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Hippocampal Sclerosis of Aging, a Prevalent and High-Morbidity Brain Disease

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Abstract

Hippocampal sclerosis of aging (HS-Aging) is a causative factor in a large proportion of elderly dementia cases. The current definition of HS-Aging rests on pathologic criteria: neuronal loss and gliosis in the hippocampal formation that is out of proportion to AD-type pathology. HS-Aging is also strongly associated with TDP-43 pathology. HS-Aging pathology appears to be most prevalent in the oldest-old: autopsy series indicate that 5–30 % of nonagenarians have HS-Aging pathology. Among prior studies, differences in study design have contributed to the study-to-study variability in reported disease prevalence. The presence of HS-Aging pathology correlates with significant cognitive impairment which is often misdiagnosed as AD clinically. The antemortem diagnosis is further confounded by other diseases linked to hippocampal atrophy including frontotemporal lobar degeneration and cerebrovascular pathologies. Recent advances characterizing the neurocognitive profile of HS-Aging patients have begun to provide clues that may help identify living individuals with HS-Aging pathology. Structural brain imaging studies of research subjects followed to autopsy reveal hippocampal atrophy that is substantially greater in people with eventual HS-Aging pathology, compared to those with AD pathology alone. Data are presented from individuals who were followed with neurocognitive and neuroradiologic measurements, followed by neuropathologic evaluation at the University of Kentucky. Finally, we discuss factors that are hypothesized to cause or modify the disease. We conclude that the published literature on HS-Aging provides strong evidence of an important and under-appreciated brain disease of aging. Unfortunately, there is no therapy or preventive strategy currently available.

Keywords

TDP43; TDP-43; TARDBP; Dementia; Aging; Neuropathology; FTLD; Epidemiology; Genetics; Cognition; Neuroradiology; MRI; Hippocampus; Pathology; Arteriolosclerosis; Cerebrovascular; Oldest-old

Introduction

Based on prior studies [30, 47, 61, 80] and recent consensus group diagnostic guidelines [72], hippocampal sclerosis of aging (HS-Aging) is defined as neuronal loss and gliosis in hippocampal CA1 and subiculum that is out of proportion to Alzheimer's disease (AD) neuropathologic changes in the same structures. There is an evolving awareness that HS-Aging is a prevalent brain disease with an enormous impact on public health. Selected references and how they have helped move the field forward are shown in Table 1. Note, however, that there is overlap in the research subjects included in some of these reports, and further, the field has advanced in recent years so caution must be exercised in interpreting older literature.

This review is organized to convey the rapidly evolving understanding about HS-Aging in terms of neuropathologic findings, epidemiologic considerations, cognitive domains affected in HS-Aging, neuroradiologic reports, and current insights into the mechanisms underlying HS-Aging. One emphasis of this review is to highlight features that distinguish HS-Aging

from other brain diseases. This challenge is not unique to HS-Aging, because neurodegenerative diseases tend to share clinical and/or pathological characteristics despite clearly distinct underlying disease mechanisms. Table 2 provides a summary description of the diseases that have most pathological overlap with HS-Aging. This review underscores that HS-Aging preferentially afflicts individuals in advanced age (>85 years of age), a part of the brain aging spectrum that is currently imperfectly understood. We also present data on clinical and radiological findings in a subset of autopsy subjects evaluated at the University of Kentucky Alzheimer's Disease Center (UK-ADC).

Neuropathology of HS-Aging

As stated above, the definition of HS-Aging rests primarily on neuropathologic findings. From a neuropathologist's perspective, the term "hippocampal sclerosis" is potentially misleading. The pathologic changes of HS-Aging generally extend beyond the hippocampus proper. Further, the pathologic features are not fully conveyed by the term "sclerosis", which signifies "hardening" and which has been used to also designate distinct brain diseases, such as those associated with epilepsy, FTLD, and others as described below. In a very recent paper, a panel of experts addressed HS pathologic classification terminology [92]. We note that this study focused on a patient cohort mostly younger than 80 years at death, which in our experience shows a pathologic spectrum incompletely overlapping with the boundaries of HS-Aging pathology as described below.

