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Journal
Neurology, 91(19)

ISSN
0028-3878

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Publication Date
2018-11-06

DOI
10.1212/wnl.0000000000006455

ARTICLE

Risk factors of hippocampal sclerosis in the oldest old

The 90+ Study

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Neurology® 2018;91:e1788-e1798. doi:10.1212/WNL.0000000000006455

Abstract

Objective

To examine the risk factors and comorbidities of hippocampal sclerosis (HS) in the oldest-old.

Methods

A total of 134 participants with dementia from The 90+ Study with longitudinal evaluations and autopsy were included in this investigation. Participants were divided into 2 groups, one with and one without HS pathology, and differences in clinical and pathologic characteristics were compared.

Results

Persons with HS tended to have a longer duration of dementia compared to participants without HS (mean 4.0 years vs 6.7 years, odds ratio [OR] 1.26; 95% confidence interval [CI] 1.11–1.42; $p < 0.001$). HS was more likely in participants with a history of autoimmune diseases (rheumatoid arthritis or thyroid disease, OR 3.15; 95% CI 1.30–7.62; $p = 0.011$), high thyroid-stimulating hormone (OR 4.94; 95% CI 1.40–17.46; $p = 0.013$), or high thyroid antibodies (OR 3.45; 95% CI 1.09–10.88; $p = 0.035$). Lewy body disease (LBD) pathology was also associated with an increased likelihood of HS (OR 5.70; 95% CI 1.22–26.4; $p = 0.027$).

Conclusion

We identified autoimmune conditions (rheumatoid arthritis and thyroid disease) as potential risk factors for HS in our cohort. LBD was the only pathology that was associated with increased odds of HS and those harboring HS pathology had a longer duration of dementia. This suggests multiple pathways of HS pathology among the oldest-old.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CI = confidence interval; **CVD** = cerebrovascular disease; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **H&E** = hematoxylin & eosin; **HS** = hippocampal sclerosis; **LBD** = Lewy body disease; **OR** = odds ratio; **RA** = rheumatoid arthritis; **TPO** = thyroid peroxidase; **TSH** = thyroid-stimulating hormone.

People over the age of 90 are the fastest growing age group in much of the world and in the United States.[1] Dementia is very common in the oldest old, with an overall prevalence of all-cause dementia in this age group of 41.2%.[2] Hippocampal sclerosis (HS) is strongly associated with dementia in the oldest old.[3] HS is a neuropathologically defined condition characterized by severe and disproportionate gliosis and neuronal loss in the CA1 region of the hippocampus and subiculum.[3–6] The prevalence of HS pathology in the elderly population has been reported to be up to 26% in previous studies,[6–12] making HS an important condition to investigate in the oldest old.[13]

Despite its importance,[14] the clinical characteristics, neuropathologic comorbidities, and risk factors of HS remain poorly understood.[15,16] To overcome these knowledge gaps, we studied data from 134 participants with dementia from The 90+ Study, a population-based study of people aged 90 years and older.[17] The aim of this study was to compare, in a group of participants with dementia, characteristics of those with HS at autopsy to individuals without HS. Participants were compared in terms of medical histories and neuropathologic findings to identify risk factors and neuropathologic characteristics of HS in the oldest old.

Methods

Participants

Participants who had agreed to longitudinal in-person assessments and postmortem brain examination came from The 90+ Study, a population-based epidemiologic study of individuals aged 90 years and over in Laguna Woods, California. The 90+ Study began in 2003 to study the physical and mental health of the fastest-growing age group in the United States. As of September 30, 2015, 421 participants had enrolled in the autopsy program, representing 39% of those invited, and 264 had come to autopsy (93% autopsy rate) (figure). The inclusion criteria for the present study were (1) postmortem analysis (autopsy) of the brain and (2) clinical diagnosis of dementia at the time of death from a multidisciplinary case conference as described below. The focus of the study was on individuals with dementia as almost all participants who had HS at postmortem had a diagnosis of dementia. Inclusion of participants without dementia would have only added 3 cases to the HS group at the expense of subjecting the study to confounding effect of a cognitively heterogeneous sample. However, to ensure that restricting the analysis to only participants with dementia did not lead to finding of spurious associations, we also performed the analyses on the full autopsied cohort (n = 264) for variables with significant associations in the dementia group.

Standard protocol approvals, registrations, and patient consents

All participants or their designated surrogates provided consent to participate in the study. Procedures were reviewed and approved by the Institutional Review Board at the University of California, Irvine.

Assessments

The cognitive and physical status of the participants was evaluated in-person every 6 months. Clinical evaluation included a battery of neuropsychological tests, neurologic examination, and self or informant completed questionnaires for demographics and medical history. Furthermore, after a participant's death, additional information was obtained from informants regarding cognition and function since the last evaluation.

