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%; χ²=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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Original Contribution

Author affiliations are listed at the end of this article.

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.1,4,7,8 However, behavioral disturbances and subtle neuropsychologic deficits may differentiate these patients from those with AD.5,7,11 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 methodology has been described in detail elsewhere. We previously examined a 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 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; χ² = 3.43, P = .06).
inception).22 Braak stages were established in the HS cases after review of sections stained by the modified Bielschowsky method. Although severe pathologic findings in AD can be associated with CA-1 neuronal loss, only one case (9) was at a Braak stage that might have been associated with severe CA-1 neuronal loss.21 In this and the other HS cases with neuropathologic diagnoses of AD, HS was associated with a CA-1 neuronal loss out of proportion to the severity of the AD pathologic change, significant subicular neuronal loss, and a virtual absence of either intraneuronal or extracellular (‘ghost’) neurofibrillary tangles within the affected CA-1 regions.

For each HS case, we selected 2 pathologically confirmed AD cases from the same ADPR autopsy sample based on a comparable date of autopsy. Age and sex were not matched so that relationships of these variables to HS could be explored.

MEDICAL RECORD REVIEW

Two investigators (D.T. and E.P.) examined the medical records of all 48 cases (16 HS and 32 AD comparison cases). These investigators were blinded to the neuropathologic diagnoses. Clinical information was classified into the following categories: neurologic (head trauma, seizures, parkinsonism, falls), cerebrovascular (cerebrovascular accident by clinical history, cerebrovascular and/or white matter changes by brain imaging [based on official radiology report]), cardiovascular (myocardial infarction, congestive heart failure, cardiomegaly by chest x-ray, hypertension, arrhythmias, syncope, high cholesterol or other lipids, smoking), endocrine (hypothyroidism, diabetes), pulmonary (chronic obstructive pulmonary disease, sleep apnea) and miscellaneous (height, weight, alcohol abuse). Behavioral symptoms were also assessed based on the major categories of the Neuropsychiatric Inventory (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior).23 In cases where there was disagreement, consensus was established by discussion between the 2 raters.

Height, weight, and height-weight ratios were the same for both groups (data not shown).

CLINICAL CHARACTERISTICS

There was an increase in clinical history of stroke in the HS cases (9 [56%] of 16 vs 8 [25%] of 32; $\chi^2=4.55, P=.05$). There also was a trend toward greater frequency of white matter changes on computed tomographic scans in the HS group (4 [25%] of 16 vs 2 [6%] of 32; $\chi^2=3.43, P=.06$). In contrast, the HS group had a lower frequency of electrocardiogram abnormalities (2 [13%] of 16 vs 14 [44%] of 32; $\chi^2=4.69, P=.05$) and diabetes mellitus (0 of 16 vs 7 [22%] of 32; $\chi^2=4.10, P=.05$). The frequencies of the remainder of the clinical characteristics outlined in the “Methods” section did not differ between HS and comparison AD groups.

Behavioral disturbances were common in both the HS and AD groups. 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 TESTING

Neuropsychologic data from the initial study visit for 11 pure HS cases (without concomitant CERAD-based neuropathologic AD) and their matched AD cases were examined. These data included baseline Folstein Mini-Mental State Examination (MMSE).24 Trails A Time and Errors (there was insufficient Trails B data points for analysis),25 Wechsler Adult Intelligence Scale–Revised Block Design,26 Wechsler Memory Scale (Logical Memory Immediate and Delayed),27 and the Conceptualization and Construction subcales of the Coblenz Dementia Rating Scale.28 Previous studies in HS had suggested that these tests might differentiate HS from other dementias.2,8,11 First and last MMSE scores were also used to assess the rate of cognitive decline.

APOE GENOTYPING

The APOE genotype was obtained from either blood samples or paraffin-embedded tissue. For blood, the genotyping was performed using the dot blot method29 and replicated using a restriction enzyme digest method.30 The 2 methods yielded the same APOE genotype on all cases. In paraffin-embedded tissue, DNA was extracted, amplified by the polymerase chain reaction, and genotyped using a restriction enzyme digest method.30,31 The reliability of the paraffin method has been previously demonstrated.32 The APOE genotype was available for 15 HS and 31 AD cases.

STATISTICAL ANALYSIS

The 2-sample t test was used to compare continuous variables (ie, age, duration of illness). When distribution assumptions of the 2-sample t test were not met, distributions were compared by the rank sum test. The Cochran-Mantel-Haenszel $\chi^2$ statistic for stratified data was used to compare categorical variables (ie, presence of systemic vascular disease, stroke history, behavioral disturbances). The rate of progression of cognitive decline was determined using the first and last MMSE scores, adjusting for the number of months elapsed between the 2 examinations.

