Acta Neuropathol (2007) 114:335–345
DOI 10.1007/s00401-007-0262-1

REVIEW

Hippocampal sclerosis dementia: a reappraisal

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Received: 11 June 2007 / Revised: 23 June 2007 / Accepted: 25 June 2007 / Published online: 17 July 2007

Abstract Hippocampal sclerosis (HpScl) is characterized by neuronal loss and gliosis in CA1 and subiculum of the hippocampus, and may be one contributing factor to dementia in old age. The term hippocampal sclerosis dementia (HpSclD) designates the presence of both hippocampal sclerotic lesions and a dementia syndrome. In the present review, we outline the pathological heterogeneity underlying HpSclD and discuss related disorders due to tau protein pathology and frontotemporal dementia with ubiquitin positive inclusions (FTLD-U). We also provide a detailed morphological description of ten of our own autopsied HpSclD cases, and compare these pathological findings with those reported in the literature. The lateralization of HpScl and the atrophy of the mammillary bodies were striking features in most of our cases. The main pathology consisted of tau positive lesions with a predominance of neuronal and glial pretangles in Ammon's horn and the dentate gyrus. Neurofibrillary and ghost tangles in CA1 and the subiculum were scarce and thus insufficient to explain the hippocampal pyramidal cell loss. In some cases, tau pathology in the hippocampal formation coexisted with glial tau pathology in the frontal cortex. The most striking finding besides the tau pathology was the presence of concomitant neuronal cytoplasmic inclusions and neurites immunoreactive for the transactive response DNA-binding protein-43 (TDP-43) in the dentate gyrus and temporal neocortex, similar to those found in FTLD-U. Taken together, the pathology of HpSclD is indicative of a degenerative rather than a hypoxic/ischemic etiology of HpSclD. Presently, HpSclD may best be deemed a disorder with various neurodegenerative etiologies, most notably tauopathy and TDP-43 proteinopathy (i.e. FTLD-U). Each of these disease processes could either independently or concertedly account for the dementia syndrome in HpSclD.

Keywords Hippocampal sclerosis dementia · Tauopathy · Frontotemporal lobar degeneration · FTLD-U · TDP-43

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Introduction

Dementia is one of the most serious conditions affecting elderly individuals. While Alzheimer's disease (AD) is the most common cause of dementia in the very old (i.e. 80 years of age and older), other conditions are also preferentially associated with dementia in this age group, in particular argyrophilic grain disease (AgD) [11, 20, 40], senile dementia of the neurofibrillary tangle type [24, 42, 46], and hippocampal sclerosis (HpScl) dementia (HpSclD) [19].

HpScl is a selective neuronal loss and astrocytic gliosis of the hippocampus, with a predilection for the cornu ammonis field CA1 and subiculum [18, 19]. In the majority of cases, HpScl in very old individuals coexists with dementia [8, 18, 30], and this syndrome is referred to as HpSclD.

Neuronal loss and gliosis is also prominent in CA1 in seizure-associated "mesial temporal sclerosis" or "Ammon's

horn sclerosis", mainly following prolonged seizures in early infancy. Contrary to the HpScl seen in elderly individuals, however, the CA4 sector is often also severely involved and may even bear the brunt of damage. In such cases, the granular layer of the dentate gyrus may be severely depleted, disorganized and essentially dispersed in the gliotic tissue (see [13] and references therein). Some neuronal loss in the endplate and the granule cell layer of the dentate gyrus is occasionally found in HpSclD [19] but is atypical [2, see also the findings in our own cases below].

The etiology of HpSclD is uncertain. HpSclD is commonly associated with vascular encephalopathy or a degenerative disorder, particularly AD [6, 15, 17, 19, 23, 45] and frontotemporal lobar degeneration with ubiquitin immunoreactive inclusions (FTLD-U) [9, 22]. The large number of neuropathologies associated with HpSclD (see Table 1) suggests that more than one mechanism of hippocampal cell destruction may be involved. Indeed, HpSclD could conceivably be caused by any one of the associated nosological conditions, or, alternatively, by several neuropathological processes acting in concert.

This review focuses on the pathological aspects of HpSclD and the various nosological conditions with which it is associated, most notably FTLD-U and disorders hallmarked by tau protein cellular inclusions (i.e. AD). We will discuss the role of vascular lesions, as some authors have suggested that HpScl represents a marker for vascular dementia or cerebral ischemia [18, 43]. We also report detailed morphological findings from ten of our own autopsied HpSclD cases, and discuss their histopathological features in relation to previous reports on HpSclD pathology. Our findings highlight some hitherto neglected features of HpSclD, such as the hemispheric lateralization of lesions and secondary shrinkage of the mammillary bodies which may prove to be valuable brain imaging markers for the diagnosis and differential diagnosis of HpSclD.

Table 1 Conditions found to be associated with hippocampal sclerosis dementia

Hippocampal sclerosis dementia, "pure" form [1].
Amnestic mild cognitive impairment (no pathological confirmation) [37, 39].
FTLD-U with and without progranulin mutations (i.e. TDP-43 proteinopathy) [3, 9, 17, 22, 28].
Dementia lacking distinctive histology [29].
Frontotemporal dementia with motor neuron disease [34].
Limbic tauopathy with features of FTLD-U (TDP-43 proteinopathy) [present study].
Sporadic multisystem tauopathy [8].
Alzheimer's disease [6, 17, 19, 23].
Argyrophilic grain disease [8, 19].
Corticobasal degeneration [38].
Dementia with Lewy bodies [19].
Vascular encephalopathy [43].

FTLD-U frontotemporal dementia with ubiquitin positive inclusions

Demographics and clinical characteristics of HpSclD

The prevalence of HpSclD among dementia patients is 12–13% [7, 30]. The mean age of onset of HpSclD has been situated at 79.8 (±1.4) years [30], comparable to the age of onset of AD patients [7, 30]. The age of death of HpSclD patients most likely depends on the presence, type and severity of concomitant pathology. Thus, patients with concomitant HpSclD and AD may die later [7, 17] than patients with HpScl and dementia lacking distinctive histology (DLDH) (72 years) [25] or patients with HpScl and FTLD-U (65 years) [2]. However, patients with concomitant AD and HpScl pathology died earlier than pure AD cases [6]. The frequency of HpSclD in men and women is comparable [7].

