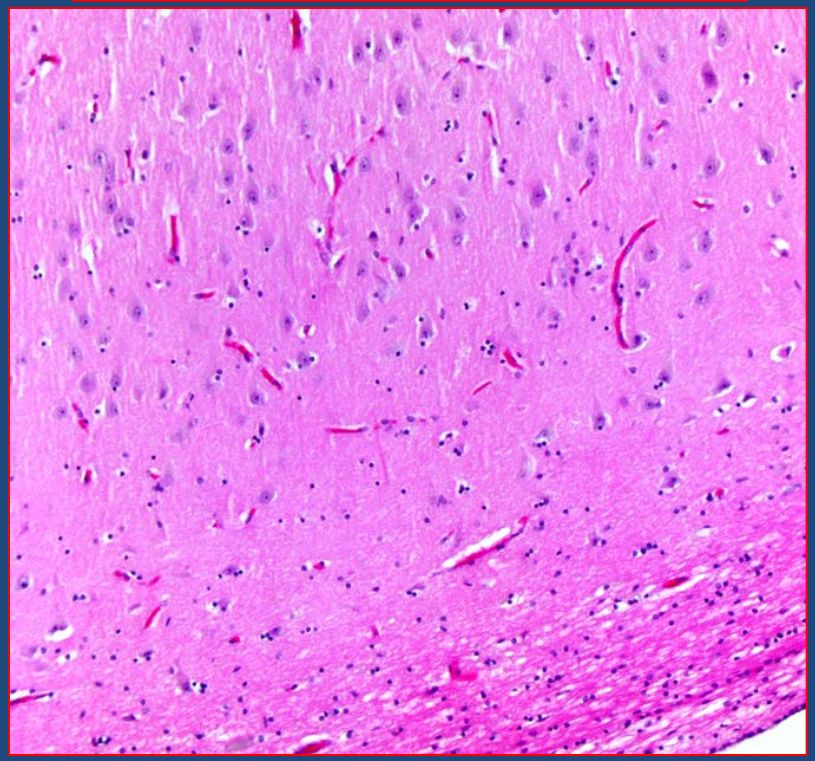


Bennett DA, et al. *Neuroepidemiology.* 2005;25:163–175.

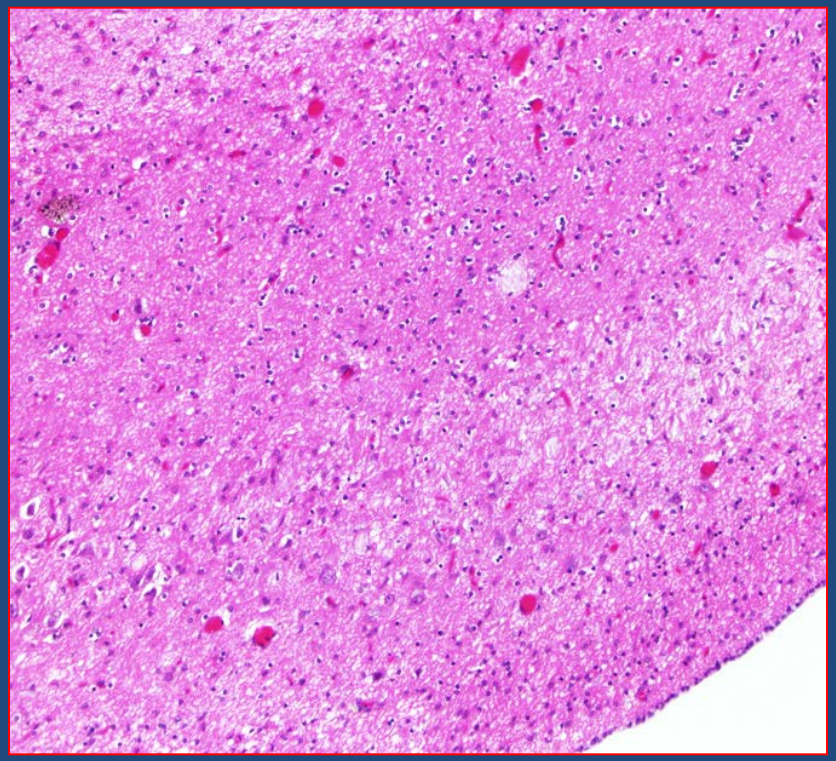
Pathology

- Hippocampal sclerosis
  - H&E single section of hippocampus at level LGN. Requiring severe loss of neurons and gliosis of CA1 +/- other sectors
- NIA-Reagan diagnoses of Alzheimer's disease
  - Requiring minimum of moderate neocortical neuritic plaques and Braak3/4
- Lewy bodies by phospho-specific abs to alpha synuclein
- Gross Infarcts – detected on 1 cm slabs; confirmed by microscopy
- Microinfarcts using at least 9 H&E 6 micron sections
- TDP-43 phospho specific antibodies
  - Amygdala, hippo, entorhinal, midfrontal, midtemporal

No Sclerosis



Hippocampal Sclerosis



Statistics

- Chi-squares and t-test for unadjusted differences between groups

- Multiple linear and logistic regression to investigate pathology predictors of HS and the relation of HS to dementia, cognition

