Risk Factors for dementia, neuritic plaques, neurofibrillary tangles, and vascular amyloid in autopsied, aged Japanese-American men:

HONOLULU-ASIA AGING STUDY

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The Honolulu-Asia Aging Study

- Started as the Honolulu Heart Program in 1965. N=8006 Japanese-American men born 1900-1919. Exams and tests for heart dis., stroke
- HAAS established 1991-93, 3734 examined for cognitive and motor function, dementia, stroke, and Parkinson's disease
- HAAS re-exams q 2-3 years x 5 more times; most recent exam cycle completed 2005

HONOLULU-ASIA AGING STUDY EXAMINATION CYCLES

exam	YEAR	age range	N
• HHP/HAAS 4	1991-93	71-93yr	3734
• HHP/HAAS 5	1994-96	74-95	2705
• HHP/HAAS 6	1997-99	77-98	1991
• HHP/HAAS 7	1999-00	79-100	1523
• HHP/HAAS 8	2001-03	81-103	1200
• HHP/HAAS 9	2004-05	83-104	997

Cognitive Function

Cognitive Abilities Screening Instrument (CASI)

- Developed for cross-national and cross-cultural comparisons
- Composite of the Hasegawa, MMSE and 3MS (Evelyn Teng et al)
- 9 cognitive domains
- Score range 0-100

HAAS research on AD; BRAIN AUTOPSY METHODS

- **N~ 665 brain autopsies done to date, with complete info now available for 502.**

- **AD lesions observed by microscopic examination -- modified Bielschowski and Gallyas silver stains, and immunohistochemically for amyloid in vessels and plaques. Neocortical counts based on 20 fields chosen based on high neuritic plaque numbers.**

35% of decedents diagnosed with dementia came to autopsy

17% of decedents *not* diagnosed with dementia came to autopsy

Autopsied decedents diagnosed with dementia are representative of all demented decedents

Autopsied decedents *not* diagnosed with dementia are representative of all non-demented decedents

The only risk factors consistently associated with AD to date are advanced age, the Apo E4 allele, and possibly education

- This might reflect a heterogeneous or multi-factoral pathogenesis for the clinical condition.

- ***Use of the specific neuropathologic lesions as endpoints might allow the identification of additional or "new" risk factors.***

Characteristics of 502 autopsied HAAS men -- Age at death

age (years)	*Number*	*%*
73-79	70	14
80-84	167	33
85-89	154	31
90-94	84	17
>= 95	27	5

Mean age = 85.7 years, s.d.= 5.2

Characteristics of autopsied HAAS subjects (Japanese-American men) Apolipoprotein E 4 zygosity

Negative for E 4	*82%*
Heterozygous	*17%*
Homozygous	*1%*

Characteristics of autopsied HAAS subjects (Japanese-American men)

cognitively normal	*44 %*
marginal / uncertain	*23 %*
DSM III-R demented	*33 %*

Characteristics of 502 autopsied HAAS subjects (Japanese-American men)

Braak stage

stage	*%*
1	*5*
2	*13*
3	*33*
4	*21*
5	*19*
6	*9*

Characteristics of 502 autopsied HAAS subjects (Japanese-American men) neocortical neuritic plaques

	%
negligible	*50*
sparse	*42*
moderate numbers	*4*
high numbers	*4*

Characteristics of 502 autopsied HAAS subjects (Japanese-American men) neocortical neurofibrillary tangles

	%
Negligible	*43*
sparse	*38*
moderate numbers	*7*
high numbers with >=1 occipital	*12*

Characteristics of 502 autopsied HAAS subjects (Japanese-American men) vascular amyloid index

		%
0	*None observed*	*50*
1	*few vessels involved*	*40*
2	*moderate*	*3*
3	*high number of vessels involved*	*7*

Intercorrelations among AD lesion indices (Spearman coefficients)

	Braak stage	neocx NP	neocx NFT	vasc. amyloid
Braak stage	*1.0000*			
Neocx NP	*0.43* *p<.0001*	*1.0000*		
Neocx NFT	*0.59* *p<.0001*	*0.58* *p<.0001*	*1.000*	
Vasc. Amyloid	*0.29* *p<.0001*	*0.61* *p<.0001*	*0.42* *p<.0001*	*1.0000*

Ordinal logistic regression model

dependent variable = normal, marginal or demented

Independent variable	*OR*	*(95% CI)*	*p*
Age at death	1.09	(1.05-1.13)	<.0001
Education	0.94	(0.89-0.99)	0.022
Apo E4 zygosity	1.52	(0.99-2.36)	0.057
intracranial volume	1.00	(0.99-1.01)	ns

Ordinal logistic regression model

dependent variable = neocortical neuritic plaque index

Independent variable	*OR*	*(95% CI)*	*p*
Age at death	1.07	(1.03-1.11)	0.001
Education	1.04	(0.98-1.10)	ns
Apo E4 zygosity	3.37	(2.14-5.33)	<.0001
intracranial volume	1.00	(0.99-1.01)	ns

Ordinal logistic regression model

dependent variable = neocortical NFT index

Independent variable	*OR*	*(95% CI)*	*p*
Age at death	1.02	(0.98-1.05)	ns
Education	0.97	(0.92-1.02)	ns
Apo E4 zygosity	2.23	(1.45-3.41)	0.0002
intracranial volume	1.00	(0.99-1.01)	ns

Ordinal logistic regression model

dependent variable = vascular amyloid index

Independent variable	*OR*	*(95% CI)*	*p*
Age at death	1.09	(1.05-1.13)	<.0001
Education	0.94	(0.89-0.99)	0.022
Apo E4 zygosity	1.52	(0.99-2.36)	0.057
intracranial volume	1.00	(0.99-1.01)	ns

the following candidate risk factors have been weakly linked to at least one of the AD neuropathologic lesion indices in ordinal logistic regression models:

- Elevated midlife BP (stronger for NFT)
- Moderate (but not very high) lifetime cigarette smoking
- Diabetes and/or glucose-insulin dysregulation
- Elevated HDL levels, likely related to low Apolipoprotein A1 levels
- Family history of Down syndrome

No significant association with the neuropathologic lesions of AD have been identified for the following candidate risk factors:

Midlife or late life coronary heart disease; history of stroke; orthostatic hypotension; ankle-arm blood pressure ratio; use of anti-hypertensive meds.

late life fibrinogen levels or wbc counts; use of NSAIDS or aspirin; levElevated midlife BP (stronger for NFT).

Self-reported childhood personality or scholastic performanc; childhood residence; birth order.

Midlife alcohol consuption; history of shingles or warts.

Conclusions

- **Advanced age and the Apo E4 allele are associated with AD neuropathologic lesions.**
- **Education and head size (intracranial volume are not associated with NP, NFT, or CAA in HAAS men.**
- **Weak associations with AD lesions are observed for midlife hypertension, moderate smoking, glucose-insulin dysregulation, and possibly elevated HDL or low apoA1 levels.**
- **No other risk factors have been linked to AD lesions to date in analyses controlling for age and ApoE4 zygosity.**