The relationship between HpScl and dementia has often been considered a problem since pure hippocampal damage without concomitant lesions in other parts of the brain normally produces pure anterograde amnesia, but not impairments in an additional cognitive domain that would warrant a clinical diagnosis of dementia and impairments in daily living (DSM-IV) [4, 18]. However, isolated cases of HpScl have been reported with less severe changes of the hippocampi and clinical deficits restricted to the amnestic domain. For example, HpScl was clinically diagnosed in a patient with a 1-year history of amnestic mild cognitive impairment (aMCI) [39]. T2-FLAIR-weighted images revealed bilaterally altered signal in the hippocampi but no evidence of hippocampal atrophy. Interestingly, this patient's cerebrospinal fluid beta-amyloid (1–42) concentration was low (565 pg/ml; normal values: 943±258 pg/ml) and phospho(181)-tau concentration increased (68 pg/ml; normal values <61 pg/ml), reflecting the profile found in AD [10]. Correspondingly, a neuropathologic study of aMCI found HpScl lesions in 3 of 15 patients [37]. All three patients evidenced NFT pathology corresponding to Braak stage II (2 cases) or III [12], and argyrophilic grains (ArGs) were additionally found in two cases. Thus, when HpScl pathology is less severe and restricted to anteromesial temporal lobe structures, the clinical expression appears restricted to amnestic deficits.

However, in most reported series [8, 9, 17], patients presented with memory and other cognitive problems, as well as decrements in activities of daily living, consistent with the diagnosis of dementia (DSM-IV [4]). The primary cognitive disturbances in HpSclD are similar to those in AD [17, 18, 30], i.e. significant deficits in episodic memory functioning and language (i.e. picture naming). HpSclD patients appear less impaired on measures of visuospatial and executive

(i.e. dorsolateral frontal lobe) functions than AD patients [17, 30]. While a recent study [9] reported that the cumulative prevalence of behavioral deficits in HpSclD patients (with no concomitant pathology) were more similar to those of an unmatched group of frontotemporal lobe dementia (FTD) patients than a matched AD group, no data on the severity of these symptoms, nor neuropsychological test data, were available. Thus, the clinical dementia syndrome associated with HpScl appears to mimic AD, consistent with the primary loci of pathology in these two syndromes.

Brain imaging

Information on the structural brain imaging correlates of HpSclD is scarce. Unilateral or bilateral hippocampal atrophy together with an increased hippocampal T2-weighted signal constituted the prominent findings in the HpSclD patients reported by Mahieux et al. [32]. Notably, elevated T2-weighted signal is not a feature of the hippocampal atrophy associated with AD [33]. Increased signal intensity on T2-weighted scans was found in the periventricular white matter and centrum semiovale in the three of four HpSclD patients who received MRI scans in the study of Dickson et al. [19]. Unfortunately, less attention was prested to the structural integrity of these patients' hippocampi as measured by MRI. However, all 13 patients in this study received CT scans, which showed an attenuation of signal in the periventricular white matter consistent with leukoaraiosis in four and infarcts in three patients.

Neuropathology of ten own HpSclD cases

Ten cases who met the morphological criteria for HpScl were collected over a period of 10 years in our Institute. HpScl was defined as a neuronal loss and astrocytic gliosis restricted to the cornu ammonis of the hippocampus (mainly CA1) and the subiculum with occasional extension of lesions to the parahippocampal gyrus (i.e. entorhinal, perirhinal and parahippocampal cortices). All patients died at an advanced age (Table 2), and dementia was documented in all cases for which clinical data were available (9/10 cases). Two patients were neuropsychologically examined, and received diagnoses of multiple domain MCI (case 7) and probable AD (case 8).

Gross findings

All ten HpScl cases showed moderate to severe volume loss in the hippocampus and adjacent subiculum (Fig. 1a, b). Some showed atrophy of the entire mesial temporal cortex including the parahippocampal gyrus. One or both mammillary bodies were reduced in size and altered in color in the majority of patients (6/10 cases) (Fig. 1b). Case 8 additionally had enlarged lateral ventricles and an old encephalomalacia in the left temporo-occipital region. No gross ischemic cerebral lesions or lacunar infarcts were observed in the remaining cases.

Microscopic appearance

The main histological features in the hippocampus, subiculum, entorhinal cortex and middle frontal gyrus are listed in Tables 3 and 4. Neuronal cell loss and gliosis were restricted to the CA1 sector and the subiculum in four cases (Fig. 1c). Cell loss and gliosis extended to other temporomesial structures, mainly the entorhinal and temporobasal cortices, in six other cases (Fig. 1d). The amygdala was severely gliotic in case 8 and contained abundant NFT and senile plaques. The amygdala of the remaining cases showed only moderate astrocytic gliosis with scattered

Table 2 Clinicopathological findings in our hippocampal sclerosis dementia cases

Case	Gender	Age	Dementia	Brain weight (g)	Neuropathological findings (see also Tables 3 and 4)
1	F	94	n.a.	n.a.	Atrophy of mammillary bodies
2	F	90	Yes	n.a.	–
3	M	84	Yes	1,080	Cribriform state of the striatum
4	F	95	Yes	1,270	Atrophy and gliosis of ncl. accumbens, Atrophy of mammillary bodies
5	F	84	Yes	990	ArGs of right hippocampus and entorhinal cortex, Atrophy of mammillary bodies
6	M	90	Yes	1,430	–
7	M	79	Yes	1,340	Severe microangiopathy
8	M	88	Yes	1,350	Old infarction of the left occipitotemporal region, Atrophy of mammillary bodies
9	F	89	Yes	980	Atrophy of mammillary bodies
10	F	90	Yes	1,000	Atrophy of mammillary bodies