Results

- 1054 subjects
- 84 (8%) subjects with HS
  - Most common additional region = subiculum

	Hippocampus		
	No Sclerosis n=968, 92%	Sclerosis n= 84, 8%	Total N= 1052
Age at death (mean)	87.86	91.07***	
Gender, female	622 (64%)	62 (74 %)	684 (65%)
Dementia	378 (40%)	65 (79%)**	443 (43.1%)
NIA-Reagan, score 1-2	593 (61%)	66 (79 %)*	659 (62.6%)
Macroinfarcts	338 (35%)	35 (42 %)	373 (35.4%)
Microinfarcts	269 (28 %)	30 (36 %)	299 (28.42%)
Lewy bodies	197 (20%)	27 (32%)*	224 (21.3%)

Hippocampal sclerosis – Age and the oldest old

- Oldest old in cohort = 420/1054 (39 %)
  - (Oldest old in group with HS: 51/84 (60.7%))

- HS frequency
  - Relatively common in the oldest old = 12% (51/420)
  - compared to 33/634 in old = 5.2%

Using logistic regression age had an independent association with HS even after controlling for AD, LB, and vascular pathology

HS – clinical diagnoses

- 65 of 84 (77.4%) had clinical dx of dementia
- 62 of 84 (73.8%) all but 3 dx AD

- 1 with FTLD
- 2 with other dementia diagnoses

- 10 with MCI (11.9%)
- 7 with NCI (8.3%)

Pathologic diagnoses

- Concomitant AD pathology diagnosis in 70/84 (83.3%)

- HS without AD pathologic diagnosis; in only 14/84 subjects (16.7%)

  4 had FTLD, 1 had LBD, 11/14 had infarcts…however,

- Neither infarcts (or vessel disease) showed an independent association with HS after controlling for age, AD path dx, or Lewy bodies.

HS – pathologic predictors

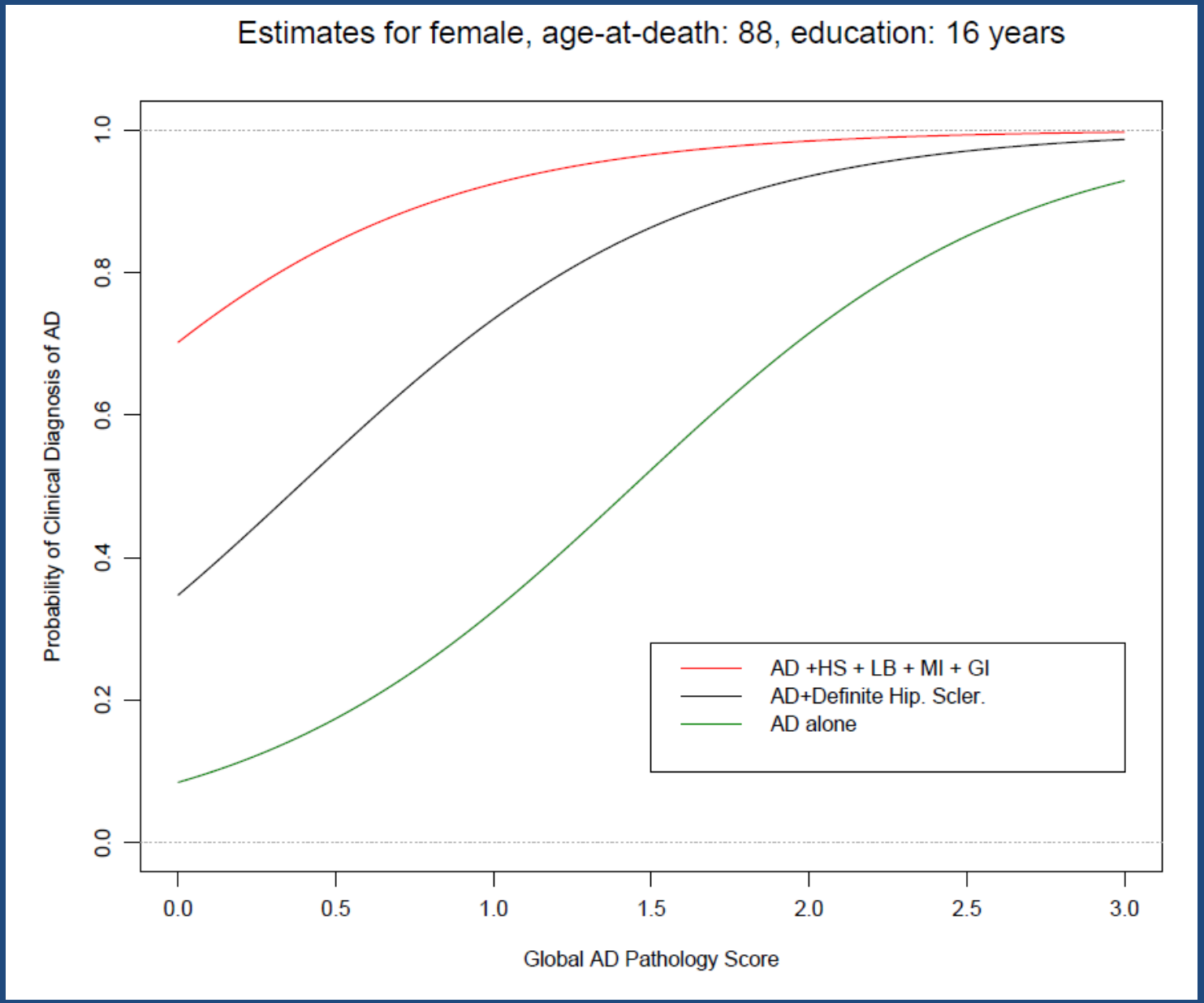
- Using logistic regression controlling for age, sex, education and infarcts,