Key diagnostic features of HS-Aging pathology are found on hematoxylin and eosin (H&E) stained brain sections (Fig. 1), whereas more specific features are visualized using immunohistochemical techniques (Figs. 2, 3). H&E stains typically reveal neuronal dropout in CA1 of hippocampus, subiculum, entorhinal cortex, and amygdala. Atrophy can be marked in these areas. In severely affected cases, normal cellular components are replaced by reactive astrocytes and the neuropil becomes highly rarefied (cell-, and neurite-sparse) or frankly cavitary. Lymphocytic infiltrates or perivascular cuffing are not typically seen. We have observed in affected hippocampi many abnormal small blood vessels, sometimes with multiple small lumens and/or arteriolosclerosis (Fig. 1d, e).

Astrocytosis—astrocyte hypertrophy and hyperplasia—is a histopathologic feature of HS-Aging [72], with the caveat that astrocytosis is also seen in innumerable other pathologic conditions. In cases with HS-Aging pathology, reactive astrocytes are observed with abundant eosinophilic cytoplasm, and glial fibrillary acidic protein (GFAP)-immunoreactive cells and astrocyte processes in and near areas of neuron dropout (see composite; Fig. 3). Currently, the relationship between astrocytosis and the HS-Aging disease process is not understood. The astrocytic response may be exclusively reactive in HS-Aging brains. However, an alternative hypothesis is that the astrocytes themselves play a contributory pathogenetic role. Reactive astrocytes secrete neuroinflammatory signals that may exacerbate other pathologies [1, 33, 83, 106]. It has been previously shown that in brains with FTLD and TDP-43 pathology (FTLD-TDP), GFAP—the key intermediate filament of astrocytes—is hyperphosphorylated and a target of damaging oxidative modifications [40, 66]. We found that a conspicuously large amount of detergent-insoluble (but urea-soluble) GFAP protein is present in HS-Aging hippocampi (Fig. 4). This increase of GFAP led us to consider that HS-Aging pathologic process, rather than severe NFTs, may strongly induce astrocytic proliferation. Moreover, the strong induction of GFAP expression suggests that TDP-43-positive inclusions might have a neurotoxic effect that might be comparable to or stronger than that of NFTs (see below). There has not been previously a systematic study of "cross-talk" between astrocytic and TDP-43 pathologies in HS-Aging to the best of our knowledge. Ultimately, it remains unknown, like many other aspects of glial cell pathology, whether this insoluble GFAP protein is benign or toxic.

HS-Aging is also strongly linked to aberrant TDP-43 pathology (see Table 1; Figs. 2, 3). In a recent study assessing brains of older patients (average age 88.6 years at death), both right and left sides of the brain were sampled, including central hippocampal, rostral (entorhinal) hippocampal, and amygdala tissue blocks [98]. Using this study design, among 79 HS-Aging cases and 227 controls, 89.9 % of HS-Aging cases demonstrated aberrant TDP-43 pathology in contrast to only 9.7 % of non-HS-Aging control cases with TDP-43 pathology [80]. Aberrant TDP-43 immunoreactivity is often seen in cells of the dentate granule layer, CA1, subiculum, entorhinal cortex, and amygdala in HS-Aging cases [4]. In addition to TDP-43-immunoreactive neurons, TDP-43-immunoreactive dystrophic neurites can also be observed, particularly in CA1 and subiculum (Figs. 2, 3).