ArGs argyrophilic grains, *n.a.* not available

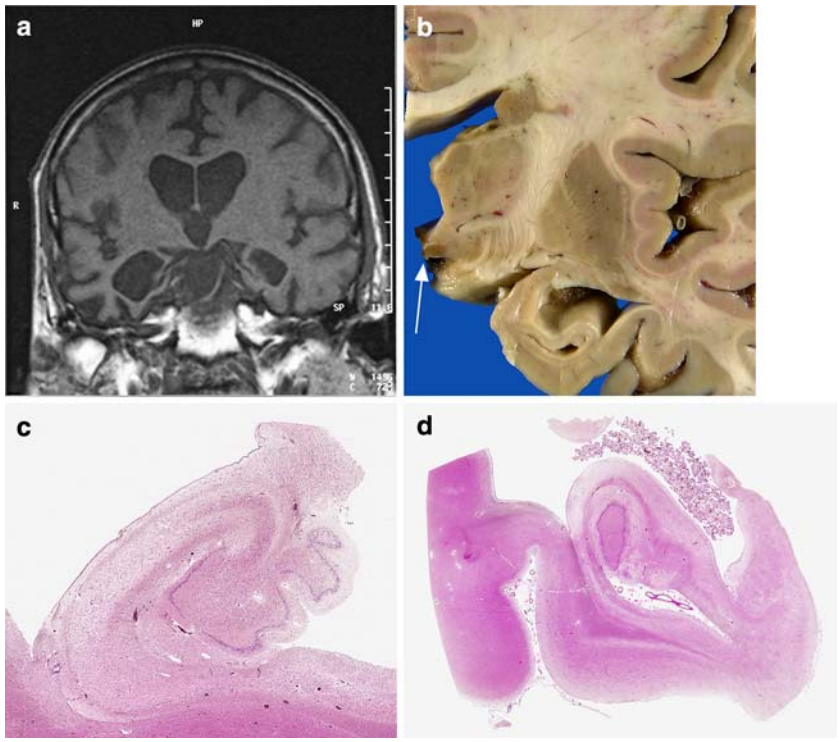

Fig. 1 **a**,**b** T1-weighted MRI image of case 8. Severe hippocampus and temporo-mesial atrophy on both sides. Considerably enlarged temporal horns, right-lateralized. Also note the severe atrophy of the mammillary bodies. **b** Macroscopic view of case 10 reveals atrophy of the anterior hippocampus and severe atrophy and discoloration of the mammillary body (*arrow*) **c** Case 8 stained with H&E shows neuronal loss in sector CA1 of the hippocampus and subiculum and secondary degeneration of the alveus and fimbria. Note better preservation of the cell population in CA3-4 and in the dentate gyrus and the looser neuropil texture in CA1 than in the subiculum. **d** In case 4, cell loss and gliosis extend to the entorhinal and transentorhinal cortices

NFT in some cases. In seven cases, HpScl lesions were more marked and hippocampal volume loss more pronounced in one hemisphere, with the majority of cases showing more left hemisphere involvement (5/7). Sclerotic lesions were focally distributed in the hippocampi in most cases. Only one case showed an asymmetry of lesion load along the anterior to posterior axis of the hippocampus, with the anterior hippocampus more severely affected (case 3). Severe microangiopathic changes were observed in the basal ganglia of case 7. Vascular fibrosis with thickening of small leptomingeal hippocampal arteries was observed in case 4. No cases showed a calcification of the hippocampal microvessels [44]. Staining with H&E revealed varying degrees of neuronal loss and an evident contraction of the pyramidal layer in CA1, but less pronounced shrinkage in the subiculum. Devastation of nerve fibers in the alveus and the fimbria hippocampi was observed to varying extents. In some cases, the CA1 sector and the subiculum were almost completely depleted of nerve cells with the exception of some swollen neurons which were often filled with granulovacuoles (data not shown). The neuropil of CA1 was vacuolated in all cases and often appeared lucent due to more severe cell and neuropil loss, whereas brain parenchyma was better preserved in the subiculum (Fig. 1c). Large gemistocytic astrocytes were observed in the subiculum, suggesting acute or more recent tissue damage, whereas CA1 mainly contained fibrous astrocytes compatible with a chronic gliosis. Pyramidal shaped empty spaces (reminiscent of "empty cell beds" described in motor neuron disease), often filled with cell remnants, were found in the hippocampus (cases 5, 8 and 10), suggesting ongoing destruction of pyramidal cells (Fig. 2a).

The principal pathology consisted of tau immunoreactive lesions in neurons and glial cells, as observed using the phosphorylation-dependent anti-tau antibody AT8. The main lesion consisted of a diffuse intracytoplasmic reactivity for tau in CA1 (Fig. 2b), CA2 and CA3-4 (Fig. 2c) neurons and in the granule cell layer of the dentate gyrus (Fig. 5a). Tau positive threads were found scattered in the sclerotic CA1 as well as in the alveus-fimbria tracts. Most tau immunoreactive lesions corresponded to "pretangles" as they were not stained by the Gallyas technique. One exception consisted of NFT in sectors CA4 and CA2 (Fig. 2d). In cases 2 and 3, numerous "ghost tangles" were found selectively in sector CA2 of the hippocampus. ArGs were present in the anterior part of hippocampal sector CA1 in case 5 (Fig. 2f). Immunohistochemistry with monoclonal antibodies directed against three- (3R) or four-repeat (4R) tau isoforms revealed an admixture of 3R and 4R tau in all our cases (Figs. 3a–c). Thus, NFT stained for both 3R and 4R antibodies (with a preponderance for 4R tau in "pretangles" and 3R tau in "ghost tangles"; reviewed in [24]) while ArGs, tufted astrocytes and astrocytic plaques (see below) were exclusively stained with the 4R antibody. None of our cases, however, met the current diagnostic criteria for one of the 4R tauopathies AgD, PSP or CBD.

Numerous NFT, "ghost tangles" (Fig. 2e) and "pretangle" neurons were found throughout the entorhinal and perirhinal cortices in cases 1–4, and 8. Especially in cases with numerous "ghost tangles" in layer II of the entorhinal

Table 3 Main histological lesions in hippocampus and subiculum

Case	Site	Histological features and immunohistochemistry							
		Neuron loss	Ecb in CA1	Vacuolation	SP	Gallyas	AT8	TDP-43	α-Syn
1	L = R	CA1, Sub++	–	CA1++	–	T, Th+ in CA2, CA4, Alveus (glia)	p.t. in CA1–4++, DG+, Alveus (glia)	–	–
2	L = R	CA1+++, Sub++	+	CA1++	–	GT+++ in CA2, T+ in CA4	p.t. in CA1–3++	–	–
3	L = R	CA1, Sub+++	+	CA1–4++	–	GT++ in CA2, T+ in CA4	p.t. in CA1–4, DG++, Th++ in CA4, Alveus	+	–
4	L > R	CA1, Sub, Presub+++	+	CA1++	–	T+ in CA3–4	p.t. in CA2–4, DG+	–	–
5	L > R	CA1++	++	CA1, Sub+	–	ArGs+	p.t. CA1–4++, ArGs++	–	–
6	L > R	CA1, Sub++	+	CA1+	+	–	p.t. CA1–4++	–	LB, LN+
7	L >> R	CA1, Sub++	+	CA1+	–	T+ in CA1	p.t. in CA1–4, DG+	–	–
8	L << R	CA1, Sub+	+	CA1++	–	T+++ in CA2, CA4, T+ in CA1	p.t. in CA1+, DG++	+	–
9	L >> R	CA1, Sub+++	–	CA1+++	+	–	p.t. in CA1, DG+	+	–
10	L << R	CA1, Sub++	++	CA1+++	–	–	p.t. in CA1–4+	–	–

