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Hippocampal and Mesial Temporal Sclerosis in Early-Onset Frontotemporal Lobar Degeneration Versus Alzheimer's Disease

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Abstract

Hippocampal sclerosis (HS) and mesial temporal sclerosis (MTS) may occur with frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) as well as with normal aging. Prior studies suggest that HS/MTS may be more closely associated with FTLD but have not directly compared the prevalence and clinical characteristics of HS/MTS between neuropathologically confirmed early-onset (age $\leq$ 65) cohorts of FTLD and AD. We identified patients with early-onset FTLD (n = 136) and AD (n = 267) from National Alzheimer's Center Consortium databases and compared neuropathological and clinical data between these 2 groups. The FTLD group had a significantly higher prevalence of HS/MTS than that of the AD group. However, HS/MTS was associated with increasing age and memory impairment in the AD group but not in the FTLD group. These findings are consistent with the hypothesis that HS/MTS in FTLD occurs as part of the primary pathological process, rather than as a secondary, nonspecific effect of aging on memory and hippocampal function.

Keywords

frontotemporal lobar degeneration, behavioral variant frontotemporal dementia, Alzheimer's disease, hippocampal sclerosis

Introduction

Hippocampal sclerosis (HS) and mesial temporal sclerosis (MTS) are neuropathological changes that may contribute to the clinicopathological manifestations of neurodegenerative disease. The HS includes neuronal loss and astrocytic gliosis of the hippocampus with a predilection for CA1 and the subiculum,[1] while MTS encompasses more extensive changes across broader regions of the hippocampus and surrounding regions. Overall, the prevalence of HS on autopsy ranges from 2.8% to 23.4%,[2] with the highest rates found in the oldest individuals.[3] The HS can occur both independently of and in conjunction with a number of other pathologies, including Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and vascular dementia.[2,3]

Comparisons across studies indicate that HS may be significantly more common in FTLD than in AD.[3-5] The presence of 43-kDa TAR DNA-binding protein (TDP-43) immunopositive inclusion bodies in around 90% of patients with HS and a majority of those with FTLD suggests a special relationship between these 2 neuropathologies.[3,5] Some investigators, however, report that HS in FTLD, which has a mean onset in the 50s, is related to increased age,[6,7] similar to the associations that have been reported in other neurodegenerative conditions.[3] The relationship of HS to memory and cognitive symptoms in FTLD also remains unclear. One study indicated that HS in FTLD is associated with more pronounced memory deficits,[7] but another reported similar cognitive deficits among patients with FTLD with and without HS.[4] Moreover, few clinicopathological studies have directly compared HS/MTS in FTLD with other neurodegenerative disorders, such as early-onset AD, in terms of prevalence, age-related effects, and relationship to clinical symptoms.[5]

We examined the clinical and cognitive implications of HS/MTS in the presence of primary FTLD or AD neuropathology in a large cohort of individuals with early-onset dementia included in the National Alzheimer's Coordinating Center (NACC) Neuropathological Database (NPD) and Uniform Data Set (UDS).[8] This study addresses the issue of whether HS/MTS

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is an isolated finding associated with increasing age or whether it has a greater association with specific types of neurodegenerative pathology, even in patients with early-onset disease. Our hypothesis was that among patients with early-onset (age ≤65) dementia, HS/MTS would be more common in FTLD than in AD, regardless of age or clinical symptoms, therefore supporting the view that HS/MTS has a specific association with FTLD.

Methods

Participants

The study cohort consisted of individuals diagnosed with dementia who were included in both the NACC NPD and UDS.[8] Participant data were collected between 2005 and 2012 at the 34 AD centers (ADCs) with current or prior funding from the National Institute on Aging. We identified patients with primary neuropathological diagnoses of FTLD or AD with age of initial symptom onset ≤65 and examined clinical data from their initial UDS visits. These 2 cohorts were matched by gender and age of symptom onset (±3 years), with a goal of 2 matched patients with AD for each patient with FTLD, yielding a final study sample of 136 patients with FTLD and 267 patients with early-onset AD. Clinical diagnoses in the FTLD group included behavioral variant frontotemporal dementia (bvFTD; n = 83), primary progressive aphasia (PPA; n = 22), AD (n = 12), progressive supranuclear palsy (n = 11), and corticobasal degeneration (CBD; n = 9). Clinical diagnoses in the AD group included probable AD (n = 174), possible AD (n = 27), bvFTD (n = 23), CBD (n = 14), dementia with Lewy bodies (n = 11), PPA (n = 10), prion disease (n = 1), and dementia of unknown or unspecified etiology (n = 7). Institutional review boards (IRBs) at each participating ADC approved the NACC data collection, and the University of California Los Angeles IRB approved our specific analyses.