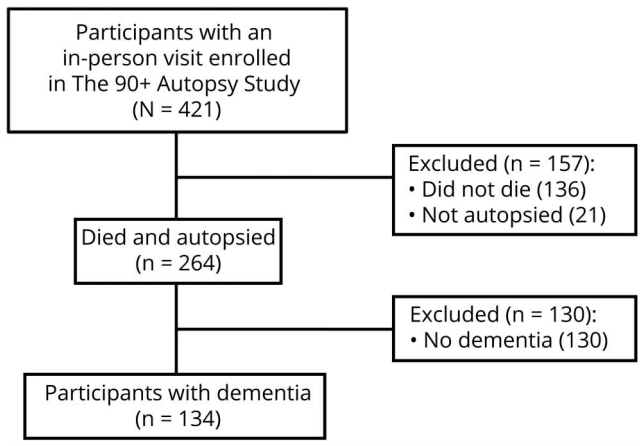
Determination of dementia

Clinical diagnoses of dementia were made applying DSM-IV criteria in a multidisciplinary consensus diagnostic conference done after a participant's death, with conferees blinded to pathologic findings. All available information on the participant was used in determination of dementia. This included neuropsychological test scores, neurologic examination, information collected from informants, available medical records including laboratory tests and brain imaging (CT/MRI), videos from the time of visit, and death certificate.

Pathologic evaluations

All postmortem tissue procurement and preparation was performed at the University of California, Irvine, between 2003 and 2012 with Alzheimer's Disease Research Center

Figure Flow chart for participant inclusion



protocols in use during this interval. Before dissection, the whole brain was weighed and then one hemisphere was selected based on the clinician's impression of any asymmetry in clinical features. The selected hemisphere was fixed with 4% paraformaldehyde for 2 weeks and subsequently paraffin-embedded and cut at 8 μm. HS pathology was assessed using hematoxylin & eosin (H&E) staining and rated as present (severe gliosis and neuronal loss in CA1 and subiculum) or not present (minor or no observed gliosis or neuronal loss in CA1 and subiculum). Senile plaques and neurofibrillary tangles were identified using sections stained with the modified Bielschowsky procedure. We used Braak and Braak criteria[18] to assess neurofibrillary tangle staging and Consortium to Establish a Registry for Alzheimer's Disease criteria to estimate the frequency of neuritic plaques.[19] Lewy body disease (LBD) was identified by immunostaining for α-synuclein according to established recommendations.[20]

The potential contribution of vascular factors was assessed in the following manner: large infarcts identified grossly were evaluated for size, location, and number. Atherosclerosis was evaluated by creating consecutive transverse sections of arteries at the base of the brain and visually estimating the degree of luminal narrowing according to the following scale: normal 0%, mild ≤25%, moderate 26%–60%, and severe >60%. Arteriolosclerosis was assessed semiquantitatively, in H&E- or Masson trichrome–stained sections, along an axis perpendicular to the widest vascular diameter. The ratio of luminal diameter to external diameter was calculated and the result was subtracted from 1; values <0.50 were regarded as mild, 0.50–0.75 as moderate, and ≥0.75 as severe. The presence of microinfarcts was evaluated through H&E-stained sections of 6 predefined brain regions: middle frontal, inferior parietal, superior temporal, occipital, basal ganglia, and thalamus. Each section was surveyed for microinfarcts. Lacunar infarcts (<1 cm in diameter) and large infarcts (>1 cm) were also localized. The presence of cerebral amyloid angiopathy was assessed with β-amyloid immunostaining of cerebral blood vessels and classified as absent, mild, moderate, or severe. Leukoencephalopathy of vascular origin was diagnosed, in the absence of microinfarcts or lacunar infarcts, if all the following features were present: hyaline arteriolar sclerosis, widening of perivascular (Virchow-Robin) spaces, pallor of myelin staining, and reactive white matter astrocytosis.

Demographics and medical history variables

Demographics and medical history variables were obtained from participants or their informant at the first visit and were updated at every follow-up visit. Due to reported association of HS with vascular pathologies,[21] we selected histories of cardiovascular and cerebrovascular diseases for analyses. The relevant diseases included hypertension, high cholesterol, heart disease, cerebrovascular disease, syncope, and diabetes. History of heart disease was considered present if any of the following were reported: coronary artery disease, myocardial infarction, heart valve disease, congestive heart failure, atrial fibrillation or other arrhythmias, coronary bypass surgery, and pacemaker insertion. History of cerebrovascular disease was considered present if either a history of stroke or TIA were reported. Because of the early involvement of amygdala in HS[22,23] and its salient role in affective disorders,[24] we investigated history of depression or anxiety. We examined history of thyroid disease given a recent report implicating thyroid dysfunction in the pathogenesis of HS.[25] We also selected history of rheumatoid arthritis (RA) as an additional autoimmune condition that was sufficiently prevalent in our cohort.

Medication use

Medication use was ascertained by examining medication containers at each visit. We selected medications related to the medical histories of interest (i.e., antidepressants and levothyroxine). Given a recent report of an association between a sulfonylurea receptor gene (*ABCC9*) and HS,[25] we also intended to study the association of sulfonylurea drug exposure with HS, but as only 2 participants reported using any antidiabetic medication, this association could not be examined.

