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Hippocampal sclerosis: a common pathological feature of dementia in very old (≥80 years of age) humans

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Abstract In a neuropathological study of 81 brains of prospectively studied subjects of 80 years of age or older at the time of death, 13 cases (16%), including 4 men and 9 women, had hippocampal sclerosis (HpScl) affecting the vulnerable region of the hippocampus. In demented subjects of 80 years of age or older, the frequency of HpScl was even higher, 26%. Cases with HpScl had significantly fewer hippocampal senile plaques (SP) and neurofibrillary tangles (NFT) and parahippocampal NFT than cases without HpScl, but did not differ significantly in any of the other measured pathological parameters. Enzyme-linked analysis of synaptic protein immunoreactivity in a subset of 33 cases demonstrated significant decreases in the hippocampus, but not in frontal, temporal, parietal or parahippocampal cortices. All but 1 of the cases with HpScl had Blessed information, memory and concentration scores (BIMC) of 8 or more, and all were considered to be demented. In some patients memory disturbance was disproportionate to deficits in other cognitive areas. All but 4 of the cases with HpScl had many non-neuritic, amyloid plaques in the neocortex meeting NIA criteria for Alzheimer's disease (AD); however, given the advanced age of the subjects, amyloid plaques were considered to represent age-related cerebral amyloid deposition ("pathological aging") in most cases. Only 3 cases had both many SP and NFT in multiple cortical regions consistent with AD. Another case had brain stem and cortical Lewy bodies consistent with diffuse Lewy body disease (DLBD). A few ballooned neurons were present in the limbic cortices in 3 cases, including one case of dementia with argyrophilic grains (DAG) in limbic and orbital frontal and temporal cortices. The 8 cases without AD, DLBD or DAG included 4 cases in which no other obvious cause of dementia was detected and 4 cases in which HpScl was accompanied by either multiple cerebral infarcts or leukoencephalopathy, or both, that could have contributed to dementia. Patients with HpScl had risk factors, clinical signs and post-mortem pathological findings of cardiovascular disease, but due to the high prevalence of these conditions in very old humans, no significant correlation with HpScl was detected. This study demonstrates that HpScl is a common post-mortem finding in demented, but not normal, elderly subjects. It may contribute to, or be a marker for, the increased risk of dementia in subjects with documented cardiovascular disease or a history of myocardial infarction.

Key words Dementia · Hippocampus · Ischemia
Synaptic proteins · Vascular disease

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Introduction

The aging of the population in the Western world is associated with increasing frequency of late life disorders [6], among which is cognitive decline. Although a number of pathological studies have addressed the etiology of dementia in old people (>65 years of age) [43], few have addressed the pathological substrate of dementia in the "very old" (≥80 years). It is generally assumed that the most common cause of dementia in this age group is Alzheimer's disease (AD), but this remains to be proven. Recent studies have renewed

interest in vascular causes of dementia [40]. It has even been suggested by some that the frequency of AD may decrease in the very old [8, 10, 22, 40]. Diagnosis is further complicated in this age group due to the fact that many cases have multiple pathological processes [26]. To learn more about the pathological substrate of dementia in the very old, we have examined brains of subjects, including those that were initially cognitively normal and those with varying degrees of cognitive impairment, who had been prospectively studied for periods of up to 10 years before their death.

In previous pathological studies of a subset of this autopsy population, including only those subjects who were not demented at the time of death, we have shown that some cognitively normal humans have extensive cerebral amyloid deposition [17]. Other studies have independently demonstrated this same phenomenon [9, 13, 27]. We have referred to age-associated cerebral amyloid deposition as pathological aging and cases with few or no amyloid deposits as normal aging [17]. The pathological features that distinguish pathological aging from AD appear to be cytoskeletal alterations in neurons, neurofibrillary tangles (NFT) and their neuritic processes [15–17]. Other studies have also shown that neuritic and synaptic pathology correlates better with cognitive decline than does amyloid deposition [11, 36, 42, 45].

In a review of neuropathology of our autopsy sample, we sometimes found cases with pathological aging who, surprisingly, had cognitive deficits. Closer examination of these cases invariably revealed other pathological processes, including diffuse Lewy body disease (DLBD) [16] or ischemic lesions. The purpose of this report is to describe one such pathology that characterized by neuronal loss in the vulnerable region of the hippocampus.