Ecb empty cell beds, *SP* senile plaque (mainly diffuse plaques), *L* left, *R* right, *CA* cornu ammonis, *T* tangles, *Th* threads, *p.t.* pretangle neuron, *DG* dentate gyrus, *Sub* subiculum, *GT* ghost tangles, *ant* anterior, *post* posterior, *Presub* presubiculum, *ArGs* argyrophilic grains, *LB* Lewy bodies, *LN* Lewy neurites, *TDP-43* TDP-43 stained intracellular and/or intranuclear inclusions in granule cells of the dentate gyrus, + few, ++ moderate, +++, abundant, – absent

cortex, diffuse neuronal loss with blurred cortical lamination and shrinkage of the cortical ribbon was observed.

Tau and Gallyas positive cellular structures were also found in the cerebral cortex in some cases. These lesions consisted of tufted astrocytes (Fig. 4a) and some "pretangle" neurons. Both tufted astrocytes and astrocytic plaques were found in case 8 (Fig. 4b, c). No evidence of vacuolation or astrocytic gliois was found in the temporal and frontal cortices. A small number of ubiquitin immunoreactive (tau and alpha-synuclein negative) neuronal cytoplasmic inclusions and neurites were found in the temporal cortices of cases 3, 8, and 9. In these cases, ubiquitin reactive cytoplasmic and intranuclear inclusions (Fig. 5b) were also found in the granule cells of the dentate gyrus. These ubiquitinated inclusions were strongly stained with an antibody directed against the transactive response DNA-binding protein-43 (TDP-43) (Fig. 5c, d). Thus, in some cases we observed the simultaneous occurrence of AT8 positive/Gallyas negative, ubiquitin and TDP-43 immunoreactive inclusions in granule cells of the dentate gyrus (Fig. 5a–c).

Additional neuropathological findings consisted of a small number of alpha-synuclein stained Lewy bodies and Lewy neurites in the hippocampal regions and middle frontal gyrus in one case (case 6) and some diffuse beta-amyloid plaques in five cases (Tables 3 and 4).

Table 4 Main histological findings in the middle frontal gyrus

Case	Vacuolation in layer II–III	Gallyas+ inclusions	AT8	SP	TDP-43*	α-Syn
1	–	TA+	TA+, p.t.+	–	–	
2	–	TA+	TA+	+	–	
3	–	TA+	p.t.+, th+, TA+	–	–*	
4	–	–	–	–	–	
5	–	–	p.t.+	–	–	
6	–	–	p.t.+	+	–	LB, LN+
7	–	–	TA+	+	–	
8	–	TA++, T+, AP+	TA++, T+, AP+	++	–*	
9	–	–	–	+	–*	
10	–	–	–	–	–	

SP senile plaques (mainly diffuse plaques), *TA* tufted astrocyte, *p.t.* pretangle neurons, *th* threads, *LB* Lewy bodies, *LN* Lewy neurites, *AP* astrocytic plaque, *TDP-43** few TDP-43 stained intracellular inclusions and neurites were present in the temporal cortex, + few, ++ moderate, – absent

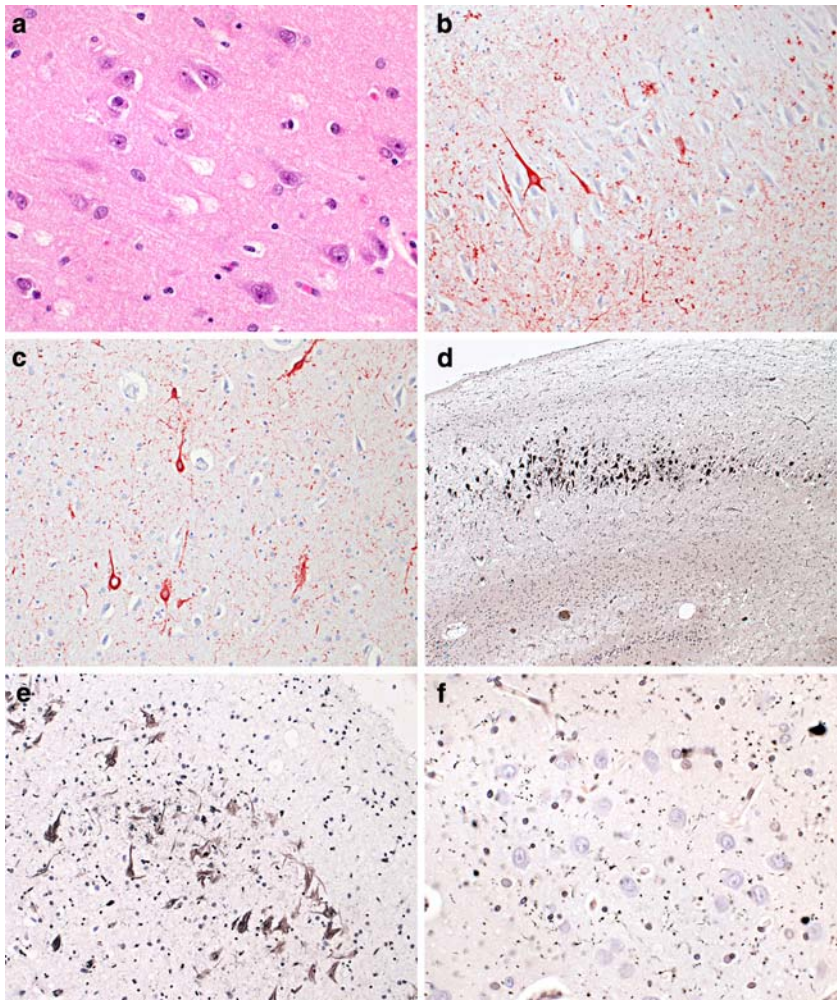

Fig. 2 **a**–**e** CA1, case 5. Pyramidal-shaped empty spaces in the neuropil, probably corresponding to destroyed neurons (reminiscent of "empty cell beds"). **b** CA1, case 1. Immunostaining with phosphorylation-dependent anti-tau antibody AT8. "Pretangle" pyramidal cells in the cortical ribbon and myriads of AT8-labelled structures, probably corresponding to glia, in the stratum oriens and the alveus. **c** CA4, case 3. AT8 stained "pretangle" neurons. **d** CA2, case 8. Abundant Gallyas stained neurofibrillary tangles. **e** Entorhinal cortex, case 3. Gallyas stained "ghost tangles" in layer II. **f** CA1, case 5. Gallyas stained argyrophilic grains

Discussion

Pathological findings in HpSclD

HpScl is defined as a selective neuronal loss and gliosis of CA1 and the subiculum of the hippocampus. An extension of lesions to the mesial temporal cortex including the entorhinal cortex or entire parahippocampal gyrus and to the amygdala has been reported [19, 30] and was also evident in some of our cases.