Blood biochemistry

Given our interest in thyroid disease, we analyzed the association between HS and free thyroxine (free T4), thyroid-stimulating hormone (TSH), and antithyroid antibodies including anti-thyroglobulin and thyroid peroxidase (anti-TPO). We began collecting blood for biochemistry measures, including thyroid function, in 2004. Initially, blood was drawn at every visit but starting in 2012, blood was obtained only at the baseline visit. Therefore, participants included in this study had between 1 and 12 blood draws for thyroid function. Seventy-two (54%) of the 134 participants had at least one visit with thyroid function data. For each of the 4 thyroid function measures, we created a binary variable that described

Table 1 Characteristics of autopsied participants with dementia in The 90+ Study (n = 134)

Characteristic	Mean (range) (SD) or n (%)
Age at death, y	98.0 (90.6–110.6) (3.7)
MMSE score at last visit[a]	12.6 (0–28) (8.4)
Years between first visit and death	4.1 (0.07–11.9) (2.7)
Months between last visit and death	4.3 (0.1–29.9) (4.4)
Duration of dementia (years between dementia diagnosis and death)	4.7 (0–16) (3.4)
Women	102 (76.1)
College education or greater	59 (44.4)
Hippocampal sclerosis at autopsy	35 (26.1)

Abbreviation: MMSE = Mini-Mental State Examination.
[a] MMSE scores were not available for 6 participants at last visit.

Table 2 Clinical characteristics of participants stratified by hippocampal sclerosis (HS) pathology

Characteristic at last visit[a]	Without HS (n = 99), mean (range)	With HS (n = 35), mean (range)	*p* Value[b]
Demographics			
Age at last visit, y	97.5 (90.5–110.4)	98.0 (91.8–105.7)	0.59
Age at death, y	97.9 (90.6–110.6)	98.5 (92.1–106.2)	0.51
Duration of dementia (years between dementia diagnosis and death)	4.0 (0–16)	6.7 (1–16)	<0.001
Brain weight, g	1,130.6 (871–1,434)	1,058.4 (898–1,348)	0.003

Characteristic at last visit[a]	Without HS (n = 99), n (%)	With HS (n = 35), n (%)	*p* Value[b]
Demographics			
Women	73 (73.7)	29 (82.9)	0.36
College education or greater	43 (43.4)	16 (47.1)	0.84
APOE ε4	22 (23.4)	10 (28.6)	0.65
APOE ε2	16 (17.0)	3 (8.6)	0.28
Medical history			
Hypertension	50 (52.1)	13 (37.1)	0.17
High cholesterol	18 (19.0)	10 (31.3)	0.22
Diabetes	2 (2.1)	2 (5.7)	0.29
Cerebrovascular disease (composite)	46 (50.6)	11 (32.4)	0.07
TIA	39 (42.4)	10 (29.4)	0.22
Stroke	22 (23.9)	3 (8.6)	0.08
Heart disease (composite)	41 (42.3)	15 (42.9)	1.00
Coronary artery disease	14 (14.6)	5 (14.3)	1.00
Myocardial infarction	8 (8.3)	1 (2.9)	0.44
Heart valve disease	6 (6.3)	3 (8.6)	0.70
Congestive heart failure	16 (16.7)	7 (20.0)	0.80
Atrial fibrillation/arrhythmias	28 (29.2)	5 (14.3)	0.11
Coronary bypass	3 (3.2)	1 (2.9)	1.00
Pacemaker	15 (16.0)	2 (5.7)	0.15
Autoimmune disease (composite)	31 (33.7)	20 (58.8)	0.01
Rheumatoid arthritis	7 (7.5)	5 (14.7)	0.30
Thyroid disease	27 (29.0)	15 (42.9)	0.15
High anti-thyroglobulin[c]	8 (15.4)	7 (35.0)	0.10
High anti-TPO[c]	9 (17.3)	8 (40.0)	0.06
High anti-thyroglobulin or anti-TPO[c]	13 (25.0)	10 (50.0)	0.05
High free T4[c]	35 (67.3)	15 (75.0)	0.58
High TSH[c]	7 (13.5)	8 (40.0)	0.02
Syncope	17 (17.9)	4 (11.4)	0.43
Depression	34 (35.8)	6 (18.8)	0.08

Continued

Table 2 Clinical characteristics of participants stratified by hippocampal sclerosis (HS) pathology *(continued)*

Characteristic at last visit[a]	Without HS (n = 99), n (%)	With HS (n = 35), n (%)	*p* Value[b]
Anxiety	18 (19.0)	7 (20.0)	1.00
Cancer (not skin)	28 (29.2)	9 (25.7)	0.83
Antidepressant use	47 (50.0)	19 (54.3)	0.56
Levothyroxine use	33 (33.7)	18 (51.4)	0.07

Abbreviations: T4 = thyroxine; TPO = thyroid peroxidase thyroid peroxidase; TSH = thyroid-stimulating hormone.
[a] Missing data for each variable: education (n = 1); hypertension (n = 3); high cholesterol (n = 7); diabetes (n = 2); cerebrovascular disease (n = 9); TIA (n = 8); stroke (n = 7); heart disease (n = 2); CAD (n = 3); myocardial infarction (n = 3); heart valve disease (n = 4); congestive heart failure (n = 3); arrhythmias (n = 3); coronary bypass (n = 4); pacemaker (n = 5); autoimmune disease (n = 8); rheumatoid arthritis (n = 6); thyroid disease (n = 6); anti-thyroglobulin, anti-TPO, free T4, and TSH (n = 62); syncope (n = 4); depression (n = 7); anxiety (n = 4); cancer (n = 3); antidepressant (n = 1); levothyroxine (n = 1); *APOE* (n = 5).
[b] *p* Values are for Wilcoxon rank-sum 2-sample tests for continuous variables, Fisher exact test for categorical variables.
[c] Only 72/134 (54%) participants had serum thyroid testing.

whether a person's thyroid function level was ever in the higher than normal range.