Materials and methods

Case material

The brains in this study were derived from participants in two longitudinal studies of aging (Bronx Aging Study – BAS) and dementia (Teaching Nursing Home Study – TNH). The patient population and study design have been reported previously [1, 28]. The patients were followed on a yearly basis with a battery of laboratory tests in addition to evaluations of medical, neurological, neuropsychological and psychosocial status. CT and MRI data were obtained from review of radiologists reports. Gait was assessed as normal or abnormal by the examining neurologist. Included in the neuropsychological profile were the American version of the Blessed Information, Memory and Concentration (BIMC) test [3] and the Fuld Object Memory Evaluation (FOME) test [19]. Additional evaluations were undertaken to work-up the cause of dementia in initially normal patients who developed major cognitive change. Some of the subjects with varying degrees of cognitive decline were enrolled in the TNH. The subjects were followed for up to 10 years. The average interval between the last clinical exam and death for all cases was 14.2±12.2 months (see [10] for datails).

Pathological methods

We have performed 108 autopsies on prospectively studied elderly subjects, 43 from BAS and 65 from TNH. Of these 108 autopsies 76 were women (70%) and 32 men (30%). The 81 cases in this report are all subjects who were 80 years of age or older at the time of death and include 42 cases from BAS and 39 from TNH, 60 women and 21 men. The post-mortem interval for the cases was 7.2±10.9 h. The post-mortem interval for cases with HpScl (12.5±18.4 h) was longer than those without (6.2±4.8 h), which reflects the fact that several patients with HpScl died in acute care hospitals rather than the affiliated nursing home.

Tissue sampling

At the time of autopsy, the standard protocol for this study was to dissect the right cerebrum and to freeze it for biochemical studies. The left cerebrum with entire brain stem and cerebellum and the intact circle of Willis was fixed in formalin for 10 days to 2 weeks before cutting it. In addition to samples from the formalin-fixed brain, multiple tissue samples were dissected from the right hemisphere at the time of autopsy for immunocytochemistry. Included in these samples were sections from five cortical areas, hippocampus, amygdala, basal ganglia, thalamus, midbrain and cerebellum. Of the 13 cases with HpScl 1 case was fixed in its entirety and bilateral hippocampal pathology was demonstrated in formalin-fixed tissue. In 4 cases only one hippocampus was available for histological study, the other half brain having been frozen in its entirety. The hippocampus from these cases was, however, available for biochemical studies (see below).

A calculated brain weight was determined from the available fixed tissue at the time of brain cutting by doubling the weight of the hemisphere and adding it to the weight of the entire brain stem and cerebellum or doubling the weight of the fixed hemibrain if the brain stem and cerebellum were also halved.

To assure uniformity in sampling, sections were taken from five cortical areas before cutting the brain in the coronal plane. Additional sections were then taken from the brain slices. The routinely sampled areas were the midfrontal cortex; superior temporal gyrus; inferior parietal lobule; motor cortex in the watershed area; calcarine cortex; hippocampus at the level of the lateral geniculate nucleus, including the parahippocampal gyrus; basal forebrain, including amygdala, perirhinal cortex and basal nucleus of Meynert (nbM); basal ganglia, including the lentiform nucleus; thalamus, including the subthalamic nucleus; midbrain rostral to the decussation of the superior cerebellar peduncle; pons at the level of the isthmus; medulla at the level of the hypoglossal nucleus; cerebellar vermis, taken from the sagittal section; and cerebellar cortex, including deep nuclei and lateral hemisphere.

The cortical, hippocampal, basal forebrain and cerebellar sections were studied with H&E stains and thioflavin S fluorescence microscopy. The number of senile plaques (SP) was counted in three contiguous 10x fields along the perpendicularly sectioned side of the gyrus. The 10x field subtended a 2-mm^2 area. Plaque counts were arbitrarily truncated at 50 when they were numerous. Neurofibrillary tangles (NFT) were counted in three 40x fields that were selected to maximize the NFT counted (generally from layers 3 and 5). The 40x field subtended a 0.125-mm^2 area. Counts of lesions in the hippocampus were obtained from CA1, with hippocampal sectors as described by Kemper [29].

The presence of amyloid angiopathy was assessed using thioflavin-S fluorescence microscopy, as previously reported [46]. Arteriosclerotic hyalinosis was assessed on H&E-stained section. If there was any suspicion of white matter pathology in the multiple sections examined with H&E, additional sections were stained with Bodian's stain for axons and luxol fast blue stain for myelin. White matter pathology was assessed based upon the presence of rarefaction of the neuropil, dilation of perivascular spaces and the presence of reactive astrocytes and less often macrophages.

The nbM neuronal population was assessed on a three point scale: 0, within normal limits; 1, mild depopulation; and 2, marked depopulation. In the nbM NFT were counted in three 40x fields with the highest density of lesions.