HpScl has been reported in patients with a variety of neuropathological diseases (see Table 1) including AD [6, 15, 17, 19, 23, 45], AgD [19], and some other tauopathies [8, 38], dementia with Lewy bodies (DLB) [19], vascular

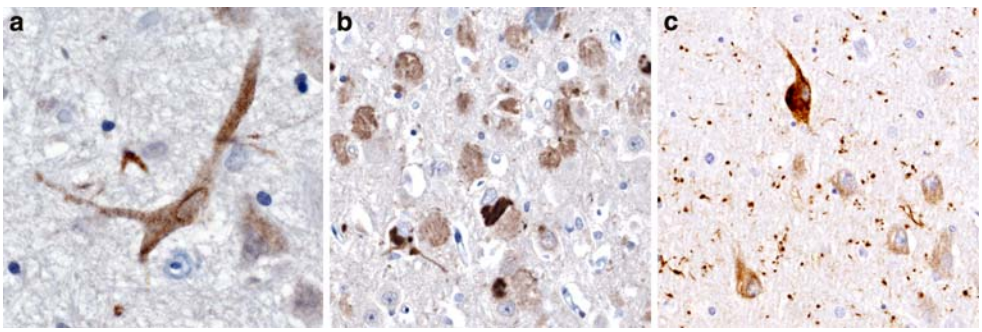

Fig. 3 **a** Immunohistochemistry with an antibody directed against four-repeat (4R) tau isoforms stains a "pretangle" neuron in sector CA4 in case 6. **b** Numerous "ghost tangles" in addition to some NFT are stained with an antibody against three-repeat tau isoforms in sector CA2 in case 3. **c** Strongly 4R stained argyrophilic grains, "pretangles" and a NFT in sector CA1 in case 5

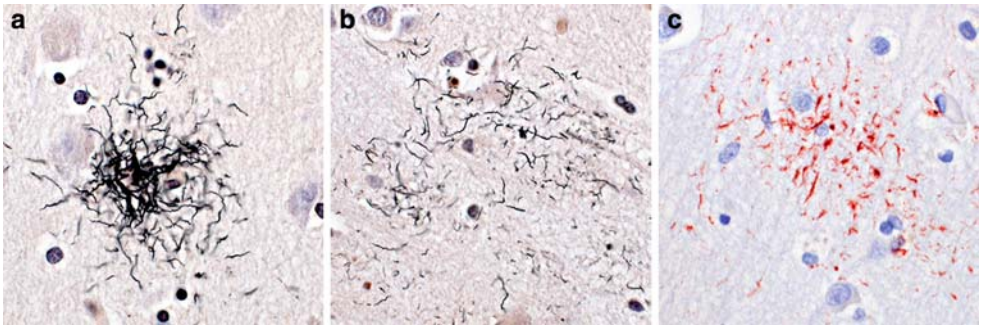

Fig. 4 **a**–**c**. Cerebral cortex, case 8. **a** Gallyas positive tufted astrocyte. **b** Gallyas and **c** AT8 positive astrocytic plaque

encephalopathy [15, 43, 45], and FTLD-U with and without progranulin gene mutations [9, 21, 25, 26, 28, 31]. HpSclD may also be associated with the DLDH syndrome insofar as the majority of these cases most likely correspond to FTLD-U. Variable degrees of hippocampal atrophy or even sclerosis have been reported in DLDH [21, 27], and a retrospective search for ubiquitin positive inclusions was positive in the dentate gyrus and/or frontotemporal cortices in more than 70% of cases in one study [25], consistent with a diagnosis of FTLD-U.

Ubiquitinated, tau negative neuronal cytoplasmic inclusions as well as neurites and lentiform intranuclear inclusions constitute the defining histological features of FTLD-U. Not surprisingly, such features have been reported in the dentate gyrus of all reported HpScl cases diagnosed with FTLD-U, but these features may have extended to frontal and temporal cortices in some cases [22] (as in the present series temporal involvement in cases 3, 8 and 9). TDP-43 has been identified as the main protein constituent of the neuronal inclusions of most FTLD-U entities with and without associated motor neuron disease [5, 35]. Both our findings and recent studies have shown that a significant proportion of HpSclD cases in the elderly have TDP-43 immunoreactive inclusions and neurites similar to those of FTLD-U [3, 14], consistent with previous studies using ubiquitin immunohistochemistry to investigate the frequency of FTLD-U in HpScl [16]. Patients with concomitant HpScl and FTLD-U pathology may show more pronounced cortical atrophy than patients with isolated HpScl lesions [27], as well as a dementia syndrome with clinical features of FTD [9, 22].

HpSclD has also been tentatively considered a sporadic multisystem tauopathy, for which the term “hippocampal sclerosis dementia with tauopathy” was introduced [8]. Further, the pathological evidence suggests that at least some HpSclD cases occur within the pathological framework of a sporadic multisytem tauopathy. For example, 12 out of 14 HpSclD cases reported by Beach et al. [8]