Statistical analyses

Participants with dementia were divided into 2 groups: those with HS pathology, as determined at autopsy, vs those without HS. Differences in continuous variables between the 2 groups were analyzed using the Wilcoxon rank-sum test and differences in categorical variables were analyzed with Fisher exact tests. We used separate logistic regressions to estimate the odds of HS pathology in relation to each of the characteristics of interest. We estimated both unadjusted odds of HS and odds of HS after adjusting for duration of dementia. For continuous variables, we assessed the linearity of log odds by visual inspection of the empirical logit plot. Because the linearity in the log odds for brain weight was not clear, we categorized brain weight into quartiles for regression analyses. For multiple category variables (i.e., tangle stage and brain weight quartiles), we report the type 3 χ^2 *p* value as a measure of the overall variable effect. Results at $p < 0.05$ were considered significant. Due to the exploratory nature of the study, correction for multiple comparisons was not performed. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Data availability

Data for all the analyses and results reported in this article were acquired from The 90+ Study. Data not published within the article will be shared by request from any qualified investigator.

Results

Table 1 shows the characteristics of the 134 participants in this study. The average age at death was 98.0 years; most participants were women (76.1%) and well-educated (44.4% had a college degree or greater). The average Mini-Mental State Examination score at last visit was 12.6 (SD 8.4), consistent with the fact that all had a dementia diagnosis. The prevalence of HS in this sample of individuals with dementia was 26.1%, and the average follow-up time from first study visit to death was 4.1 (SD 2.7) years.

Tables 2 and 3 compare the demographics, medical history, and neuropathologic findings of the participants with and without HS pathology. The 2 groups did not differ in most respects, except that on average, the HS group had longer duration of dementia before death (6.7 vs 4.0 years, $p < 0.001$) and had lower brain weights (1,058.4 vs 1,130.6 g, $p = 0.003$). In addition, participants with HS were more likely to have had a history of thyroid disease or RA (autoimmune disease composite: 58.8% vs 33.7%, $p = 0.01$), have ever had an above normal TSH level (40.0% vs 13.5%, $p = 0.02$), and to have LBD pathology (14.3% vs 3.0%, $p = 0.03$).

Table 4 shows results of logistic regression analyses of all variables that had a *p* value ≤0.1 in tables 2 and 3. Table 5 shows results of logistic regression analyses of all variables regardless of *p* value. For the composite variables of autoimmune disease and cerebrovascular disease, the individual components were also analyzed. In unadjusted logistic regression models, there was a higher likelihood of having HS in participants with a longer duration of dementia (odds ratio [OR] 1.26, 95% confidence interval [CI] 1.11–1.42, $p < 0.001$), LBD pathology (OR 5.33, 95% CI 1.204–23.64, $p = 0.028$), history of autoimmune disease (OR 2.81, 95% CI 1.25–6.31, $p = 0.012$), high TSH (OR 4.29, 95% CI 1.29–14.20, $p = 0.017$), and high thyroid antibodies, both composite (OR 3.00, 95% CI 1.02–8.82, $p = 0.046$) and high anti-TPO (OR 3.19, 95% CI 1.01–10.03, $p = 0.048$). There was also an association between brain weight ($p = 0.014$) and tangle stage ($p = 0.049$). When adjusting for duration of dementia, most associations with HS remained, including LBD pathology (OR 5.68, 95% CI 1.22–26.39, $p = 0.027$), history of autoimmune disease (OR 3.15, 95% CI 1.30–7.62, $p = 0.011$), high TSH (OR 4.94, 95% CI 1.40–17.46, $p = 0.013$), and high thyroid antibodies, both composite (OR 3.45, 95% CI 1.09–10.88, $p = 0.035$) and high anti-TPO (OR 3.95, 95% CI 1.17–13.29, $p = 0.027$). However, after adjustment for

Table 3 Pathologic characteristics of participants stratified by hippocampal sclerosis (HS) pathology