Across the centers, the neuropathological criteria for HS included selective neuronal loss and gliosis in the hippocampal CA1, subiculum, and CA2 sectors. The patients with MTS included additional neuronal loss and gliosis in medial temporal lobe structures beyond the hippocampus, including the amygdala and entorhinal cortex. A total of 18 patients with FTLD and 14 patients with AD had HS or MTS. Overall, 31 of these 32 patients met the criteria for MTS; only a single patient with FTLD was noted to have HS alone. Patients with FTLD were further subcategorized as having τ-positive (Pick's disease, progressive supranuclear palsy, corticobasal degeneration, FTLD and parkinsonism with τ-positive or argyrophilic inclusions, or other tauopathy) or τ-negative (FTLD with ubiquitin-positive/τ-negative inclusions and FTLD with no distinctive histopathology [τ-negative, ubiquitin-negative, and no argyrophilic inclusions]) pathology.

Statistical Analyses

We first compared the prevalence of HS/MTS between patients with neuropathologically diagnosed FTLD and AD. Subsequent analyses were performed to determine the associations between HS/MTS and gender, age, and cognitive/functional symptoms (using the Clinical Dementia Rating Scale [CDR][9]) and behavioral symptoms (using the Neuropsychiatric Inventory Questionnaire [NPI-Q][10]) in these cohorts. Statistical analyses were performed using SPSS 20 (SPSS, Chicago, Illinois). Group comparisons were performed using chi-square (χ^2) or Mann-Whitney *U* tests for categorical variables and unpaired *t* tests for continuous variables. Patients with missing or unknown data for individual variables were excluded from analyses involving those variables.

Table 1. Demographic Data for the Early-Onset FTLD and AD Groups.

N	FTLD 136	AD 267	$t_{401}/\chi^2(403)$
% Male	58.8%	59.1%	0.01
Education (SD)	15.1 (3.0)	15.2 (3.0)	−0.21
% Nonhispanic white	91.1%	92.3%	3.80
CDR SOB at initial visit (SD)	9.7 (5.7)	11.4 (5.7)	−2.80[a]
Age at symptom onset (SD)	56.3 (6.2)	57.2 (6.0)	−1.19
Age at first visit (SD)	62.0 (6.9)	64.4 (7.7)	9.81[a]
Age at death (SD)	63.9 (7.1)	67.1 (7.7)	−3.90[a]
% HS/MTS	13.2%	5.2%	7.80[a]

Abbreviations: AD, Alzheimer's disease; CDR SOB, Clinical Dementia Rating Scale Sum of Boxes; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; MTS, mesial temporal sclerosis; SD, standard deviation.
[a] $P < .05$.

Results

Comparisons of the FTLD and AD groups (matched by gender and age of symptom onset) are shown in Table 1. Patients with FTLD were significantly more likely to have HS and/or MTS on neuropathological examination ($P = .003$) than patients with AD. Relative to patients with FTLD, patients with AD had significantly greater cognitive and functional deficits (as measured by the CDR Sum of Boxes) on initial visit ($P = .004$) and were older, both at the time of initial visit ($P = .002$) and at time of death ($P < .001$).

We conducted separate analyses of the FTLD and AD groups to determine the relationship between the presence of HS/MTS and gender, age, cognitive, and behavioral variables (see Table 2). In the FTLD group, there were no differences between patients with or without HS/MTS in gender distribution; age at symptom onset, initial study visit or death; or on any of the individual CDR indices at the initial study visit. In the AD group, but not the FTLD group, the HS/MTS+ patients were significantly older than the HS/MTS− patients at the time of their initial study visit ($P = .004$) and at time of death ($P = .008$). Additionally, the HS/MTS+ patients had marginally higher (ie, poorer) CDR memory scores ($P = .09$) than the HS/MTS− patients.

The prevalence of behavioral symptoms assessed with the NPI-Q is shown in Table 3. There were no differences in the

Table 2. Clinical Features Associated With HS/MTS in Early-Onset FTLD and AD.