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; $t=0.50, P=.62$) or the last visit (10.4±2.5 vs 11.6±2.1; $t=0.36, P=.72$). 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; $t=2.30, P=.02$) and...
case was homozygous for APOE with HS alone (3 [60%] of 5 vs 2 [18%] of 11). One HS were more frequently APOE of HS is presented in of AD (case 14, Braak stage II A).

The performances on Boston Naming, Wechsler Adult sufficient data points to compare performances on Trails B. rank sum 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 e4-positive cases was significantly greater in the AD comparison group (19 [61%] of 31) than in the HS group (5 [31%] of 16; χ²=3.81, P =.05). The 5 cases with concomitant neuropathologic AD and HS were more frequently APOE e4 positive than the cases with HS alone (3 [60%] of 5 vs 2 [18%] of 11). One HS case was homozygous for APOE e4. 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). Using CERAD criteria for probable or definite AD,22 significant pathologic changes of AD was observed in 5 HS cases. One of these cases (case 2, Braak stage II-B) did not fulfill the more recently described Reagan criteria23 because of insufficient neurofibrillary tangle pathologic findings. Despite the clinical evidence on medical record review of increased stroke in the HS cases, there was no difference in the frequency of pathologic stroke between the HS and AD cases.

### PURE HS AND HS WITH AND WITHOUT SIGNIFICANT PATHOLOGIC FINDINGS IN AD

Frequency of HS in our study sample was 16 (12%) of 134 using the criteria outlined in the “Subjects and Methods” section. We found that only 3 (2%) of 134 of our sample had HS, using the significantly more restrictive criteria for pure HS (severe neuronal loss in CA-1, Braak stage II or lower, and/or other neuropathologic explanation for dementia). If HS cases diagnosed neuropathologically as having AD (based on CERAD criteria)22 were eliminated, HS frequency was 11 (8%) of 134. Analysis of demographic, clinical, neuropsychologic, and genetic data after elimination of these 5 HS cases with concomitant AD did not reveal any additional significant differences between our HS and AD comparison groups.

### COMMENT

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,34,35 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 groups18 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, 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 ages in more selected samples,3-6,34 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, we found a much lower frequency (2%), although modestly higher than that reported by 2 other groups using more selected samples (0.4% and 0.5%, respectively).

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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.35,36 In more recent case series, it has been unclear if there is an increased frequency of vascular risk factors in HS.1-5 Although a clinical history of stroke and the presence of white matter changes on neuroimaging were increased in our HS group, neuropathologic evidence for stroke was not more abundant in the HS cases. In addition, we did not find an increase in history of cardiovascular or pulmonary disease, or vascular risk factors, such as diabetes mellitus or smoking, in HS cases. The link between vascular disease and HS remains uncertain.

We are aware that epilepsy is a risk factor for HS in individuals with recurrent seizures.37,38 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 al2 and Crystal et al,3 we found that the neuropsychologic profiles and rates of cognitive decline did not substantially differ between HS and AD. In contrast, Zabar et al8 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.39 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 on the initial visit. Corey-Bloom et al2 found a similar trend for enhanced performance on Trails A in HS patients. Impairment on Trails A is a sensitive indicator of early AD.40 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>
</tr>
</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</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 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>. No</td>
<td>IV-C</td>
<td>Yes</td>
<td>Multiple infarcts</td>
<td></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>. . .</td>
<td>. . .</td>
<td>V-C</td>
<td>Yes</td>
<td>Parkinson disease; 1 old infarct</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>81</td>
<td>0</td>
<td>. . .</td>
<td>No</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>IV-C</td>
<td>Yes</td>
<td>Multiple lacunes</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>82</td>
<td>0</td>
<td>. . .</td>
<td>. . .</td>
<td>No</td>
<td>. . .</td>
<td>. . .</td>
<td>III-C</td>
<td>No</td>
<td>Multiple lacunes</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>
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<tr>
<td>14</td>
<td>M</td>
<td>84</td>
<td>0</td>
<td>. . .</td>
<td>. . .</td>
<td>Yes</td>
<td>++</td>
<td>Diffuse</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>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>I-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 \(\epsilon4\) allele and AD is well established.\(^41\,\,42\) In our study groups, there were more APOE–\(\epsilon4\) 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 \(\epsilon4\) 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 \(\epsilon4\) 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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