Clinical and Neuropathological Characteristics of Hippocampal Sclerosis

A Community-Based Study

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Background: Hippocampal sclerosis (HS) is a neuropathologic finding characterized by neuronal loss and gliosis in the CA-1 and subiculum of the hippocampus. Previous studies of HS have shown that this is a common postmortem finding in elderly subjects with dementia. However, these studies were from selected samples and therefore are not necessarily representative of patients seen in the general medical community.

Objectives: To examine the clinical and pathologic characteristics of HS in a community-based case series of dementia and to compare these characteristics with those observed in subjects with Alzheimer disease (AD) from the same study sample.

Methods: One hundred thirty-four autopsy cases were available from a community-based registry of dementia. Sixteen cases (12%) had a postmortem diagnosis of HS. Thirty-two comparison control cases with a neuropathologic diagnosis of AD were selected from the same files. Each case of HS was reviewed for HS neuropathologic features, including severity, distribution, and additional pathologic processes. Blinded review of clinical characteristics for the HS and control groups was performed to assess risk factors.

Results: There was a wide range of severity and distribution of HS lesions between cases and substantial variability in lesion severity and age within individual cases. Serial neuropsychologic and behavioral assessments revealed similar clinical features and rates of dementia progression between HS and AD groups. Of all neuropsychologic tests performed at enrollment, only enhanced performance on Trails A differentiated the HS from the AD group (64 seconds, 0 errors vs 114 seconds, 0.6 errors; $P < .05$). The number of AD cases with at least 1 apolipoprotein E4 allele was significantly greater than the HS cases (61% vs 31%; $\chi^2 = 3.81, P < .05$). Although medical record review indicated higher frequencies of clinical stroke and neuroradiologic white matter abnormalities in the HS group, risk factors for vascular disease and neuropathologic evidence of cerebrovascular disease did not differ between the groups.

Conclusions: Our results suggest that HS is a frequent neuropathologic finding in community-based dementia. Individuals with HS have similar initial symptoms and rates of dementia progression to those with AD and therefore are frequently misclassified as having AD. Our clinical and pathologic findings suggest that HS has characteristics of a progressive disorder although the underlying cause remains elusive.

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Dementing disorders are a major source of disability in elderly persons and are of increasing public health concern as the number of elderly persons in our society increases. While Alzheimer disease (AD) remains the most common cause of dementia in elderly persons, other disorders, such as Lewy body dementias, may be causal as well. Recently, several studies have suggested that hippocampal sclerosis (HS), a pathologically diagnosed entity in which there is severe neuronal loss and gliosis in the CA-1 and subiculum region of the hippocampus, may also be an important cause of non-AD dementias.1-6 While some of these studies have found that up to 17% of individuals with dementia have HS, others have suggested that HS may be a rare cause of dementia.

The clinical signs and symptoms of HS are generally quite similar to those seen in AD, with recent memory loss being prominent. There is evidence that, similar to AD, dementia in HS may progress over time.1-3,7-8 However, behavioral disturbances and subtle neuropsychologic deficits may differentiate these patients from those with AD.2,7-13 Pathologically, HS...
SUBJECTS AND METHODS

SUBJECTS

The University of Washington—Group Health Cooperative Alzheimer’s Disease Patient Registry (ADPR) is a population-based registry of incident dementia cases in a Puget Sound-area health maintenance organization with 350,000 members in Washington State. The ADPR case–finding strategy has been described in detail elsewhere. Patients with new symptoms of possible dementia (based on surveillance of computed tomography logs, computerized hospital admission and discharge records, clinic registration lists, and primary care physician referrals) underwent a complete standardized diagnostic workup, including (1) medical history; (2) physical, neurologic, and neuropsychologic examinations; (3) laboratory testing; and (4) brain computed tomographic imaging. All subjects gave informed consent according to guidelines approved by the human subjects review committee at the University of Washington (Seattle) and Group Health Cooperative. When the workup was completed, the physicians and psychologists reviewed the results and arrived at a consensus diagnosis for each case based on criteria of the National Institute of Neurologic and Communicative Disorders and Stroke—Alzheimer Disease and Related Disorders Association (NINCDS–ADRDA) and the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. Patients in the ADPR received annual follow-up with interim history, neuropsychologic testing, and additional physical and neurologic examinations if indicated by a change in clinical symptoms.