Characteristic	Without HS (n = 99), n (%)[b]	With HS (n = 35), n (%)[b]	*p* Value[a]
Neuritic plaques			0.59
None	15 (15.2)	5 (14.3)	
Sparse	23 (23.2)	5 (14.3)	
Moderate	37 (37.4)	13 (37.1)	
Frequent	24 (24.2)	12 (34.3)	
Braak tangle stage			0.04
I–II	15 (15.2)	6 (17.1)	
III–IV	43 (43.4)	7 (20.0)	
V–VI	41 (41.4)	21 (60.0)	
Atherosclerosis[b]			0.95
None	19 (19.8)	6 (18.2)	
Mild	48 (50.0)	18 (54.6)	
Moderate	16 (16.7)	6 (18.2)	
Severe	13 (13.5)	3 (9.1)	
Arteriolosclerosis			0.38
None	53 (53.5)	17 (48.6)	
Mild	22 (22.2)	10 (28.6)	
Moderate	21 (21.2)	5 (14.3)	
Severe	3 (3.0)	3 (8.6)	
Microinfarcts			0.54
None	80 (80.8)	27 (77.4)	
Single field	10 (10.1)	6 (17.1)	
Multiple fields	9 (9.1)	2 (5.7)	
Lacunes			0.92
None	83 (83.8)	29 (82.9)	
Single field	12 (12.1)	4 (11.4)	
Multiple fields	4 (4.0)	2 (5.7)	
Large infarcts			0.12
None	96 (97.0)	31 (88.6)	
Single field	2 (2.0)	3 (8.6)	
Multiple fields	1 (1.0)	1 (2.9)	
Amyloid angiopathy			0.11
None	54 (54.6)	18 (51.4)	
Mild	34 (34.3)	8 (22.9)	
Moderate	5 (5.0)	6 (17.1)	
Severe	6 (6.0)	3 (8.6)	
Lewy body disease			0.03
Absent	96 (97.0)	30 (85.7)	
Present	3 (3.0)	5 (14.3)	
Leukoencephalopathy			0.76
Absent	89 (89.9)	31 (88.6)	
Present	10 (10.1)	4 (11.4)	

[a] *p* Values are for Fisher exact test and compare participants without HS vs participants with hippocampal sclerosis.
[b] Missing data for each variable: atherosclerosis n = 5.

duration of dementia, brain weight ($p = 0.126$) and tangle stage ($p = 0.191$) were not associated with HS. In contrast, history of depression and history of cerebrovascular disease became associated with a lower likelihood of HS (depression OR 0.20, 95% CI 0.06–0.65, $p = 0.008$; cerebrovascular disease OR 0.40, 95% CI 0.16–0.99, $p = 0.048$).

To investigate the potential bias of restricting the analysis to those with dementia, we repeated the analyses for the identified significant associations on the full cohort (those with and without dementia, n = 264). In the full cohort analysis, histories of depression and cerebrovascular disease (CVD) were not associated with HS but most of the identified associations remained (LBD pathology OR 8.05, 95% CI 2.06–31.48, $p = 0.003$; high anti-thyroglobulin OR 2.87, 95% CI 1.08–7.63, $p = 0.035$; high anti-TPO OR 2.70, 95% CI 1.02–7.15, $p = 0.046$; high thyroid antibodies OR 2.89, 95% CI 1.17–7.13, $p = 0.021$; and high TSH OR 3.06, 95% CI 1.18–7.90, $p = 0.021$). History of autoimmune conditions (composite of RA and thyroid disease) was not associated with HS in the full cohort (OR 1.97, 95% CI 0.98–3.96, $p = 0.058$), although there was a trend towards an association. When examined individually, the ORs for thyroid disease and for RA histories were similar in magnitude (thyroid disease OR 1.32, 95% CI 0.66–2.64, $p = 0.438$; RA OR 1.94, 95% CI 0.72–5.24, $p = 0.189$), suggesting that both conditions contribute equally to the composite score.

Discussion

In this study, we examined risk factors, clinical features, and neuropathologic characteristics associated with HS pathology in a population-based cohort. The most intriguing result was the observed association between autoimmune conditions (RA/thyroid disease combined frequency) and increased likelihood of HS. Moreover, the significant association between high levels of TSH and anti-TPO antibody

Table 4 Results from logistic regression models for the odds of hippocampal sclerosis pathology in relation to clinical and pathologic characteristics in The 90+ Study

		Unadjusted[a]		Adjusted[b]	
Characteristics	**N**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Duration of dementia[a]	134	1.26 (1.11–1.42)	<0.001	—	—
Brain weight	125		0.014		0.126
Quartile 2 vs 1		0.44 (0.15–1.24)		0.47 (0.16–1.44)	
Quartile 3 vs 1		0.15 (0.04–0.54)		0.22 (0.06–0.83)	
Quartile 4 vs 1		0.26 (0.08–0.80)		0.38 (0.12–1.25)	
Lewy body disease pathology	134	5.33 (1.20–23.64)	0.028	5.68 (1.22–26.39)	0.027
Braak tangle stage III–IV vs I–II	134	0.41 (0.12–1.40)	0.049	0.38 (0.10–1.35)	0.191
Braak tangle stage V–VI vs I–II		1.34 (0.46–3.95)		0.87 (0.27–2.77)	
History of cerebrovascular disease (stroke or TIA)	125	0.47 (0.20–1.07)	0.072	0.40 (0.16–0.99)	0.048
History of stroke	127	0.30 (0.08–1.07)	0.063	0.36 (0.09–1.38)	0.135
History of TIA	126	0.57 (0.24–1.32)	0.188	0.50 (0.20–1.27)	0.147
History of depression	127	0.41 (0.16–1.11)	0.078	0.20 (0.06–0.65)	0.008
History of autoimmune disease (thyroid disease or rheumatoid arthritis)	126	2.81 (1.25–6.31)	0.012	3.15 (1.30–7.62)	0.011
History of rheumatoid arthritis	128	2.14 (0.63–7.27)	0.222	3.76 (0.66–14.67)	0.057
History of thyroid disease	128	1.83 (0.82–4.10)	0.140	1.85 (0.78–4.41)	0.165
High anti-thyroglobulin	72	2.96 (0.90–9.72)	0.073	3.54 (0.99–12.64)	0.052
High anti-TPO	72	3.19 (1.01–10.03)	0.048	3.95 (1.17–13.29)	0.027
High anti-thyroglobulin or anti-TPO	72	3.00 (1.02–8.82)	0.046	3.45 (1.09–10.88)	0.035
High TSH	72	4.29 (1.29–14.20)	0.017	4.94 (1.40–17.46)	0.013
Levothyroxine use	133	2.09 (0.95–4.57)	0.066	2.07 (0.89–4.80)	0.090