	FTLD			AD		
	HS/MTS−	HS/MTS+	$\chi^2(136)/t_{(134)}$	HS/MTS−	HS/MTS+	$\chi^2(267)/t_{(265)}$
N	118	18		253	14	
% Male	58.1%	63.2%	0.04	61.9%	70.6%	0.25
Age						
Onset	56.2 (6.3)	57.1 (5.4)	0.03	57.0 (6.0)	59.5 (4.9)	2.30
First visit	62.1 (7.1)	61.3 (6.1)	0.15	64.1 (7.6)	70.2 (6.9)	8.50[a]
Death	64.1 (7.3)	63.3 (5.8)	0.17	66.8 (7.7)	72.4 (6.3)	7.07[a]
CDR			*Z*(136)			*Z*(267)
Memory	1.38 (1.04)	1.63 (0.92)	−1.23	1.99 (0.94)	2.47 (0.75)	−1.67
Orientation	1.28 (1.09)	1.69 (0.90)	−1.75	1.91 (1.01)	2.20 (0.99)	−1.38
Judgment	1.79 (1.00)	2.16 (0.75)	−1.26	1.92 (1.02)	2.30 (0.92)	−1.61
Community	1.73 (1.02)	2.05 (0.80)	−1.26	1.87 (0.96)	2.25 (1.10)	−1.40
Home/hobby	1.82 (1.04)	1.91 (0.95)	−0.28	1.99 (1.05)	2.35 (1.00)	−1.30
Personal care	1.46 (1.25)	1.72 (1.07)	−0.79	1.62 (1.20)	1.92 (1.20)	−1.01
Sum of Boxes	9.4 (5.8)	11.1 (4.90)	−1.23	11.3 (5.70)	13.6 (5.70)	−1.62

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; MTS, mesial temporal sclerosis.
[a] $P < .05$.

Table 3. NPI-Q Symptoms Associated With HS/MTS in Early-Onset FTLD and AD.[a,b]

	FTLD			AD		
	HS/MTS−	HS/MTS+	$\chi^2(128)$	HS/MTS−	HS/MTS+	$\chi^2(247)$
N	112	16		236	11	
Delusions	15.1%	18.7%	0.13	26.6%	36.3%	0.49
Hallucinations	7.1%	6.2%	0.01	20.7%	18.1%	0.04
Agitation	42.8%	43.7%	0.05	47.8%	63.6%	1.00
Depression	43.7%	25%	2.0	47.8%	36.3%	0.44
Anxiety	47.3%	31.2%	1.4	49.1%	63.6%	0.88
Elation	17.8%	25%	0.46	9.3%	9.09%	0.00
Apathy	70.5%	81.2%	0.79	61.0%	81.8%	1.90
Disinhibition	53.5%	68.7%	1.3	30.9%	63.6%	5.10[b]
Motor	55.3%	75%	2.2	39.4%	36.3%	0.04
Nighttime	41.9%	37.5%	0.11	30.0%	27.2%	0.04
Appetitive	50.0%	56.2%	0.21	31.7%	45.4%	0.89
Irritability	49.1%	43.7%	1.6	43.6%	36.3%	0.22

Abbreviations: AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; HS, Hippocampal sclerosis; MTS, mesial temporal sclerosis.
[a] NPI-Q data not available for 8 patients with FTLD and 20 patients with AD.
[b] $P < .005$.

prevalence of any individual behavioral symptoms between HS/MTS+ and HS/MTS− patients in the FTLD group. However, in the AD group, the HS/MTS+ patients were significantly more likely to exhibit symptoms of disinhibition than the HS/MTS− patients ($P = .02$).

We performed further analyses in the neuropathologically confirmed FTLD group to examine possible associations between HS/MTS pathology and specific clinical diagnoses or the presence/absence of FTLD spectrum τ pathology. A similar prevalence of HS/MTS was seen in the clinically diagnosed bvFTD (14.5%) and PPA (13.6%) groups ($\chi^2 = 1.6$, $P = .44$). We further analyzed the presence of HS/MTS within the FTLD group with clinical diagnosis such as bvFTD, PPA, AD, CBD, and PSP. No significant differences were observed ($\chi^2 = 4.6$, $P = .58$). Among the patients in the FTLD cohort, 30 (22.1%) had τ-positive pathology and 106 (77.9%) had τ-negative pathology. A similar prevalence of HS/MTS was seen in the τ-positive (16.7%) and τ-negative (12.3%) subsets ($\chi^2 = 0.53$, $P = .35$).

Discussion

This study of patients with early-onset dementia included in the NACC databases indicates that HS/MTS is more commonly associated with FTLD than with AD. These findings are consistent with a prior report demonstrating a higher prevalence of HS in FTLD than in AD in a clinical cohort that included a significant percentage of patients with late-onset dementia.[5]

Taken together, these findings support the hypothesis that HS/MTS in FTLD occurs as part of the primary pathological process, rather than as a secondary, nonspecific effect of aging on memory and hippocampal function.[11]