A total of 1028 patients were enrolled in the ADPR from 1987 to 1996. Of these, 970 individuals came to the evaluation with 77% meeting NINCDS–ADRDA diagnostic criteria for any dementia and 58% with probable or possible AD. From this group, 425 deaths occurred and autopsies were performed on 134 cases. A recent comparison of autopsied and nonautopsied cases from this sample found similar age and sex distribution between the 2 groups as well as similar dementia severity at initial evaluation and at last evaluation. However, there was a higher frequency of clinically diagnosed vascular disease and minorities in the nonautopsied vs autopsied groups (19% vs 8% diagnosed vascular dementia and 13% vs 5% minorities, respectively; $P \leq .05$).

NEUROPATHOLOGIC EVALUATION

Neuropathologic evaluation was performed at the University of Washington Medical Center by neuropathologists (J.B.L., D.N.) from the department of pathology and the Alzheimer’s Disease Research Center. Neuropathologic examinations focused on the cingulate gyrus, superior and middle frontal gyri, medial orbital cortex, superior, middle, and inferior temporal gyri, inferior parietal lobule, medial occipital cortex, hippocampus, amygdala, entorhinal cortex, parahippocampal gyrus, hypothalamus, mammillary bodies, thalamus, midbrain, pons, medulla, and cerebellum. When possible, multiple anterior to posterior blocks of the medial temporal lobe were taken from both the left and right hemispheres. Standard tissue stain consisted of hematoxylin–eosin (H&E), thioflavin S, and the modified Bielschowsky silver methods, on 8-µm-thick paraffin-embedded sections. Neuropathologic results from this sample have been previously described.

Individuals with HS were identified from a review of all 134 ADPR cases that were autopsied. Hematoxylin–eosin–stained sections of the available hippocampal blocks were examined for evidence of HS (severe neuronal loss with gliosis in the CA-1 of the hippocampus and/or subiculum with relative sparing of the CA-2/3 region). All hippocampal sections from both hemispheres were assessed semiquantitatively for severity of pathologic findings (absent, mild, moderate, or severe; 0 to ++/+). The distribution of the pathologic evidence was defined, for each hemisphere, as “diffuse” if present at all hippocampal levels or “patchy” if restricted to less than all levels. Subicular involvement was also noted. The cases were staged for neurofibrillary tangle and senile plaque pathologic changes. The presence of neuropathologic AD, using the Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria, was noted for all HS cases (criteria were chosen for the neuropathologic AD diagnosis on study

is generally defined by the severe loss of neurons and concomitant gliosis in the CA-1 and subiculum region, with relative sparing of other hippocampal fields. However, there is some suggestion that other hippocampal fields, medial temporal structures, and even cortical and subcortical structures may also be involved.

Previous published studies of HS have been performed in selected research samples, such as cases from Alzheimer disease research centers. There is a possible selection bias in such samples that could be important in the interpretation of demographic and clinical characteristics. We previously examined a community-based case series of autopsies of incident cases of dementia. From this investigation, 16 cases had a pathologic diagnosis of HS. Our current study compares the demographic, genetic, and clinical characteristics of these cases with a group of AD cases from that same study sample. We also examined in detail the distribution and severity of the pathologic findings in HS within the medial temporal lobe. By examining cases of HS selected from this community-based case series, we hope to provide a more accurate picture of the clinical and neuropathologic characteristics of HS and begin to identify potential risk factors for this disorder.