Abbreviations: CI = confidence interval; OR = odds ratio; T4 = thyroxine; TPO = thyroid peroxidase thyroid peroxidase; TSH = thyroid-stimulating hormone. Separate models were done for each characteristic. For multiple category variables (i.e., tangle stage and brain weight quartiles), we report the type 3 χ^2 *p* value.
[a] OR and CI estimated from unadjusted logistic regressions models.
[b] OR and CI estimated from logistic regression models adjusted for duration of dementia.

corroborated the recently suggested role of thyroid hormone in HS.[26] LBD pathology was the only pathology associated with increased likelihood of HS. We found histories of cerebrovascular disease and depression were associated with decreased likelihood of HS pathology but these associations were no longer significant when we added participants without dementia to the analysis. Furthermore, we did not identify an association between HS and various cardiovascular risk factors.

In this study, we found a possible relationship between autoimmune disease and HS in the oldest old. We chose thyroid disease and RA as 2 common autoimmune conditions that were sufficiently common in our cohort. A potential association between RA and increased odds of dementia has been reported in a recent review of hospital admission records.[27] The authors found increased odds of overall dementia diagnosis and vascular dementia diagnosis in those with a hospital admission due to RA, but lower odds of Alzheimer disease in the same cohort. We are not aware of any previously reported associations between HS and RA. Thyroid dysfunction, on the other hand, was recently implicated in HS pathogenesis where increased levels of T3 were found in the postmortem spinal fluid analysis of patients with HS.[26] The association between history of thyroid disease and HS in our study was further corroborated by associations between HS and high levels of TSH and antithyroid antibodies. To ensure the observed association between HS and TSH was not mediated by thyroid medications, we ran an additional regression analysis with both TSH and thyroid medication as independent variables and found the association between TSH and HS remained significant (results not shown). The

Table 5 Results from logistic regression models for the odds of hippocampal sclerosis pathology in relation to all clinical and pathologic characteristics explored in The 90+ Study

		Unadjusted[a]		Adjusted[b]	
Characteristics	**N**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Demographics					
Age at last visit	134	1.04 (0.94–1.15)	0.484	1.05 (0.94–1.17)	0.381
Age at death	134	1.05 (0.94–1.16)	0.383	1.06 (0.95–1.19)	0.288
Duration of disease	134	1.26 (1.11–1.42)	<0.001	—	—
Brain weight	125		0.014		0.126
Quartile 2 vs 1		0.44 (0.15–1.24)		0.47 (0.16–1.44)	
Quartile 3 vs 1		0.15 (0.04–0.54)		0.22 (0.06–0.83)	
Quartile 4 vs 1		0.26 (0.08–0.80)		0.38 (0.12–1.25)	
Female	134	1.72 (0.64–4.62)	0.281	1.17 (0.41–3.32)	0.773
College education or greater	133	1.16 (0.53–2.53)	0.714	1.07 (0.47–2.45)	0.879
***APOE* ε4**	129	1.31 (0.55–3.14)	0.546	1.22 (0.47–3.15)	0.681
***APOE* ε2**	129	0.46 (0.13–1.68)	0.238	0.38 (0.10–1.48)	0.163
Medical history					
Hypertension	131	0.54 (0.25–1.20)	0.133	0.68 (0.29–1.58)	0.371
High cholesterol	127	1.94 (0.79–4.81)	0.151	2.51 (0.94–6.72)	0.066
Diabetes	132	2.88 (0.39–21.26)	0.300	4.33 (0.56–33.64)	0.162
Cerebrovascular disease (composite)	125	0.47 (0.20–1.07)	0.072	0.40 (0.16–0.99)	0.048
TIA	126	0.57 (0.24–1.32)	0.188	0.50 (0.20–1.27)	<0.001
Stroke	127	0.30 (0.08–1.07)	0.063	0.36 (0.09–1.38)	0.135
Heart disease (composite)	132	1.02 (0.47–2.24)	0.951	1.06 (0.46–2.45)	0.891
Coronary artery disease	131	0.98 (0.32–2.94)	0.966	1.37 (0.43–4.38)	0.594
Myocardial infarction	131	0.32 (0.04–2.69)	0.296	0.55 (0.06–4.72)	0.584
Heart valve disease	130	1.39 (0.33–5.89)	0.654	1.81 (0.39–8.34)	0.449
Congestive heart failure	131	1.25 (0.47–3.35)	0.658	1.23 (0.42–3.66)	0.706
Atrial fibrillation/arrhythmias	131	0.40 (0.14–1.15)	0.090	0.39 (0.13–1.21)	0.105
Coronary bypass	130	0.90 (0.09–8.97)	0.930	1.39 (0.13–14.38)	0.782
Pacemaker	129	0.32 (0.07–1.47)	<0.001	0.39 (0.08–1.90)	0.244
Autoimmune disease (composite)	126	2.81 (1.25–6.31)	0.012	3.15 (1.30–7.62)	0.011
Rheumatoid arthritis	128	2.14 (0.63–7.27)	0.222	3.76 (0.96–14.67)	0.057
Thyroid disease	128	1.83 (0.82–4.10)	0.140	1.85 (0.77–4.41)	0.165
High anti-thyroglobulin	72	2.96 (0.90–9.72)	0.073	3.54 (0.99–12.64)	0.052
High anti- TPO	72	3.19 (1.01–10.03)	0.048	3.95 (1.17–13.29)	0.027
High anti-thyroglobulin or anti-TPO	72	3.00 (1.02–8.82)	0.046	3.45 (1.09–10.88)	0.035
High free T4	72	1.46 (0.45–4.68)	0.527	1.96 (0.55–7.04)	0.301
High TSH	72	4.29 (1.29–14.20)	0.017	4.94 (1.40–17.46)	0.013