Enzyme-linked immunoassays (ELISA)

Tissue samples were obtained from the partially thawed right hemisphere. Gray matter was carefully dissected from white matter. The tissue was homogenized in TRIS-HCl with 140 mM NaCl, pH 7.4. The homogenate was dried to bottom of 96-well plates and reacted with a monoclonal antibody (EP10) that has been previously characterized and which recognizes a stable epitope in a synaptic protein similar to synaptophysin [24]. The primary antibody was detected with a peroxidase-linked secondary antibody. Each sample assay was performed in triplicate. The results were normalized with respect to protein content measured with a standard method (Lowry assay). The results are expressed in arbitrary units.

Statistical analysis

Statistical analysis was performed with software programs supplied with Jandel SigmaStat (San Rafael, Calif.) and Microsoft Excel 5.0 (Redmond, Wash.). Comparisons of clinical and pathological parameters used a Mann-Whitney rank sum analysis for nonparametric data. Chi-square analysis of contingency tables was used to assess clinical and pathological cardiovascular disease parameters. Comparisons of ELISA data was with the two-tailed Student-*t*-test. A $P < 0.05$ was considered statistically significant.

Results

Clinical features

Demographics

In the series of 108 brain autopsies, HpScl was detected in 16 cases (15%), in 10 women and 6 men. In autopsies of people of 80 years of age or older, HpScl was detected in 13 cases (16%), including 9 women and 4 men. The latter group is the subject of this report. The average age for the 13 cases with HpScl (89.2±4.1 years) was not statistically different from cases without HpScl (88.0±4.6 years).

Neuropsychology (Table 1)

The average BIMC score obtained closest to the time of death for cases 80 years of age or older was 16.5±12.8 and included 31 cases with scores of less than 8, an operational cut off score for dementia. HpScl was detected in only one person with a BICM score of less than 8, but this subject (no. 011) was considered to be demented by other clinical criteria. HpScl was detected in more than 25% (13 of 50) of the cases 80 years of age or older and a BIMC score of greater than or equal to 8. The average BIMC for cases with HpScl was 19.9±2.5 (S.E.M.) (median 17; 25th percentile – 75th percentile: 11.75–27.00) and was not statistically different from the cases without HpScl, 15.9±1.6 (median 13; 25 percen-

Table 1 Neuropsychological studies. Serial neuropsychological test scores during longitudinal course. 'FOME' best score is 10, 'Blessed test scores' best score is 0 (*FOME* Fuld object memory elevation, *Path. Dx.* pathological diagnosis, *NA* normal aging, *VaD* vascular dementia, *DAG* dementia with argyrophilic grains, *PA* pathological aging, *DLBD* diffuse Lewy body disease, *AD* Alzheimer's disease)

Case no.	Blessed (BICM) scores									First recall (FOME)								
(Path. Dx.)	I	II	III	IV	V	VI	VII	VIII	IX (year)	I	II	III	IV	V	VI	VII	VIII	IX (year)
144 (NA)	2	4	2	9	12					8	8	6	5	1				
055 (NA)	2	7	5	3	4	5	8			4	5	4	6	NA	4	3		
1021 (VaD/NA)	4	6	8	16						NA	6	6	4					
011 (VaD/DAG)	2	1	2	1	6	4	6			6	8	10	6	6	6	NA		
Cases meeting NIA criteria for AD																		
2270 (PA)	14	23	24							3	2	NA						
244 (PA)	1	4	0	1	NA	5	7	9	17	8	6	7	10	NA	10	10	9	0
436 (VaD/PA)	7	12	6	10	14	17				4	NA	5	5	NA	NA	6		
2021 (VaD/PA)	24	33	33							0	NA	NA						
1009 (VaD/PA)	23	33								3	NA							
313 (DLBD/PA)	0	5	7	11	12	30				8	7	7	7	6	3			
2004 (AD)	3	4	4	7	7	24				5	NA	5	4	3	NA			
2283 (AD)	26	26								2	2							
1008 (AD)	4	5	4	4	6	5	9	11		10	NA	7	6	6	4			
HpScl (+)	Last BICM: 19.1±8.4 (n = 13)									Last FOME: 2.85±1.83 (n = 13)								
HpScl (−)	Last BICM: 15.7±12.7 (n = 62)									Last FOME: 4.55±3.09 (n = 53)								

tile – 75 percentile: 3–32). The greater variance in the cases without HpScl is due to inclusion of both nondemented and demented subjects in cases without HpScl, but only demented subjects in cases with HpScl.

The yearly neuropsychological test scores for the subjects with HpScl are shown in Table 1. It is clear that some subjects developed dementia during the course of the study, while others were initially demented (BICM > 8). The latter had a shorter survival and usually more impaired cognitive function at death. Although only 1 case with HpScl had a BIMC score less than 8, only 2 had maximal impairment (a score of 33). In only a few cases (nos. 055 and 436) did the scores fluctuate or show sudden deterioration (no. 2004). Most subjects showed a gradual worsening of cognitive functioning.