RESULTS

DEMOGRAPHICS

Patient characteristics are presented in Table 1. Mean±SD age of dementia onset did not significantly differ between the HS and AD groups (79.8±1.4 years vs 77.3±1.4 years; $t=1.10$, $P=.28$). Mean±SD age at death (84.8±1.2 years vs 83.2±1.5 years; $t=0.74$, $P=.46$) and duration of illness were also similar in the HS and comparison AD groups (5.1±0.7 vs 5.9±0.5 years; $t=0.92$, $P=.36$). There was a trend for a preponderance of men in the HS group (10 men [63%] and 6 women vs 11 men [34%] and 21 women; $\chi^2=3.43, P=.06$).
matter changes on computed tomographic scans in the HS cases as compared to AD cases. The frequency of the subtypes of behavioral disturbances were remarkably similar except for apathy/indifference, which was more frequent in the AD group but did not reach statistical significance ($\chi^2 = 2.59, P = .11$).

**NEUROPSYCHOLOGIC CHARACTERISTICS**

Enrollment visit MMSE scores were available for all HS and comparison AD cases and a follow-up MMSE was available for 13 HS and 18 AD cases. Mini-Mental State Examination scores did not differ between subjects with HS and AD for either the initial visit (mean±SD, 20.1±1.6 vs 19.0±1.3; $t=0.39$, $P = .72$). The rate of change in MMSE score did not differ significantly between HS and AD groups (mean±SD, $-0.39±0.6$ vs $-0.30±0.8$ points per month; $t=0.78$, $P = .44$).

At enrollment, the AD comparison group performed worse on Trails A time to completion (mean±SD, 114±19 seconds vs 64±11 seconds; $t=2.30$, $P = .05$) and
number of errors (0.6±0.2 errors vs 0 errors; Wilcoxon rank sum \( P = .09 \)) than the HS group. There were insufficient data points to compare performances on Trails B. The performances on Boston Naming, Wechsler Adult Intelligence Scale–Revised Block Design, Logical Memory (Immediate and Delayed), Coblentz Construction, and Conceptualization were not significantly different between the HS and comparison AD groups.

GENETICS

The frequency of APOE ε4-positive cases was significantly greater in the AD comparison group (19 [61%] of 31) than in the HS group (5 [31%] of 16; \( \chi^2 = 3.81, P = .05 \)). The 5 cases with concomitant neuropathologic AD and HS were more frequently APOE ε4 positive than the cases with HS alone (3 [60%] of 5 vs 2 [18%] of 11). One HS case was homozygous for APOE ε4. Interestingly, this patient did not manifest significant neuropathologic changes of AD (case 14, Braak stage II A).

NEUROPATHOLOGIC CHARACTERISTICS

A detailed neuropathologic characterization of the 16 cases of HS is presented in Table 2. Thirteen of 16 HS cases had hippocampal sections available from both the right and left hemispheres, and in all cases, at least 2 anterior to posterior levels of the hippocampus were available. Hippocampal sclerosis was frequently more severe on 1 side, and within the same side it was often patchy (Table 1 and Figure 1). This included marked differences in severity of gliosis between affected and unaffected regions (Figure 1B and D). Also notable was evidence of acute and chronic gliosis within the HS lesions of the same patient (Figure 2). Subicular neuronal loss and gliosis usually coexisted with HS pathologic change in CA-1, although there were 3 cases (cases 2, 3, and 12) with CA-1 involvement without subicular changes, at the same level, and 1 case (case 14) with subicular neuronal loss and gliosis without CA-1 change (although there was CA-1 involvement in the contralateral hippocampus). In 3 cases (cases 1, 4, and 15), neuronal loss and gliosis extended into the parahippocampal and inferior temporal gyri. This latter change was always associated with severe neuronal loss in the CA-1 and subiculum. Occasionally, there also appeared to be an extension of neuronal loss into the CA-2 regions (Figure 1A).