Continued

Table 5 Results from logistic regression models for the odds of hippocampal sclerosis pathology in relation to all clinical and pathologic characteristics explored in The 90+ Study *(continued)*

		Unadjusted[a]		Adjusted[b]	
Characteristics	**N**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Syncope	130	0.59 (0.18–1.90)	0.378	0.64 (0.19–2.14)	0.467
Depression	127	0.41 (0.16–1.11)	0.078	0.20 (0.06–0.65)	0.008
Anxiety	130	1.07 (0.40–2.83)	0.893	0.47 (0.14–1.54)	0.214
Cancer (not skin)	131	0.84 (0.35–2.02)	0.700	0.81 (0.31–2.11)	0.668
Antidepressant use	133	1.29 (0.59–2.79)	0.521	0.66 (0.26–1.65)	0.371
Levothyroxine use	133	2.09 (0.95–4.57)	0.066	2.07 (0.89–4.80)	0.090
Neuritic plaques	134		0.586		0.795
Sparse vs none		0.65 (0.16–2.64)		0.62 (0.15–2.62)	
Moderate vs none		1.05 (0.32–3.48)		0.75 (0.21–2.65)	
Frequent vs none		1.50 (0.44–5.11)		1.09 (0.30–3.98)	
Braak tangle stage	134		0.049		0.191
III–IV vs I–II		0.41 (0.12–1.40)		0.38 (0.10–1.35)	
V–VI vs I–II		1.34 (0.46–3.95)		0.87 (0.27–2.77)	
Atherosclerosis	129		0.908		0.831
Mild vs none		1.19 (0.41–3.45)		0.99 (0.32–3.03)	
Moderate vs none		1.19 (0.32–4.41)		0.86 (0.21–3.51)	
Severe vs none		0.73 (0.15–3.46)		0.50 (0.10–2.63)	
Arteriolosclerosis	134		0.423		0.576
Mild vs none		1.42 (0.56–3.58)		1.40 (0.52–3.77)	
Moderate vs none		0.74 (0.24–2.27)		0.78 (0.24–2.51)	
Severe vs none		3.12 (0.58–16.91)		2.77 (0.44–17.39)	
Microinfarcts	134		0.486		0.829
Single field vs none		1.78 (0.59–5.35)		1.43 (0.44–4.70)	
Multiple fields vs none		0.66 (0.13–3.24)		0.92 (0.17–4.82)	
Lacunes	134		0.917		0.919
Single field vs none		0.95 (0.29–3.19)		1.15 (0.32–4.11)	
Multiple fields vs none		1.43 (0.25–8.22)		1.41 (0.22–8.92)	
Large infarcts	134		0.198		0.239
Single field vs none		4.65 (0.74–29.09)		4.56 (0.68–30.36)	
Multiple fields vs none		3.10 (0.19–50.99)		2.88 (0.14–59.24)	
Amyloid angiopathy	134		0.144		0.076
Mild vs none		0.71 (0.28–1.80)		0.54 (0.19–1.54)	
Moderate vs none		3.60 (0.98–13.23)		4.44 (1.10–17.93)	
Severe vs none		1.50 (0.34–6.62)		1.24 (0.24–6.38)	
Lewy body disease	134		0.028		0.027

Continued

Table 5 Results from logistic regression models for the odds of hippocampal sclerosis pathology in relation to all clinical and pathologic characteristics explored in The 90+ Study *(continued)*

Characteristics	N	Unadjusted[a] OR (95% CI)	*p* Value	Adjusted[b] OR (95% CI)	*p* Value
Present vs absent		5.33 (1.20–23.64)		5.68 (1.22–26.39)	
Leukoencephalopathy	134		0.825		0.827
Present vs absent		1.15 (0.34–3.93)		0.86 (0.22–3.30)	

Abbreviations: CI = confidence interval; OR = odds ratio; T4 = thyroxine; TPO = thyroid peroxidase thyroid peroxidase; TSH = thyroid-stimulating hormone. Separate models were done for each characteristic. For multiple category variables, the type 3 χ^2 *p* values are shown.
[a] OR and CI estimated from unadjusted logistic regressions models.
[b] OR and CI estimated from logistic regression models adjusted for duration of disease.

association between antithyroid antibodies and HS further supports an autoimmune underpinning for the observed relation between thyroid function and HS. It should be noted, however, that when the association between histories of autoimmunity and HS was examined in the full cohort, the association only trended toward significance, with seemingly comparable contribution from both thyroid disease and RA histories.

