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HIPPOCAMPAL AND MESIAL TEMPORAL SCLEROSIS IN EARLY-ONSET FRONTOTEMPORAL LOBAR DEGENERATION vs. ALZHEIMER 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 65) cohorts of FTLD and AD. We identified cases of early-onset FTLD (n=136) and AD (n=267) from National Alzheimer's Center Consortium databases and compared neuropathological and clinical data between these two groups. The FTLD group had a significantly higher prevalence of HS/MTS than 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 (FTLD); behavioral variant frontotemporal dementia (bvFTD); 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. HS includes neuronal loss and astrocytic gliosis of the hippocampus with a predilection for CA1 and the subiculum¹, 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 individuals³. 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 FTLT than in AD³⁻⁵. The presence of TDP-43 immunopositive inclusion bodies in around 90% of patients with HS and a majority of those with FTLT suggests a special relationship between these two neuropathologies^{3,5}. Some investigators, however, report that HS in FTLT, which has a mean onset in the 50's, is related to increased age,^{6,7} similar to the associations that have been reported in other neurodegenerative conditions³. The relationship of HS to memory and cognitive symptoms in FTLT also remains unclear. One study indicated that HS in FTLT is associated with more pronounced memory deficits⁷, but another reported similar cognitive deficits among FTLT patients with and without HS⁴. Moreover, few clinicopathological studies have directly compared HS/MTS in FTLT with other neurodegenerative disorders, such as early-onset AD, in terms of prevalence, age-related effects, and relationship to clinical symptoms⁵.

We examined the clinical and cognitive implications of HS/MTS in the presence of primary FTLT 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 Dataset (UDS)⁸. This study addresses the issue of whether HS/MTS 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 FTLT than AD, regardless of age or clinical symptoms, therefore supporting the view that HS/MTS has a specific association with FTLT.

METHODS

Participants

The study cohort consisted of individuals diagnosed with dementia who were included in both the NACC NPD and UDS⁸. Participant data was collected between 2005 and 2012 at the 34 Alzheimer's Disease Centers (ADCs) with current or prior funding from the National Institute on Aging. We identified patients with primary neuropathological diagnoses of FTLT or AD with age of initial symptom onset < 65 and examined clinical data from their initial UDS visits. These two cohorts were matched by gender and age of symptom onset (+/- 3 years), with a goal of two matched AD subjects for each FTLT subject, yielding a final study sample of 136 FTLT and 267 early-onset AD subjects. Clinical diagnoses in the FTLT 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 NACC data collection, and the UCLA 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. MTS cases included additional neuronal loss and gliosis in medial temporal lobe structures beyond the hippocampus, including the amygdala and entorhinal cortex. A total of 18 FTLT 14 AD subjects had HS or MTS. Overall, 31 of 32 of these subjects met criteria for MTS; only a single FTLT subject was noted to have HS alone. FTLT cases were further subcategorized as having tau-positive (Pick's disease, progressive supranuclear palsy, corticobasal degeneration, FTLT and parkinsonism with tau-positive or argyrophilic inclusions, or other tauopathy) or tau-negative (FTLT with ubiquitin-positive/tau-negative inclusions and FTLT

with no distinctive histopathology (tau-negative, ubiquitin-negative, and no argyrophilic inclusions) pathology.

Statistical Analyses

We first compared the prevalence of HS/MTS between patients with neuropathologically diagnosed FTLN and AD. Subsequent analyses were performed to determine the associations between HS/MTS and gender, age, 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, IL). Group comparisons were performed using chi-square 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.

RESULTS

Comparisons of the FTLN and AD groups (matched by gender and age of symptom onset) are shown in Table 1. FTLN subjects were significantly more likely to have HS and/or MTS on neuropathological examination ($p=0.003$) than AD subjects. Relative to FTLN subjects, AD subjects had significantly greater cognitive and functional deficits (as measured by the CDR Sum of Boxes) on initial visit ($p=0.004$), and were older, both at the time of initial visit ($p=0.002$) and at time of death ($p<0.001$).

We conducted separate analyses of the FTLN 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 FTLN group, there were no differences between subjects 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 FTLN group, the HS/MTS+ subjects were significantly older than the HS/MTS- subjects at the time of their initial study visit ($p=0.004$) and at time of death ($p=0.008$). Additionally, the HS/MTS+ subjects had marginally higher (i.e. poorer) CDR memory scores ($p=0.09$) than the HS/MTS- subjects.

The prevalence of behavioral symptoms assessed with the NPI-Q are shown in Table 3. There were no differences in the prevalence of any individual behavioral symptoms between HS/MTS+ and HS/MTS- subjects in the FTLN group. However, in the AD group, the HS/MTS+ subjects were significantly more likely to exhibit symptoms of disinhibition than the HS/MTS- subjects ($p=0.02$).

We performed further analyses in the neuropathologically confirmed FTLN group to examine possible associations between HS/MTS pathology and specific clinical diagnoses or the presence/absence of FTLN spectrum tau pathology. A similar prevalence of HS/MTS was seen in the clinically diagnosed with bvFTD (14.5%) PPA (13.6%) groups ($\chi^2=1.6$, $p=0.44$). We further analyzed presence of HS/MTS within FTLN group with clinical diagnosis such as bvFTD, PPA, AD, CBD and PSP. No significant differences were observed ($\chi^2=4.6$, $p=0.58$). Among the subjects in the FTLN cohort, 30 (22.1%) had tau positive pathology and 106 (77.9%) had tau negative pathology. A similar prevalence of HS/MTS was seen in the tau positive (16.7%) and tau negative (12.3%) subsets ($\chi^2=0.53$, $p=0.35$).