Table 1. Demographic and Clinical Characteristics of Subjects With Hippocampal Sclerosis and Alzheimer Disease

<table>
<thead>
<tr>
<th></th>
<th>Hippocampal Sclerosis (n = 16)</th>
<th>Alzheimer Disease (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 10</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Female 6</td>
<td>21</td>
</tr>
<tr>
<td>Age at onset, mean ± SD, y</td>
<td>79.8 ± 5.6</td>
<td>77.3 ± 7.8</td>
</tr>
<tr>
<td>Age at death, mean ± SD, y</td>
<td>84.9 ± 4.9</td>
<td>83.2 ± 8.1</td>
</tr>
<tr>
<td>Duration of disease, mean ± SD, y</td>
<td>5.1 ± 2.6</td>
<td>5.9 ± 2.6</td>
</tr>
<tr>
<td>MMSE score, mean ± SD</td>
<td>Initial 20.1 ± 6.3</td>
<td>19.0 ± 7.3</td>
</tr>
<tr>
<td></td>
<td>Closest to death 10.4 ± 8.9</td>
<td>11.6 ± 8.9</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>2</td>
<td>14†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>7†</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>8†</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>White matter changes on CT</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>History of arrhythmias</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Head trauma</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

*p* Data are given as number of patients unless otherwise indicated. MMSE indicates Folstein Mini-Mental State Examination; ECG, electrocardiogram; and CT, computed tomography. †*P < .05.*

This is the first study, to our knowledge, to describe HS in a community-based case series of dementia. Our sample provides a more representative picture of the clinical, pathologic, and genetic characteristics of HS as it exists in the general medical community. Consistent with studies in more selected samples,4,5,9,26 we found that more than 10% of individuals with dementia in the study population had HS. Using the more restrictive criteria for pure HS reported by Ala et al,1 we found a much lower frequency (2%), although modestly higher than that reported by 2 other groups16 using more selected samples (0.4% and 0.5%, respectively).

Demographic and clinical features of our HS group, including age of onset, age at death, and duration of illness, were very similar to the AD comparison group. Similar to Dickson et al,9 our HS cases were in their 80s on average (mean age at death, 84.8 years), although, as emphasized by others,1,2 this disorder can occur in younger
individuals (the youngest age at onset in our sample was 66 years).

Previous reports of an association between antemortem hypoxia or hypotension and isolated neuronal loss in the hippocampal CA-1 region have suggested a pathophysiologic connection between HS and vascular disease.\(^3\)\(^5\) In more recent case series, it has been unclear if there is an increased frequency of vascular risk factors in HS.\(^1\)\(^-\)\(^3\) Although a clinical history of stroke and the presence of white matter changes on neuroimaging were increased in our HS group, neuropathologic evidence for infarcts; thalamic/SN neuronal loss involvement; multiple old infarcts; thalamic/SN neuronal loss.

We are aware that epilepsy is a risk factor for HS in individuals with recurrent seizures.\(^3\)\(^7\)\(^6\) In addition, although seizure-associated HS is not clinically characterized by a progressive AD-like dementia, the pathologic picture could look quite similar (at least within the hippocampal formation). Therefore, we specifically addressed seizure history in our HS and comparison cases, and found that there was no evidence of an increased frequency of seizure history in our HS group.

The severity of dementia was very similar for the HS and AD comparison groups. Consistent with Corey-Bloom et al\(^2\) and Crystal et al,\(^2\) we found that the neuropsychologic profiles and rates of cognitive decline did not substantially differ between HS and AD. In contrast, Zabar et al\(^3\) reported a slower rate of cognitive decline in patients with HS. However, their HS group had higher levels of cognitive functioning at the initial visit compared with their AD comparison group, which may have accounted for these differences.\(^3\) As expected, the memory dysfunction in HS was very similar to that observed in our AD cases and is presumably related to the medial temporal lobe involvement. The frequency of behavioral disturbance and language dysfunction was again similar in the HS and AD comparison groups, supporting the hypothesis that the pathologic findings in HS may be more widespread than the medial temporal lobe.\(^1\)\(^-\)\(^3\) We found that the only neuropsychologic test result that distinguished HS from AD was a significantly better performance on Trails A performance on Trails A in HS patients. Impairment on Trails A is a sensitive indicator of early AD.\(^3\) It is possible that in the early stages of HS, the pathologic evidence is relatively restricted to the temporal lobes, while in AD, earlier frontal lobe involvement is associated with poor performance on Trails A. Hippocampal sclerosis should be considered in the differential diagnosis of patients with a mild to moderate AD-like dementia and good Trails A performance.