Memory impairment was a prominent feature in all subjects with HpScl. In 1 subject (no. 2004), the onset of memory problems was considered abrupt. This subject was treated with phenytoin for "transient global amnesia". Another subject (no. 055) had a nearly pure amnestic syndrome with disproportionate deficits on memory tests, such as the FOME, compared to tests of a more global nature (e.g., BIMC scores).

Risk factors for cerebrovascular disease

The clinical features of cases with HpScl usually included risk factors for cerebrovascular disease, including hyperlipidemia (2 cases); hypertension (5 cases); peripheral vascular disease (4 cases); electrocardiogram (EKG) abnormalities (9 cases); cardiomegaly on chest radiographs (7 cases); myocardial infarction by either history, EKG or pathological confirmation (5 cases); congestive heart failure (4 cases); or diabetes mellitus (1 case). One subject (no. 2270) had documented cognitive deterioration following general anesthesia for surgery to repair a hip fracture that occurred as a result of a fall. Another subject (no. 436) had cognitive changes following electroconvulsive therapy for depression. None of the cases had documented seizures.

Cardiovascular studies

Clinical findings

The BAS design included systematic compilation of data to investigate the role of cardiovascular disease in the cause and development of dementia in the elderly. All subjects had repeated EKG studies, including Holter monitoring, and chest radiographs (CXR). In the 43 BAS subjects that came to autopsy, 18 had CXR evidence of cardiomegaly (1 with HpScl and 17 without HpScl; $\chi^2 = 0.814$, $P = 0.367$). EKG evidence of left ventricular hypertrophy was present in 11 (1 with HpScl and 10 without; $\chi^2 = 0.001$, $P = 0.972$). Silent myocardial infarctions were detected by EKG in 6 subjects that came to autopsy (1 with HpScl and 5 without; $\chi^2 = 0.183$, $P = 0.688$). There were no significant correlations with any of the clinical cardiovascular measures and presence of HpScl.

General autopsy findings

Complete autopsies were performed on 25 subjects. Acute or healed myocardial infarctions were detected in 10 cases (4 with HpScl and 6 without; $\chi^2 = 2.34$, $P = 0.126$). Cardiomegaly (defined as heart weight greater than 350 g) was detected in 18 cases (3 with HpScl and 15 without; $\chi^2 = 0.012$, $P = 0.911$). Left ventricular hypertrophy (defined as left ventricular free wall thickness greater than 1.5 cm) was detected in 21 cases (4 with HpScl and 17 without; $\chi^2 = 0.167$, $P = 0.682$). Due to the high prevalence of cardiovascular disease in autopsies of very old humans, none of the clinical or pathological cardiovascular parameters correlated with the presence of HpScl.

Neurology

An abnormal gait, usually characterized by slowing and poor balance, was found in eight subjects and six subjects had repeated falls. Cerebellar signs were present in two and three had extrapyramidal signs.

Neuroimaging

CT scans were performed on all subjects, and three subjects also had MRI scans. Cortical atrophy was the most common CT finding. Four subjects had low attenuation in the periventricular white matter consistent with leukoaraiosis [25]. Three subjects had radiographic evidence of infarcts and two others had marked basal ganglia and cerebellar mineralization. Increased signal intensity on T2 weighting in the periventricular white matter, centrum semiovale, or both, was noted on all three subjects who had MRI scans. One subject (no. 1009) had marked ventriculomegaly, but little cortical atrophy and was considered to have normal pressure hydrocephalus because of her poor gait and urinary incontinence.

Neuropathology

Brain weight

The average fixed brain weight for the 81 cases over 80 years of age at death was 1104 ± 136 g, which was not different for the 11 cases with HpScl (1096 ± 38.2 g) compared to those without HpScl (1104 ± 17.1 g).

Hippocampal pathology

All the cases described in this repord had loss of neurons in the vulnerable region of the hippocampus, which corresponds to CA1 and the subiculum. In most cases this took the form of selective loss of neurons with gliosis and relative preservation of the neuropil (Fig. 1), but in one case the lesion was more extensive and associated with partial cyst formation. Although damage was confined to the vulnerable region of Ammon's horn in cases with mild pathology, in some cases there was also loss of neurons and gliosis in the endplate and some focal loss of dentate gyrus granular neurons. In several cases gliosis and neuronal loss was also present in the amygdala and the subjacent entorhinal cortex. Bilateral involvement was confirmed in all but four cases where the right hippocampus was used for biochemical studies (see below).