LBD was the only neuropathology that differed between the HS group and patients with non-HS dementia. We identified 2 previous studies comparing the frequency of LBD pathology between HS and non-HS participants. While a clinicopathologic cohort study of the Religious Order Study and the Rush Memory and Aging Project found that LBD pathology was more common among patients with HS,[22] another clinicopathologic study examining participants of the University of Kentucky Alzheimer Disease Center, Nun Study, and Georgia Centenarian Study did not find a difference in the frequency of diffuse/neocortical Lewy body pathologies between participants with and without HS.[28] It is worth mentioning that, unlike our study, both studies included participants with and without dementia and therefore, the results might not be directly comparable. Also, in a retrospective study of the Mayo Clinic brain bank, the frequency of HS in LBD was investigated. A total of 5.2% of 669 patients with LBD were found to harbor HS pathology with no difference in the frequency of HS between transitional and diffuse LBD cases, leading the authors to infer there was no direct association between HS and LBD pathologies.[28]

We found an association between history of CVD and decreased likelihood of HS pathology (OR 0.40, 95% CI 0.16–0.99, $p = 0.048$), suggesting a person with a history of stroke or TIA was less likely to harbor HS compared to someone without such history. However, this association was only significant when the study sample was restricted to those with dementia, opening the possibility that the finding might be spurious and due to the bias of conditioning the analysis on dementia, which might be a common effect of both the exposure (CVD) and outcome (HS).[29] It is also noteworthy that we did not find an association between history of cardiac conditions (coronary artery disease/myocardial infarction/congestive heart failure/atrial fibrillation/arrhythmias/coronary bypass/pacemaker/composite heart disease/syncope) and HS. Moreover, at a pathologic level, there was no association between various pathologic markers of large vessel disease or tentative markers of hippocampal hypoperfusion (i.e., cerebral atherosclerosis, arteriolosclerosis, microinfarcts, and lacunes) and HS pathology. Taken together, our results do not support the previously reported high prevalence of cardiovascular diseases in elderly (>80 years-old) patients with HS[6] or the reported association between HS and brain arteriolosclerosis.[21] Given the more advanced age of our study participants compared to earlier studies (average age of 98 years vs 90 years), it is conceivable that survival effect could be a potential explanation for the lack of association between cardiovascular risk and HS in our study.

We found that history of depression was associated with decreased odds of HS pathology, although this association also disappeared once participants without dementia were added to the analysis. One of the first studies on HS reported that out of 8 patients with HS (average age at onset: 72 years), 5 had depression or depressive symptoms, suggesting high prevalence of depression in HS.[15] A more recent clinicopathologic cohort study of 40 individuals with HS, however, did not identify an association between depression and HS pathology. In this study, high amyloid plaque burden was the only pathology with a possible association with depression.[30]

Another important finding was that on average, patients with HS had a longer duration of dementia compared to participants without HS (3.93 years vs 6.67 years). One possible explanation for this finding is a slower disease progression; some previous studies have suggested that patients with pure HS have a milder cognitive profile.[31,32]

A major strength of this study was the relatively large number of participants who were older than 90 years. Many other studies of HS have included few participants older than 90 years, an age

in which the prevalence of HS is believed to increase dramatically.[22] Another strength of this study was that it was a population-based study, unlike some of the previous studies of HS that were performed on selected research samples. We acknowledge that due to regional demographics, most participants were female, Caucasian, and well-educated, potentially limiting the generalizability of our results. Finally, due to the exploratory nature of the study, we did not correct our statistical analyses for multiple comparisons, leaving the possibility that some of our associations are due to chance.

We found HS was relatively prevalent in a population-based clinicopathologic study of oldest-old participants with dementia. We identified autoimmune conditions (RA and thyroid disease) as potential risk factors for HS in our cohort. LBD was the only pathology that was associated with increased odds of HS and there was a longer duration of dementia in those harboring HS pathology. The observed association between HS and autoimmune conditions deserves special attention due to the potential implications on the pathogenesis mechanisms of HS that might lead to effective prevention/treatment strategies should future clinical and pathologic studies confirm inflammation or autoimmunity as risk factors for HS.

Author contributions

Thomas Trieu: study concept and design, analysis and interpretation of data, drafting of manuscript. Seyed Ahmad Sajjadi: analysis and interpretation of data, drafting of manuscript. Claudia H. Kawas: study concept and design, critical revision of the manuscript. Peter T. Nelson: critical revision of the manuscript. María M. Corrada: study concept and design, analysis and interpretation of data, critical revision of the manuscript.

Acknowledgment

The authors thank Dr. Ronald Kim for performing postmortem neuropathologic assessment of all study samples and the participants, their relatives, and the staff of The 90+ Study.

Study funding

This study was funded by grants from the NIH (R01AG021055 and P50AG016573) and The Medical Student Training in Aging Research (MSTAR) Program from AFAR and NIA.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* July 8, 2017. Accepted in final form July 31, 2018.

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