Demographic features, putative risk factors (except for APOE genotype), and clinical symptoms, including rate of dementia progression of the HS group, were very similar to those in the AD comparison group.

Table 2. Neuropathological Features of Hippocampal Sclerosis Cases*†

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at Onset, Y</th>
<th>Severity</th>
<th>Distribution†</th>
<th>Subicular Involvement</th>
<th>Severity</th>
<th>Distribution†</th>
<th>Subicular Involvement</th>
<th>Braak Stage</th>
<th>AD Dx</th>
<th>Other Neuropathology</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>66</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>0-0</td>
<td>No</td>
<td>Bilateral temporal lobe involvement; multiple old infarcts; thalamic/SN neuronal loss.</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>75</td>
<td>+++</td>
<td>Diffuse</td>
<td>No</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>II-B</td>
<td>Yes</td>
<td>Subacute temporal lobe infarct.</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>75</td>
<td>++</td>
<td>Patchy</td>
<td>No</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>II-A</td>
<td>No</td>
<td>SN neuronal loss.</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>75</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>II-0</td>
<td>No</td>
<td>Right temporal lobe involvement; multiple old infarcts; thalamic/SN neuronal loss.</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>77</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>0</td>
<td>. .</td>
<td>. .</td>
<td>IV-C</td>
<td>Yes</td>
<td>Multiple infarcts.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>78</td>
<td>+</td>
<td>Patchy</td>
<td>Yes</td>
<td>++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>I-A</td>
<td>No</td>
<td>SN neuronal loss.</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>79</td>
<td>++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>II-A</td>
<td>No</td>
<td>Thalamic gliosis.</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>80</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>IV-B</td>
<td>Yes</td>
<td>Multiple old infarcts in basal ganglia.</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>81</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>++</td>
<td>Patchy</td>
<td>Yes</td>
<td>V-C</td>
<td>Yes</td>
<td>2 small old infarcts.</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>81</td>
<td>0</td>
<td>. .</td>
<td>No</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>IV-C</td>
<td>Yes</td>
<td>Parkinson disease; 1 old infarct.</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>82</td>
<td>0</td>
<td>. .</td>
<td>No</td>
<td>++</td>
<td>Patchy</td>
<td>Yes</td>
<td>III-C</td>
<td>No</td>
<td>Multiple lacerations.</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>83</td>
<td>+</td>
<td>Patchy</td>
<td>No</td>
<td>+</td>
<td>Patchy</td>
<td>No</td>
<td>III-A</td>
<td>No</td>
<td>Small left parietal old infarct.</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>83</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>I-C</td>
<td>No</td>
<td>CA-2 with HS involvement; old infarct in frontal cortex.</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>84</td>
<td>0</td>
<td>. .</td>
<td>Yes</td>
<td>++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>II-A</td>
<td>No</td>
<td>Right caudate old infarct.</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>87</td>
<td>+++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>++</td>
<td>Patchy</td>
<td>Yes</td>
<td>I-B</td>
<td>No</td>
<td>Left temporal lobe involvement; SN neuronal loss.</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>90</td>
<td>+</td>
<td>Patchy</td>
<td>Yes</td>
<td>++</td>
<td>Diffuse</td>
<td>Yes</td>
<td>II-A</td>
<td>No</td>
<td>Acute ischemic change in left hippocampus.</td>
</tr>
</tbody>
</table>