Senile changes of the Alzheimer type (Table 2)

Amyloid plaques counted on thioflavin-S-stained sections were numerous in most of the brains with HpScl. In fact, nine cases met NIA criteria for AD [30], but using more conservative criteria that require the presence of NFT and neuritic plaques in multiple cortical regions, only three cases had AD. Although statistical comparisons were compromised by the method used to count SP because of a "ceiling effect", using nonparametric analysis (Mann-Whitney), there were no significant differences in the number of SP in cases with HpScl compared to those without it. Four cases had less than 15 amyloid plaques/mm^2 (< 30 SP per 10x field) and would not have met even the most liberal definition of AD.

None of the measured pathological parameters was significantly different in cases with HpScl compared to those without HpScl, except for the number of SP and NFT in the hippocampus and the number of NFT in the parahippocampal gyrus, all of which were reduced in cases with HpScl. (hippocampal NFT: $P = 0.007$; hippocampal SP: $P = 0.010$; parahippocampal NFT: $P < 0.001$; Mann-Whitney rank sum test). Surprisingly, many of the cases had a few NFT in the temporal lobe, including the cases with very limited numbers of cortical SP, but NFT were present in the frontal and parietal lobes only in subjects with AD.

Basal nucleus of Meynert

In cases with HpScl, the nbM had marked neuronal depletion in the DLBD case and the three cases with coexisting AD. Neurofibrillary degeneration was sparse in all but two cases. The cases with minimal cortical pathology or with only diffuse amyloid plaques (pathological aging) had minimal or no detectable neuronal loss in the nbM and only sparse NFT.

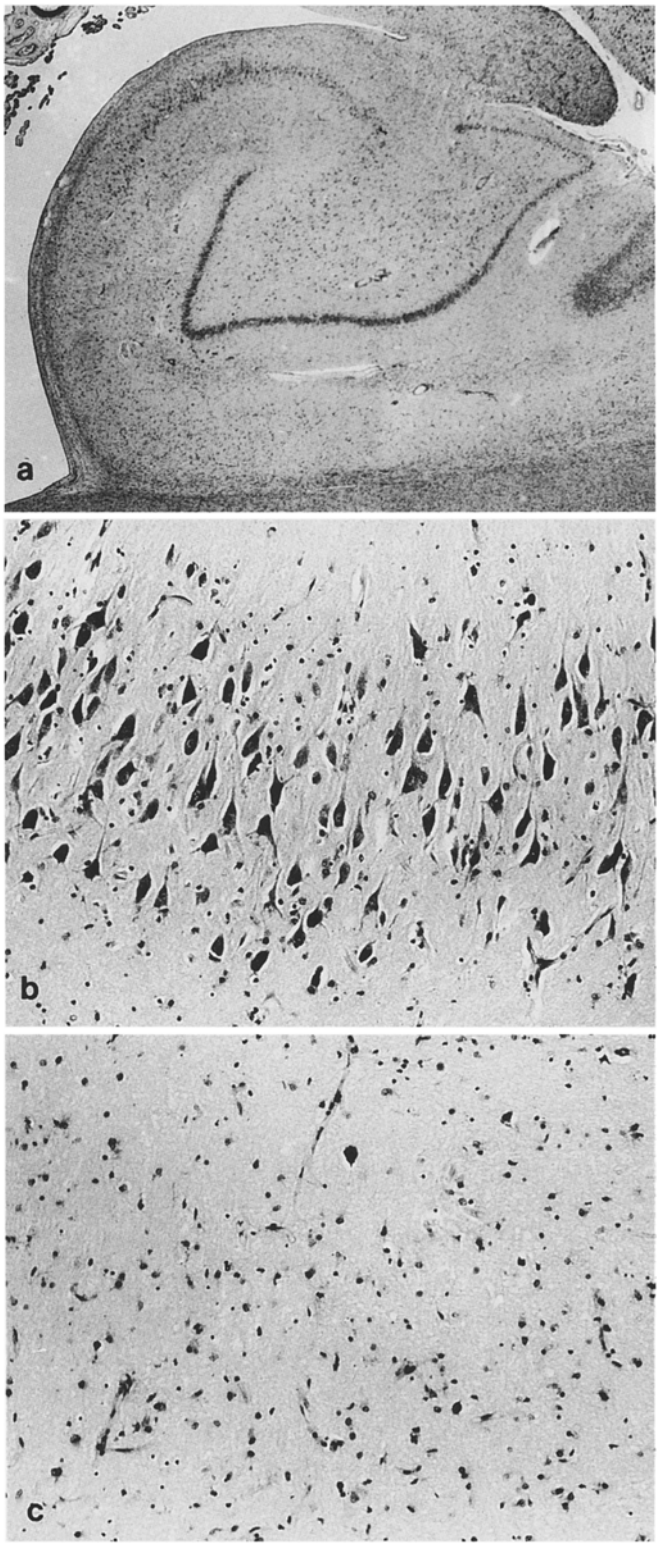

Fig. 1 a Hippocampal section (case no. 055) stained with Nissl stain shows preservation of pyramidal neurons in the dentate fascia and resistant zone, but neuronal loss in the vulnerable region (Sommer's sector). Higher magnification of the neurons in CA2/3 region show preservation of pyramidal neurons (**b**), in contrast to almost complete depletion of pyramidal neurons in CA1 (**c**). The neuropil in the areas with neuronal loss has delicate gliosis, but is not collapsed or cystic. (**c**). **a** × 20, **b, c** × 125