A number of studies have shown a relationship between HS/MTS and FTLD. Both clinical and pathological evidence suggest that uncomplicated HS with dementia (HSD) associated with FTLD pathology may be a clinical manifestation of FTLD.[12-14] In one clinical study, over half of the patients with HSD showed features of FTLD, including inappropriate behavior, stereotypic behavior, and decreased language.[12] In another neuropathological study, over half of the patients with HSD had FTLD-like ubiquitinated inclusions (which often represent TDP-43 pathology) in the dentate gyrus and temporal neocortex.[13,14] Given the links between FTLD, TDP-43 pathology, and HS, the prevalence of HS/MTS in our early-onset FTLD cohort (13.3%) may seem rather low. However, our results approximate those from another research group that reported an incidence of HS of 18% in their patients with FTLD with symptom onset before 65 years of age.[6]

The HS is age related and can occur both in the presence and in the absence of dementia.[1-3] The HS is seen most commonly in individuals diagnosed with dementia after 75 years of age; and in AD, HS appears more closely associated with increased age of symptom onset rather than the presence of underlying AD neuropathology.[3] This association was also seen in our early-onset AD cohort, as the patients with AD with HS/MTS were significantly older than those without HS/MTS. Taken together, these findings support the hypothesis that HS/MTS in AD may simply be a by-product of aging in these patients. Although a higher prevalence of HS has been reported in late-onset FTLD than in early-onset FTLD,[6,7] we did not see an association between age and prevalence of HS/MTS in our early-onset FTLD cohort, indicating that the effects of aging are not the primary reason for the higher prevalence of HS/MTS in FTLD.

Given the reported associations between the presence of HS and TDP-43 immunopositive inclusion bodies,[3,5,15] and the significant proportion of patients with FTLD with underlying TDP-43 neuropathology,[11] it is tempting to conclude that the higher prevalence of HS/MTS in the NACC FTLD cohort is driven by a higher prevalence of TDP-43 proteinopathy in these patients. However, the current version of the NACC NPD does not explicitly document the presence or absence of TDP-43 deposits. Patients with FTLD in the NPD can be subdivided into τ-positive and τ-negative pathologies, but a similar prevalence of HS/MTS was seen between these 2 groupings. Although τ and TDP-43 pathologies in FTLD have previously been thought to be mutually exclusive, recent evidence from both clinical populations[16,17] and transgenic animal models[18] of FTLD indicates that both τ and TDP-43 pathologies can be present in the same individuals.

The HS is correlated with memory dysfunction both in the presence of AD pathology and as a manifestation of HSD in the absence of AD pathology.[1,3] These findings were not robustly replicated in our analyses, as the CDR memory subscale scores were only marginally higher in patients with AD with HS/MTS relative to those without HS/MTS. In the early-onset AD cohort, the presence of HS/MTS was associated with a higher prevalence of disinhibition. Although the underlying explanation for such a clinicopathologic correlation remains uncertain, this result is consistent with prior work suggesting that HS in isolation can be associated with FTLD symptomatology.[12] The relationship of memory dysfunction and other symptoms to HS/MTS associated with FTLD also remains uncertain, as different studies have reported mixed results.[4,7] There were no significant differences in demographic, cognitive/functional (CDR), or behavioral (NPI-Q) indices between patients with FTLD with or without HS/MTS. Moreover, there were similar rates of HS/MTS in patients with FTLD with clinical bvFTD and PPA. Taken together, these results suggest that HS/MTS has lesser impact on clinical symptoms in FTLD relative to early-onset AD and other conditions.

There are a number of factors that may limit the interpretation of our results. Although the NACC NPD and UDS databases include data from ADCs across the country, the participants represent a convenience cohort rather than an epidemiological sample and may not be fully representative of the broader population of patients with early-onset FTLD and AD. We used CDR category scores to assess impairment across different cognitive and functional domains. These measures are likely less sensitive and specific than formal neuropsychological assessments for identifying impairment in individual domains. However, neuropsychological testing results were not available for a significant subset of patients included in our analyses, particularly the ones with more severe cognitive impairment. Finally, given the multicenter nature of the NACC databases, there is likely an inherent degree of heterogeneity in the interpretation of the neuropathological criteria for HS/MTS across individual ADCs. Further investigations may be needed for more comprehensive comparisons of the potential relationships between the type and extent of sclerosis in the hippocampal and mesial temporal region in early-onset FTLD and AD.[19,20]

Despite these limitations, our data indicate that in patients with early-onset dementia, HS/MTS is seen more frequently in FTLD than in AD and that the presence of HS/MTS in FTLD is not clearly associated with aging or with specific cognitive or behavioral deficits. These findings provide further support for the hypothesis that HS/MTS may be a core component of neuropathology in FTLD[11,21] but require confirmation in neuropathological samples that more comprehensively assess the roles of specific subtypes of FTLD pathology.

Declaration of Conflicting Interests

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