- Alzheimer's disease pathology and Lewy body pathology each showed independent association with HS
  - AD path diagnoses increased odds of HS by almost 2 fold (1.9; $p<.02$)
  - Lewy bodies increased odds of HS by about 80% (OR = 1.8; $p<.02$)

TDP-43

- 83% of those with HS have positive TDP-43
- Correlation .21; $p<0.0001$

Multiple variable regression, model predictors	Odds of Dementia	95% confidence interval	p-value
Alzheimer Disease Pathology	4.01	3.11-5.18	<0.001
Macroinfarcts	2.0	1.47-2.72	<0.001
Microinfarcts	1.35	0.98-1.87	0.066
Lewy bodies	2.13	1.48-3.05	<0.001
Hippocampal Sclerosis	4.60	2.42-8.75	<0.001


Estimates for female, age-at-death: 88, education: 16 years
Probability of Clinical Diagnosis of AD
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Global AD Pathology Score
AD +HS + LB + MI + GI
AD+Definite Hip. Scler.
AD alone

Multiple variable regression, model predictors	Cognitive Function (Estimate, SE, p-value)		
AD Pathology		-0.76 (0.05, <0.001)	-0.75 (0.05,<0.001)
Macroinfarcts			-0.31 (0.06,<0.001)
Microinfarcts			-0.14 (0.07, 0.03)
Lewy bodies			-0.32 (0.07,<0.001)
Hippocampal Sclerosis	-0.78 (0.13, <0.001)	-0.66 (0.11, <0.001)	-0.60 (0.12,<0.001)

Multiple variable regression, model predictors	Estimate, SE, p-value				
	Episodic Memory	Semantic Memory	Working Memory	Perceptual Speed	Visuospatial Abilities
AD Pathology	-0.90 (0.14) <0.001	-0.74 (0.06) <0.001	-0.47 (0.05) <0.001	-0.48 (0.05) <0.001	-0.44 (0.06) <0.001
Macroinfarcts	-0.35 (0.07) <0.001	-0.27 (0.08) <0.001	-0.24 (0.06) <0.001	-0.26 (0.07) <0.001	-0.13 (0.07) 0.088
Microinfarcts	-0.16 (0.08) 0.04	-0.26 (0.09) 0.003	-0.06 (0.07) 0.38	-0.25 (0.08) =0.001	-0.06 (0.08) 0.440
Lewy bodies	-0.30 (0.08) <0.001	-0.35 (0.09) <0.001	-0.20 (0.07) 0.005	-0.31 (0.08) <0.001	-0.25 (0.08) 0.003
Hippocampal Sclerosis	-0.89 (0.14) <0.001	-0.83 (0.16) <0.001	-0.20 (0.12) 0.085	-0.49 (0.14) <0.001	-0.33 (0.14) 0.019

Conclusions

- HS occurs in substantial number of older persons particularly the oldest old
- Related to dementia in most - not all (a minority have NCI/MCI). Most of those with HS who are diagnosed with dementia are clinically diagnosed with probable AD.
- Strong relationship with AD and LB; when occurs outside that context case may have FTLD or infarcts
- Very strongly adds to likelihood of dementia
- Cognitive impairment associated with HS is multi-domain – not just episodic memory. Suggest HS is reflects a more diffuse process perhaps in relation to TDP-43.

HS

- **Important future goals**
  - **clinically identify persons with HS during life**
  - **Identify risk factors (genetic and other)**
  - **Understand pathogenesis**
  - **Prevention and treatment**

Acknowledgments

- Rush University Medical Center

- Neelum Aggarwal, MD
- Konstantinos Arfanakis, PhD
- Zoe Arvanitakis, MD, MS
- Lisa Barnes, PhD
- David Bennett ,MD
- Patricia Boyle, PhD
- Aron Buchman, MD
- Ana Capuano, PhD
- Robert Dawe, PhD
- Debra Fleischman, PhD
- Bryan James, PhD
- Sue Leurgans, PhD
- **Sukriti Nag, MD, PhD** ★
- Rita Shapiro, DO
- Raj Shah, MD
- Lei Yu, PhD
- Robert Wilson, PhD

- National Institute on Aging

- Alzheimer's Association
- Illinois Department Public Health
- Elsie Heller Brain Bank Endowment Fund
- Robert C. Borwell Endowment Fund

- Study Participants
- Religious Orders Study
- Rush Memory and Aging Project