Table 2 Degenerative disease pathology (*SP* senile plaques – measured per 10x field which subtends 2 mm^2; *NFT* neurofibrillary tangles – measured per 40x field which subtends 0.125 mm^2, *nbM* basal nucleus of Meynert, *BN* ballooned neurons, *cLB* cortical Lewy bodies)

Case no. (Path. Dx.)	Frontal SP/NFT	Temporal SP/NFT	Parietal SP/NFT	Hippocampal SP/NFT	Occipital SP	Parahippocampal NFT	nbM NFT	BN	cLB
144 (NA)	0/0	0/1	16/0	0/6	0	0	1	–	–
055 (NA)	11/0	12/2	13/0	0/1	3	0	3	+	–
1021 (VaD/NA)	25/0	10/1	47/0	0/0	0	3	3	–	–
011 (VaD/DAG)	13/0	3/0	3/0	0/0	0	0	0	+	–
Cases meeting NIA criteria for AD									
2270 (PA)	>50/0	>50/0	>50/0	0/0	0	1	0	–	–
244 (PA)	>50/0	>50/1	45/0	5/2	15	4	2	–	–
436 (VaD/PA)	>50/0	>50/0	>50/0	4/3	12	1	1	–	–
2021 (VaD/PA)	>50/0	NA	NA	0/0	17	0	1	–	–
1009 (VaD/PA)	>50/0	>50/0	>50/0	0/1	>50	1	1	+	–
313 (DLBD/PA)	>50/0	13/0	>50/0	0/1	42	11	6	+	+
2004 (AD)	>50/0	>50/2	>50/1	5/0	14	1	1	–	–
2283 (AD)	>50/0	>50/1	>50/1	7/5	23	1	1	–	–
1008 (AD)	>50/1	40/0	>50/1	9/1	30	1	7	–	–
HpScl (+)	38.4±5.2 0.08±0.08	31.1±5.8 0.75±0.3	39.5±5.1 0.25±0.1	2.31*±0.9 1.54*±0.6	16±4.6	1.85*±0.8	2.31±0.7		
HpScl (−)	34.8±2.5 1.1±0.2	28.5±2.6 2.31±0.5	31.5±2.6 1.54±0.4	8.25±1.1 8.46±1.2	14.4±1.9	10.6±1.2	3.11±0.5		

Other cytoskeletal neuronal alterations

One case had Lewy bodies in the substantia nigra and widespread areas of the neocortex consistent with DLBD. This case also had a few ballooned neurons that were immunopositive with antibodies to phosphorylated neurofilament [14]. A rare ballooned neuron in the insular cortex contained a concentric hyaline inclusion with a halo consistent with a cortical Lewy body. Three additional cases had a few ballooned neurons in the limbic cortices (parahippocampal cortex, amygdala and insula). In one case ballooning neuronal degeneration was associated with tau-positive, agyrophilic grains that were present in the anterior and medial temporal lobe and the orbital frontal lobe, consistent with dementia with argyrophilic grains (DAG) [4]. It should be noted, however, that this patient had only mild cognitive impairment. Additional studies are required to determine the significance of this observation.

Synaptic markers (Table 3)

It has been suggested that synaptic loss may be the best correlate for cognitive decline in dementia disorders [42]. To investigate the role of synaptic pathology in cognitive impairment in cases with HpScl, an ELISA assay was performed to obtain a measure of the synaptic density in various cortical areas and the hippocampus. Synaptic protein immunoreactivity was not significantly different in any neocortical area or the parahippocampal cortex in cases with HpScl compared to

Table 3 Synpatic protein (EP10) immunoreactivity. EP10 is a monoclonal antibody raised to brain homogenates that recognizes a synaptic protein closely related to synaptophysin in biochemical properties and distribution. Results are expressed as mean ± SEM; numbers in parentheses are number of cases studied

	Mid-Frontal	Mid-Temporal	Inferior Parietal	Occipital	Hippocampus	Parahippocampus
HpScl (+)	2.29±0.31 (5)	3.61±0.33 (5)	3.56±0.41 (5)	2.43±0.43 (5)	2.04±0.42 (5)	1.70±0.16 (4)
HpScl (−)	2.44±0.65 (28)	3.62±0.78 (27)	3.47±0.76 (28)	2.39±0.80 (28)	2.49±0.61 (24)	1.84±0.61 (20)

those without HpScl (Table 3). There was, however, a significant reduction in synaptic protein immunoreactivity in the hippocampus [$HpScl^+$: 2.04 ± 0.42 ($n = 5$); $HpScl^-$: 2.49 ± 0.61 ($n = 24$), $P = 0.022$ (Student's two tailed t-test)].