DISCUSSION

This study of patients with early-onset dementia included in the NACC databases indicates that HS/MTS is more commonly associated with FTLN than with AD. These findings are consistent with a prior report demonstrating a higher prevalence of HS in FTLN than AD in a clinical cohort that included a significant percentage of late-onset dementia patients⁵. Taken together, these findings support the hypothesis that HS/MTS in FTLN occurs as part of the primary pathological process, rather than as a secondary, nonspecific effect of aging on memory and hippocampal function¹¹.

A number of studies have shown a relationship between HS/MTS and FTLN. Both clinical and pathological evidence suggest that uncomplicated HS with dementia (HSD) is associated with FTLN pathology may be a clinical manifestation of FTLN^{12–14}. In one clinical study, over half of the HSD patients showed features of FTLN, including inappropriate behavior, stereotypic behavior, and decreased language¹². In another neuropathological study, over half of the HSD patients had FTLN-like ubiquitinated inclusions (which often represent TDP-43 pathology) in the dentate gyrus and temporal neocortex^{13,14}. Given the links between FTLN, TDP-43 pathology, and HS, the prevalence of HS/MTS in our early-onset FTLN cohort (13.3%) may seem rather low. However, our results approximate those from another research group, which reported an incidence of HS of 18% in their FTLN patients with symptom onset before 65 years of age⁶.

HS is age-related and can occur in both the presence and absence of dementia^{1–3}. 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 neuropathology³. This association was also seen in our early-onset AD cohort, as the AD subjects 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 byproduct of aging in these patients. Although a higher prevalence of HS has been reported in late-onset FTLN than in early-onset FTLN^{6,7}, we did not see an association between age and prevalence of HS/MTS in our early-onset FTLN cohort, indicating that the effects of aging are not the primary reason for the higher prevalence of HS/MTS in FTLN.

Given the reported associations between the presence of HS and TDP-43 immunopositive inclusion bodies^{3,5,15}, and the significant proportion of FTLN cases with underlying TDP-43 neuropathology¹¹, it is tempting to conclude that the higher prevalence of HS/MTS in the NACC FTLN cohort is driven by a higher prevalence of TDP-43 proteinopathy in these subjects. However, the current version of the NACC NPD does not explicitly document the presence or absence of TDP-43 deposits. FTLN cases in the NPD can be subdivided into tau-positive and tau-negative pathologies, but a similar prevalence of HS/MTS was seen between these two groupings. Although tau and TDP-43 pathologies in FTLN have previously been thought to be mutually exclusive, recent evidence from both clinical populations^{16,17} and transgenic animal models¹⁸ of FTLN indicate that tau and TDP-43 pathologies can both be present in the same individuals.

HS is correlated with memory dysfunction in both 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 AD subjects with HS/MTS relative 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 symptomatology¹². The relationship of memory dysfunction and other symptoms to HS/MTS associated with FTLN 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 FTLN subjects with or without HS/MTS. Moreover, there were similar rates of HS/MTS in FTLN cases with clinical bvFTD and PPA. Taken together, these results suggest that HS/MTS has lesser impact on clinical symptoms in FTLN 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 early onset FTLN and AD patients. 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 subjects 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 FTLN and AD^{19,20}.

Despite these limitations, our data indicate that in early-onset dementia patients, HS/MTS is seen more frequently in FTLN than in AD, and that the presence of HS/MTS in FTLN 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 FTLN^{11,21}, but require confirmation in neuropathological samples that more comprehensively assess the roles of specific subtypes of FTLN pathology.

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Table 1

Demographic data for the early-onset FTLD and AD groups

	FTLD	AD	<i>t</i>(401)/χ^2(403)
N	136	267	
% Male	58.8%	59.1%	0.01
Education (SD)	15.1 (3.0)	15.2 (3.0)	−0.21
% Non-Hispanic White	91.1%	92.3%	3.80
CDR SOB at initial visit (SD)	9.7 (5.7)	11.4 (5.7)	−2.80*
Age at symptom onset (SD)	56.3 (6.2)	57.2 (6.0)	−1.19
Age at 1st visit (SD)	62.0 (6.9)	64.4 (7.7)	9.81*
Age at death (SD)	63.9 (7.1)	67.1 (7.7)	−3.90*
% HS/MTS	13.2%	5.2%	7.80*

*
 $p < 0.05$

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
1st Visit	62.1 (7.1)	61.3 (6.1)	0.15	64.1 (7.6)	70.2 (6.9)	8.50 *
Death	64.1 (7.3)	63.3 (5.8)	0.17	66.8 (7.7)	72.4 (6.3)	7.07 *
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

* $p < 0.05$

Table 3

NPI-Q symptoms associated with HS/MTS in Early-Onset FTLD and AD.

	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*
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

* $p<.005$.
NPI-Q data not available for 8 FTLD and 20 AD patients.