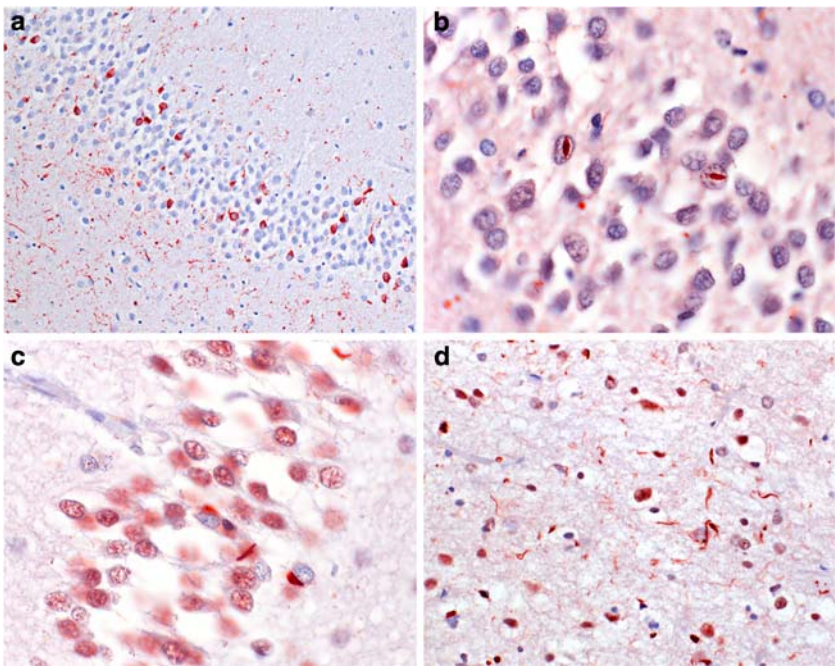

Fig. 5 **a**–**c**. Dentate gyrus, case 3. **a** AT8 reveals numerous positive granule cells. These cells were Gallyas negative and correspond to “pretangle” neurons. **b** Ubiquitin positive lenticular inclusions in granule cells nuclei. **c** Rod or half moon shaped TDP-43 positive intracytoplasmic inclusions in granule cells. Note TDP-43 clearing of the nucleus in cells containing inclusions. **d** Temporal cortex, case 3. TDP-43 positive inclusions in the cytoplasm of neurons and TDP-43 positive threads

showed a widespread distribution of tau positive inclusions in nerve and glial cells in the neocortex, basal ganglia, thalamus and/or limbic regions, and a majority of their cases also showed ArGs. Similar to the cases of Beach et al. [6], the main pathology in our cases consisted of tau immunoreactive "pretangle" and tangle lesions in nerve cells and glia, but with a more restricted anatomic distribution centered mainly in the hippocampus/subiculum and the frontal cortex. The distribution of tau pathology in the present series also differs from that encountered in AD and is more reminiscent of tau pathology observed in 4R tauopathies [47]. As noted above, the most striking finding apart from tau pathology consisted of neuronal inclusions and neurites immunoreactive for ubiquitin and TDP-43 in the dentate gyrus and the temporal neocortex, similar to those characterizing FTLD-U [5, 35]. Thus, simultaneous occurrence of AT8 positive/Gallyas negative, ubiquitin and TDP-43 immunoreactive inclusions was observed in the granule cells of the dentate gyrus and in other parts of the hippocampus in a subset of our cases. It remains unclear whether the TDP-43 immunoreactivity observed in our cases merely reflects a propensity for the co-deposition of a nosologically irrelevant protein in addition to tau protein, or if HpSclD results from two concurrent disease processes. Indeed, HpSclD may arise from the combined effects of a tauopathy and a TDP-43 proteinopathy, from a tauopathy alone, or a TDP-43 proteinopathy alone. Irrespective of the pathogenesis of the dementia syndrome, the present series suggests that the hallmarks of a tauopathy and a TDP-43 proteinopathy may coexist in some HpSclD cases.

The problem of "pure" HpSclD

Occasionally (0.4–2% of autopsies of elderly subjects) HpScl is found to be an independent pathologic explanation for a clinical dementia syndrome—so-called "pure" HpSclD [1, 7, 9, 19, 23, 31]. In such cases, no or only slight evidence for a concomitant degenerative disorder is associated with HpScl, and lesions are largely restricted to the CA1 sector and the adjacent subiculum. Additional criteria for this diagnosis should be the absence of cerebrovascular pathology or clinical evidence of syncope, hypotension or hypoxia in association with dementia onset. However, the real prevalence of "pure" HpSclD is difficult to assess from the reported cases and will conceivably depend on the neurodegenerative lesion load, especially the degree of neurofibrillary changes, "allowed" to be associated with HpScl as part of a normal aging process. Considering the advanced age of patients with HpSclD, "pure" HpSclD is likely to be an exceptional occurrence if the absence of neurofibrillary changes is required for the diagnosis. An arbitrary limit based on neurofibrillary tangles has been proposed by Ala et al. [1], with cases below Braak stage II [12] considered compatible with "pure" HpSclD.

Evidence for differentially aged lesions in HpSclD

Lesions at different stages were found in the hippocampus of a case reported by Leverenz et al. [30] and considered consistent with a progressive neurodegenerative process. Gliosis within individual cases demonstrated acutely reactive gemistocytic glia in some regions of the CA1 and chronic gliosis within other regions of CA1. In the present case series, we also found differences in reactive glia, with more gemistocytic astrocytes in the subiculum and more fibrous astrocytes in the CA1. The appearance of the neuropil also suggested different ages of the sclerotic lesions in these two areas: while CA1 often appeared "empty" of neuropil texture, the subiculum appeared more preserved. These findings suggest that the pathological process in HpSclD starts in CA1 and then progresses to the subiculum. Also in accord with this assumption is the fact that in most published HpSclD cases neuronal loss has been noted both in the subiculum and CAI while in some cases cell loss was only observed in CA1 [2]. However, in this same study [2] there were two cases of HpScl associated with FTLD-U that had isolated subicular involvement. Further studies will show if the local progression and the initiation site for neuronal loss may differ in HpScl with and without FTLD-U.

Is HpSclD due to a vascular disease process?

The hippocampus appears to be preferentially vulnerable to a variety of pathologic insults including seizures, hypoxia and neurodegeneration (e.g. AD). Particularly the CA1 region and the subiculum are thought to be prone to hypoxic/ischemic injury due to the deficient vascular supply of the hippocampus and the fact that CA1 neurons are richly endowed with glutamate receptors which may be involved in excitotoxic cell death [36]. However, the evidence to support vascular injury as a contributing factor to HpScl in the demented elderly is indirect and contradictory. Both the hemispheric asymmetry of lesion load in our own and previously reported cases (see below) and the focal distribution of lesions in the hippocampi favor a hypoxic/ischemic etiology. However, microvascular calcification of intrahippocampal vessels found to be associated with HpScl [44] were consistently absent in our cases and significant wall thickening of hippocampal arterioles only observed in one of our cases.