Cerebrovascular disease (Table 4)

Cerebrovascular disease was detected in all 13 cases with HpScl. Microvascular pathology was prominent in all cases and took the form of arteriosclerosis (12 cases) or amyloid angiopathy (6 cases) or both (5 cases). Atherosclerosis affecting the large arteries at the base of the brain was notable in 7 cases. Three cases had extensive calcific vasculopathy of the basal ganglia, hippocampus and cerebellum, associated with parenchymal calcospherites compatible with Fahr's disease; however, none had documented abnormalities of calcium metabolism.

Subcortical arteriosclerotic leukoencephalopathy [39], most marked in the periventricular region and characterized by rarefaction of the white matter with gliosis and dilation of perivascular spaces, was detected in 5 cases. In 2 cases leukoencephalopathy was associated with AD. Only 1 of the cases with amyloid angiopathy had leukoencephalopathy. In 3 cases leukoencephalopathy was associated with ischemic lesions. Grossly visible infarcts were detected in 8 cases and microscopic infarcts were detected in 3 cases. Infarcts were detected in areas (cerebral cortex, thalamus and basal ganglia) that might conceivably have contributed to cognitive decline in 6 cases, based upon current concepts of vascular dementia [12, 18, 20, 33, 37]. Less significance was placed on isolated lesions in the cerebellum (2 cases) with respect to effects on cognition.

Discussion

The pathological findings in these cases demonstrate that HpScl is a relatively common finding in elderly humans. It was detected in 16 % of patients of 80 years of age or older and more than 25 % of demented subjects in this age group. It was not detected in any of the 31 cognitively normal old subjects. It seems reasonable to assume that damage to the hippocampus contributed to cognitive decline in these subjects, and that it was most likely related to previous anoxic-ischemic injury. Although HpScl was often detected in association with other pathological processes, most notably AD or multiple infarcts, in some cases it was the major pathological marker for dementia. In several recent reviews of the anatomico-pathological classification of vascular dementia, critically placed ischemic lesions, such as the hippocampal sclerosis, are included, but not often emphasized [12, 18, 20, 33, 37].

Although only a few cases have been described in the literature, HpScl has been felt to be the pathological substrate for dementia in some people [44]. In a pathology series reported by Clark et al. [7] several subjects had HpScl as the only significant pathology in the clinical setting of what was felt to be a primary degenerative dementia. The case reported by Zweig is also of interest [47]. This demented elderly subject had many cortical SP, but few or no NFT, and preservation of the nbM and cholinergic markers. The diagnosis of AD was based upon NIA criteria [30], which do not require the presence of neocortical NFT in patients older than 75 yeras of age. Several studies have raised questions about the validity of these criteria [10, 13, 17, 27]. In particular, recent studies suggest that neuritic, but not

Table 4 Cerebrovascular pathology (location of infarcts: *Cbl* cerebellum, *F* frontal lobe, *T* temporal lobe, *P* parietal lobe, *O* occipital lobe, *BG* basal ganglia, *WM* cerebral white matter, *Th* thalamus, *Ins* insular cortex, *MB* midbrain, *Po* pons)

Case no.	Atherosclerosis	Arteriosclerosis	Amyloid Angiopathy	Cribriform Change	Leukoencephalopathy	Microinfarcts	Encephalomalacia
144 (NA)	+	+	+	+			
055 (NA)			+				
1021 (VaD/NA)		+		+	+		
011 (VaD/DAG)	+	+	+				+ (Th)
Cases meeting NIA criteria for AD							
2270 (PA)		+					
244 (PA)		+	+				+ (Cbl)
436 (VaD/PA)	+	+	+		+	+ (F, T)	+ (T)
2021 (VaD/PA)	+	+				+ (BG, MB, Cbl)	+ (O)
1009 (VaD/PA)	+	+		+	+	+ (F, P, O)	+ (O, WM, Th, Po)
313 (DLBD/PA)		+	+				+ (Cbl, Ins)
2004 (AD)	+	+		+	+		
2283 (AD)	+	+			+		+ (BG)
1008 (AD)		+		+			+ (Cbl)

amyloid-type SP correlate with dementia [10]. It is tempting to speculate that HpScl in Zweig's case may have been the best pathological marker for this patient's cognitive decline. Sections from this case have been studied with immunocytochemistry and the SP are diffuse amyloid deposits, with few or no tau-immunoreactive neurites (unpublished data). These are features that are consistent with pathological aging, which per se is not associated with cognitive impairment [17].