*AD indicates Alzheimer disease; Dx, diagnosis; ellipses, not applicable; SN, substantia nigra; and HS, hippocampal sclerosis.
†Diffuse indicates present at all levels; patchy, not present at all levels.
Because of these similarities, it is not surprising that dementia secondary to HS has frequently been clinically misclassified as AD antemortem. In our sample of HS, 8 of 11 pure HS cases were clinically diagnosed as probable AD, and in at least 2 other studies, most HS cases had been clinically diagnosed as possible or probable AD.1,2

The association between the APOE ε4 allele and AD is well established.41,42 In our study groups, there were more APOE-ε4 positive cases in the AD comparison group than in the HS group. Even within the HS group, those cases without concomitant AD had a very low frequency of the APOE ε4 allele (18%). Interestingly, it is worth noting that 1 HS case with very mild pathologic consequences of AD (case 14, Braak stage II A) was homozygous for the APOE ε4 allele. Thus, for the individual patient, APOE genotyping results must be interpreted with caution.

Figure 1. Left (A) and right (B) mid-hippocampal sections from case 5 demonstrating substantial loss of neurons and contraction of the pyramidal layer in CA-1 of the right hippocampus. Arrows indicate the transition of CA-1/CA-2 (thionin). Note the preservation of CA-1 neurons in the left hippocampus. Glial fibrillary acid protein immunostaining demonstrates significant gliosis in CA-1 of the right (D), but not the left (C), hippocampus.

Figure 2. Gliosis within individual cases demonstrated acutely reactive gemistocytic glia in some regions of the CA-1 (A, arrows) and chronic gliosis within other regions of CA-1 (B) in the same hippocampal sclerosis case (case 7).
The neuropathologic features of HS observed in our sample, neuronal loss and gliosis in the CA-1 and subiculum with occasional extension into the parahippocampal and inferior temporal gyri, were generally consistent with other reports. However, we examined both the left and right hippocampi and multiple rostral to caudal sections for each hippocampal side in most of our cases, which revealed more patchy pathologic change of HS than previously reported. Surprisingly, there was evidence of unilateral involvement in 4 cases. In addition, there was evidence of differentially aged lesions within the same case. This latter finding is consistent with a progressive neurodegenerative process. In the most severely affected cases, the neuronal loss and gliosis extended into the parahippocampal and temporal cortical regions. Corey-Bloom et al found evidence of pathologic change in the frontal cortex and have suggested that extension of the HS pathologic process beyond the medial temporal lobe may account for the development of cortical dysfunction on neuropsychologic testing. These findings in HS suggest a progressive process with increasing involvement of medial temporal lobe structures and extension to other cortical regions with the development of other broader clinical symptoms.

The pathogenesis of HS remains unclear. One hypothesis suggests that HS is related to vascular disease. However, the inconsistent association of vascular risk factors with HS suggests that alternative processes should be considered. The progressive clinical and pathologic picture observed in our HS cases suggests a possible neurodegenerative process. Two recent studies have suggested that HS has similarities to frontotemporal dementia (FTD), in particular, the subtype originally described as “dementia lacking distinctive histopathology.” However, as pointed out by other authors, the late age of onset for most HS cases would argue against this latter hypothesis.

Since HS is rarely observed in elderly persons who do not have dementia, our results suggest that HS is commonly associated with dementia in the general medical community. It is a difficult group of patients to study clinically because of its similarities to AD in presentation and progression. Subtle neuropsychologic differences, such as performance on Trails A, may be important in identifying patients with this disorder. The etiology of and risk factors for this disorder remain speculative, although both vascular and neurodegenerative processes are hypothesized to play a role. Pathologic study of HS should include additional examination of regions outside of the medial temporal lobe to better understand the full extent of the pathologic process. Further pathophysiologic investigation of this important cause of dementia in elderly persons is needed.

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