Cardiac disease is a frequent concomitant of HpSclD in some studies [17, 19, 43], and significant cardiovascular disease or a history of myocardial infarction was found in the HpSclD series reported by Dickson et al. [19]. Pathological findings have been influential in this debate, with

observations of leukoaraiosis, microinfarcts, and encephalomalacias leading Dickson et al. [19] to suggest that HpScl in their cases resulted from hypoxia/ischemia. However, other authors have failed to find increased cardiovascular risk factors in their HpSclD cases [23]. Moreover, while pathological evidence for cerebrovascular disease was found in 75% of HpSclD cases reported by Amador-Ortiz et al. [2], this frequency was comparable to that of a control group of similar age, gender and Braak stage. Notably, in this comparative study cerebrovascular pathology was found in "pure" HpScl cases but rarely in HpScl cases with FTLD-U [2]. In a large prospective longitudinal study on vascular ischemic dementia and AD, enriched with subcortical ischemic vascular disease, HpScl was a common unsuspected finding [15]. HpScl was found less frequently in pure AD, compared with mixed AD/cerebrovascular disease (CVD), CVD, or no significant AD or CVD pathology, but these differences were not significant [15]. In summary, however, most data from the literature do not support the hypothesis that episodes of syncope, hypotension, or hypoxia are precipitating factors for HpScl in demented patients [2, 17, 19].

Hemispheric lateralization of HpScl lesions and atrophy of the mammillary bodies

The hemispheric asymmetry of HpScl lesion load is noted in some published series of HpSclD [8, 30]. For example, Beach et al. [8] found unilateral HpScl in 5 of their 14 cases. However, these authors had only one contralateral anteroposterior plane at their disposal, and noted the possibility that HpScl may have been bilateral in all their cases. Indeed, HpScl lesions often have a patchy distribution along the hippocampus/subiculum, as evidenced in our cases. Most published pathological case series of HpSclD do not expressly mention the hemispheric lateralization of HpScl lesions nor the patchy distribution of HpScl. Furthermore, some case series only have one hemisphere available for examination [1]. In our own case 1, different patterns of lesion asymmetry were observed in the anterior and posterior hippocampal regions, with only mild sclerotic changes observed in the left subicular area and extensive sclerosis in the CA1, subiculum, presubiculum and entorhinal area on the right side. Thus, in spite of an evident asymmetry of lesions in some cases, the incidence of unilateral HpScl remains difficult to assess. Ideally, complete reconstruction of the "sclerotic" hippocampus should be performed using continuous (gap-less) anteroposterior sampling on both sides.

Uni- or bilateral shrinkage and discoloration of the mammillary bodies was a prominent feature in some of our cases and is likely to result from fimbria-alveus degeneration as a consequence of CA1 devastation. A 20% reduction in mammillary body size has also been reported in AD compared to MCI and control participants [16]. The degree of mammillary body shrinkage observed in some of our cases (Fig. 1a, b) was certainly greater than 20%. Moreover, mammillary body shrinkage was asymmetric in most of our cases. Thus, on MRI images, severe and lateralized mammillary body shrinkage together with T2 signal hyperintensities could aid the differentiation of HpSclD from AD.

Genetic factors in HpSclD

Scant genetic data exist on HpSclD, and the majority of available data concerns apolipoprotein E. Troncoso et al. [41] reported an apolipoprotein E4 (apoE4) allele frequency of 12.5% in their 12 cases of autopsy-confirmed HpSclD, a frequency similar to that of a control population and significantly lower than the frequency observed in AD populations (see also [30]). Also Josephs et al. [25] reported a frequency of apoE4 alleles in their patients with concomitant HpSclD and DLDH similar to the normal population. Similarly, both genotyped aMCI patients pathologically diagnosed with HpScl had an apoE3/E3 constellation in the study of Petersen et al. [37]. These results suggest that apoE4 is neither a risk nor a pathogenic factor for HpSclD, and that HpSclD is biologically different from AD.

Conclusions

HpScl is one histomorphological substrate of dementia in old age. The present and previously reported pathology findings strongly suggest a degenerative rather than a hypoxic/ischemic etiology for HpSclD. At present, HpSclD may best be deemed a dementing disorder with various neurodegenerative etiologies, in particular tauopathy and TDP-43 proteinopathy. Clearly, further studies on larger samples of HpSclD cases are needed in order to unravel the pathogenic implications of tau and TDP-43 and their possible relationship in HpScl as well as the real incidence of "pure" HpSclD cases.

References

1. Ala TA, Beh GO, Frey WH 2nd (2000) Pure hippocampal sclerosis: a rare cause of dementia mimicking Alzheimer's disease. Neurology 54:843–848
2. Amador-Ortiz C, Ahmed Z, Zehr C, Dickson D (2007) Hippocampal sclerosis dementia differs from hippocampal sclerosis in frontal lobe degeneration. Acta Neuropathol 113:245–252
3. Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, Graff-Radford NR, Hutton ML, Dickson DW (2007) TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol 61:435–445

4. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. 4th edn. American Psychiatric Press, Washington, DC
5. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T (2006) TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun 351:602–611
6. Attems J, Jellinger K (2006) Hippocampal sclerosis in Alzheimer disease and other dementias. Neurology 66:775
7. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Sheperd E, Sevush S, Graff-Radford N, Newland D, Todd M, Miller B, Gold M, Heilman K, Doty L, Goodman I, Robinson B, Pearl G, Dickson D, Duara R (2002) Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord 16:203–212
8. Beach TG, Sue L, Scott S, Layne K, Newell A, Walker D, Baker M, Sahara N, Yen SH, Hutton M, Caselli R, Adler C, Connor D, Sabbagh M (2003) Hippocampal sclerosis dementia with tauopathy. Brain Pathol 13:263–278
9. Blass DM, Hatanpaa KJ, Brandt J, Rao V, Steinberg M, Troncoso JC, Rabins PV (2004) Dementia in hippocampal sclerosis resembles frontotemporal dementia more than Alzheimer disease. Neurology 63:492–497
10. Blennow K (2004) Cerebrospinal fluid protein biomarkers for Alzheimer's disease. NeuroRx 1:213–225
11. Braak H, Braak E (1987) Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult-onset dementia without Alzheimer changes. Neurosci Lett 76:124–127
12. Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259
13. Burger PC, Scheithauer BW, Vogel FS (2002) Surgical pathology of the nervous system and ist coverings. 4th edn. Churchill Livingstone, New York pp 392–395
14. Cairns NJ, Neumann M, Bigio EH, Holm IE, Troost D, Hatanpaa KJ, Foong C, White CL 3rd, Schneider JA, Kretzschmar HA, Carter D, Taylor-Reinwald L, Paulsmeyer K, Strider J, Gitcho M, Goate AM, Morris JC, Mishra M, Kwong LK, Stieber A, Xu Y, Forman MS, Trojanowski JQ, Lee VM, Mackenzie IR (2007) TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol 171:227–240
15. Chui HC, Zarow C, Mack WJ, Ellis WG, Zheng L, Jagust WJ, Mungas D, Reed BR, Kramer JH, Decarli CC, Weiner MW, Vinters HV (2006) Cognitive impact of subcortical vascular and Alzheimer's disease pathology. Ann Neurol 60:677–687
16. Copenhaver BR, Rabin LA, Saykin AJ, Roth RM, Wishart HA, Flashman LA, Santulli RB, McHugh TL, Mamourian AC (2006) The fornix and mammillary bodies in older adults with Alzheimer's disease, mild cognitive impairment, and cognitive complaints: a volumetric MRI study. Psychiatry Res 147:93–103
17. Corey-Bloom J, Sabbagh MN, Bondi MW, Hansen L, Alford MF, Masliah E, Thal LJ (1997) Hippocampal sclerosis contributes to dementia in the elderly. Neurology 48:154–160
18. Crystal HA, Dickson D, Davies P, Masur D, Grober E, Lipton RB (2000) The relative frequency of "dementia of unknown etiology" increases with age and is nearly 50% in nonagenarians. Arch Neurol 57:713–719
19. Dickson DW, Davies P, Bevona C, Van Hoeven KH, Factor SM, Grober E, Aronson MK, Crystal HA (1994) Hippocampal sclerosis: a common pathological feature of dementia in very old (> or =80 years of age) humans. Acta Neuropathol 88:212–221
20. Ding ZT, Wang Y, Jiang YP, Yoshida M, Mimuro M, Inagaki T, Iwase T, Hashizume Y (2006) Argyrophilic grain disease: frequency and neuropathology in centenarians. Acta Neuropathol 111:320–328
21. Giannakopoulos P, Hof PR, Bouras C (1995) Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases. Acta Neuropathol 89:346–355
22. Hatanpaa KJ, Blass DM, Pletnikova O, Bigio EH, Hedreen JC, White CL 3rd, Troncoso JC (2004) Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia. Neurology 63:538–542
23. Jellinger K (1994) Hippocampal sclerosis: a common pathological feature of dementia in very old humans. Acta Neuropathol 88:599
24. Jellinger KA, Attems J (2007) Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. Acta Neuropathol 113:107–117
25. Josephs KA, Jones AG, Dickson DW (2004) Hippocampal sclerosis and ubiquitin-positive inclusions in dementia lacking distinctive histopathology. Dement Geriatr Cogn Disord 17:342–345
26. Josephs KA, Dickson DW (2006) Hippocampal sclerosis in tau-negative frontotemporal lobar degeneration. Neurobiol Aging Aug 21: Epub ahead of print
27. Josephs KA, Whitwell JL, Jack CR, Parisi JE, Dickson DW (2006) Frontotemporal lobar degeneration without lobar atrophy. Arch Neurol 63:1632–1638
28. Josephs KA, Ahmed Z, Katsuse O, Parisi JF, Boeve BF, Knopman DS, Petersen RC, Davies P, Duara R, Graff-Radford NR, Uitti RJ, Rademakers R, Adamson J, Baker M, Hutton ML, Dickson DW (2007) Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (PGRN) mutations. J Neuropathol Exp Neurol 66:142–151
29. Knopman DS, Mastri AR, Frey WH 2nd, Sung JH, Rustan T (1990) Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology 40:251–256
30. Leverenz JB, Agustin CM, Tsuang D, Peskind E, Edland SD, Nochlin D, DiGiacomo L, Bowen JD, McCormick WC, Teri L, Raskind MA, Kukull WA, Larson EB (2002) Clinical and neuropathological characteristics of hippocampal sclerosis. Arch Neurol 59:1099–1106
31. Lippa CF, Dickson DW (2004) Hippocampal sclerosis dementia: expanding the phenotypes of frontotemporal dementias? Neurology 63:414–415
32. Mahieux F (2003) Sclérose hippocampique et démences. Psychol Neuropsychiatr Vieil 1:179–186
33. Maunoury C, Michot JL, Caillet H, Parlato V, Leroy-Willig A, Jehenson P, Syrota A, Boller F (1996) Specificity of temporal amygdala atrophy in Alzheimer's disease: quantitative assessment with magnetic resonance imaging. Dementia 7:10–14
34. Nakano I (2000) Frontotemporal dementia with motor neuron disease (amyotrophic lateral sclerosis with dementia). Neuropathology 20:68–75
35. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM-Y (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314:130–133
36. Olney JW, Collins RC, Sloviter RS (1986) Excitotoxic mechanisms of epileptic brain damage. Adv Neurol 44:857–877
37. Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H, Kokmen E (2006) Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol 63:665–672
38. Schneider JA, Watts RL, Gearing M, Brewer RP, Mirra SS (1997) Corticobasal degeneration: neuropathologic and clinical heterogeneity. Neurology 48:959–969

39. Sepe-Monti M, De Carolis A, Bomboi G, Castri P, Giubilei F (2006) MRI evidence of bilateral hippocampal sclerosis in amnestic mild cognitive impairment. Eur J Neurol 13:1031–1032
40. Tolnay M, Clavaguera F (2004) Argyrophilic grain disease: a late-onset dementia with distinctive features among tauopathies. Neuropathology 24:269–283
41. Troncoso JC, Kawas CH, Chang CK, Folstein MF, Hedreen JC (1996) Lack of association of the apoE4 allele with hippocampal sclerosis dementia. Neurosci Lett 204:138–140
42. Ulrich J, Spillantini MG, Goedert M, Dukas L, Stähelin HB (1992) Abundant neurofibrillary tangles without senile plaques in a subset of patients with senile dementia. Neurodegeneration 1:257–284
43. Volpe BT, Petito CK (1985) Dementia with bilateral medial temporal lobe ischemia. Neurology 35:1793–1797
44. Wegiel J, Kuchna I, Wisniewski T, de Leon MJ, Reisberg B, Pirttila T, Kivimaki T, Lehtimaki T (2002) Vascular fibrosis and calcification in the hippocampus in aging, Alzheimer disease, and Down syndrome. Acta Neuropathol 103:333–343
45. White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross GW, Masaki K, Launer L, Markesbery WR (2002) Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann N Y Acad Sci 977:9–23
46. Yamada M (2003) Senile dementia of the neurofibrillary tangle type (tangle-only dementia): neuropathological criteria and clinical guidelines for diagnosis. Neuropathology 23:311–317
47. Yoshida M (2006) Cellular tau pathology and immunohistochemical study of tau isoforms in sporadic tauopathies. Neuropathology 26:457–470