It is of interest that many patients with dementia lacking distinctive histopathology (DLDH) also have HpScl [31]. It is tempting to speculate that cognitive impairment in at least some cases of DLDH may be related to processes that lead to HpScl. It may be worthwhile to separate DLDH cases with HpScl from those with preserved hippocampal anatomy for nosological purposes.

Hippocampal sclerosis is often seen in the setting of long-standing epilepsy. In such cases it is debatable whether HpScl is secondary to epilepsy or the cause of epilepsy. None of the cases in the present series had seizures. Although dementia is not commonly seen in epilepsy, more subtle cognitive impairment due to HpScl is reasonable. In the older subjects in this report, who have less functional reserve, similar lesions may have more profound impact (see below).

Selective neuronal vulnerability of the hippocampus to anoxic/ischemic insults has been demonstrated in a number of experimental paradigms to be mediated by excitatory amino acids, most notably glutamate [5, 21, 32]. In animals it is possible to decrease the selective vulnerability of CA1 hippocampal neurons to anoxic/ischemic injury with agents that block glutamate receptors or decrease intracellular accumulations of calcium [21]. Agents that block nitric oxide production may also prevent this type of selective neuronal injury [38]. Influx of excessive calcium may lead to neuronal death by a process that involves proteolysis of the cytoskeleton [32].

The evidence that HpScl in the very old is due to anoxic/ischemic injury is only indirect. All cases had microvascular pathology and many had other ischemic lesions in the central nervous system. Risk factors for cerebral hypoperfusion were common. Most subjects had EKG abnormalities and several cases had clinical and post-mortem evidence of myocardial infarction or fibrosis. Congestive heart failure, a very common disorder in the very old age group [6], was also frequent in subjects with HpScl. Many subjects with HpScl had gait problems. Falls, due to orthopedic and cardiovascular disorders, or both, were also common. It is reasonable to speculate that cerebral perfusion may have been compromised due to or as a consequence of falls. Nevertheless, it must be emphasized that due to the high prevalence of cardiovascular disease in very old humans, none of the clinical or pathological parameters had any statistically significant association with HpScl. Although there was no statistical significance, there was a trend for HpScl to be more frequent in patients with myocardial infarctions (Fisher exact test $P = 0.121$).

The presence of cerebral microvascular disease (e.g., arteriosclerosis and amyloid angiopathy) may limit normal compensatory mechanisms in the setting of hypoperfusion due to cardiovascular (e.g., arrhythmias or myocardial infarction) or iatrogenic causes (e.g., anesthesia). This is especially true in the elderly who have age-associated decreases in vascular capacity even in the absence of microvascular pathology [2, 34]. In one patient cognitive impairment was first noted following general anesthesia for hip surgery. Anecdotal reports of cognitive impairment following general anesthesia are well-known to geriatricians. This suggests that the very old may be less able to tolerate even mild degrees of hypoperfusion associated with general anesthesia due to the coexisting microvascular disease that is very prevalent in this age group.

Although HpScl may be an isolated pathological finding in some cases, in most it occurs with other lesions consistent with previous hypoxic/ischemic insult, including infarcts and leukoencephalopathy, or with other pathological processes, such as AD, DLBD or DAG. In these cases it is difficult to determine the contribution that hippocampal damage has to cognitive decline [26]. It seems unlikely that isolated hippocampal injury, even if bilateral, is sufficient to produce global cognitive defects. However, increasing evidence suggests that the hippocampus is critical for processing and categorizing diverse information [29, 35]. Although lesions in the hippocampus in young individuals may produce an amnestic disorder [35], in elderly subjects, who have age-related neuronal and synaptic deficits [11, 42] and decreased vascular reserve [2, 34], HpScl may have more profound cognitive effects.

Although it is an attractive hypothesis that HpScl is merely a marker for more widespread pathological alterations, such as decreases in the number or density of neocortical synapses, the results of ELISA analysis for a synaptic marker protein do not support this hypothesis. A statistically significant decrease in the synaptic marker was only present in the hippocampus, where there was also neuronal loss and also fewer of the more traditional markers for dementia disorders (e.g., SP and NFT).

A recent study by Sparks et al. [41] has drawn attention to be presence of diffuse plaques in subjects dying of cardiovascular disease. The findings in the present study are consistent with these observations in that diffuse plaques were present in most (but not all) of the cases with HpScl. It has also been suggested that dementia is more common in old people with a history of myocardial infarction [1]. The data in this study suggest that HpScl may be a pathological marker for dementia in subjects with documented cardiovascular disease or history of myocardial infarction. It is a pathological finding that is not detected in any of the brains of non-demented subjects.

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