Hippocampal TDP-43 pathology is only moderately specific to HS-Aging. Aberrant TDP-43 immunohistochemistry is a key difference between HS-Aging and a subset of other brain disorders linked to mesial temporal sclerosis, including epilepsy and vascular insufficiency (Table 2); these conditions lack pathologic TDP-43 immunostaining [60, 80, 92]. By contrast, in FTLD-TDP cases, both HS and aberrant hippocampal TDP-43 inclusions are observed. While overlapping pathologic features between FTLD and HS-Aging have been noted [14, 38], there are at least five key differences between HS-Aging and FTLD-TDP [5, 8, 20, 22, 65]: (1) FTLD-TDP tends to affect younger individuals (<65 years onset for FTLD-TDP versus >80 years onset for HS-Aging); (2) FTLD-TDP generally affects brain areas outside the mesial temporal lobe, whereas the anatomical distribution of the pathology is very different in HS-Aging; (3) symptoms of HS-Aging are dissimilar to FTLD-TDP which usually does not begin with an amnestic syndrome; (4) the genetic etiologies of FTLD-TDP are mostly known but those of HS-Aging remain to be determined (see below); and (5) FTLD-TDP is rare (<1 % of dementia cases when epidemiologic as opposed to dementia clinic cohorts are studied) [99, 103, 109], whereas HS-Aging is a very prevalent disease in community-sampled aged persons. It is important to note that TDP-43 pathology is by no means specific to FTLD-TDP, so there may be fundamentally different underlying cause[s] in HS-Aging than FTLD-TDP. HS-Aging may not be classified optimally in close relation to FTLD-TDP unless, or until, further research supports a stronger link than is now known. The analogy to FTLD may be most important to underscore the idea that diseases with overlapping clinical manifestations (e.g., disinhibition or aphasia) may reflect a large number of different underlying etiologies—FTD/FTLD can be caused by many different gene mutations as described below.

As with FLTD-TDP, there is a complicated “border zone” between HS-Aging and AD pathologies. Hippocampal TDP-43 pathology is often a co-morbid observation in cases with AD pathology (see [4, 27, 80, 92, 107, 116, 123]). Does TDP-43 pathology in AD brains relate directly to the degenerative changes seen in HS-Aging? There are good reasons that researchers might come up with contradictory answers to this deceptively simple question. Strong evidence exists for synergistic protein misfolding in AD brain. For example, some degree of α-synucleinopathy is often seen in AD amygdalae, and α-synucleinopathy can be observed along with plaques and tangles in APP gene mutation-linked familial AD cases [58, 64, 94]. These phenomena could indicate that non-Aβ, non-tau protein mis-folding in AD brains possibly includes TDP-43 as well as α-synuclein proteinopathies. However, the brains of approximately 80 % of cognitively impaired nonagenarians harbor appreciable AD (plaques and tangles) pathology [12, 18], so one can confidently predict that even if HS-Aging pathology were independent of AD pathology, a very high percentage of HS-Aging cases would still have substantial AD pathology, and vice versa! Notably, neither HS-Aging nor aberrant TDP-43 inclusions are linked to APOE genotype, which strongly correlates with AD pathology [61, 80, 84, 108]. We interpret published data to indicate that we still do not know whether TDP-43 pathology in AD cases represent incipient HS-Aging pathology, a subset of AD-related pathology, a synergistic combination, or a completely separate entity.

In summary, the null hypothesis—namely, that HS-Aging and AD pathologies are independent of each other—has neither been proven nor disproven.

Adding still more complexity to the pathologic diagnosis of HS-Aging is frequent lateral asymmetry of the pathologic changes. Investigators from different research centers have observed that HS pathologic changes seen on H&E stain may be recognized only on one side—left versus right—in 40–55 % of cases [80, 123]. The neuropathologic observations track well on radiologically observed hippocampal atrophy from the same cases [123]. However, in cases where the H&E-stained HS features are seen on only one side, the aberrant TDP-43 immunohistochemical features are seen on the contralateral side (that lacks neuronal dropout on H&E) [80]. This indicates that, despite an apparently "unilateral" disease process (via H&E stain), there is a brain-wide disease condition indicated by TDP-43 immunostaining. In support of the hypothesis that HS-Aging pathology affects areas outside of the portion with changes detectable on H&E stains, the severity of global cognitive impairment linked independently to HS-Aging pathology is similar whether the H&E-based HS changes are bilateral or unilateral [77]. As a practical point, routinely studying one side of the brain for workup with H&E stains will certainly lead to an erroneous false-negative (H&E-based) diagnostic HS detection in approximately 25 % of HS-Aging cases (also see [123]). These observations also provide insights into what may constitute early HS-Aging pathology: hippocampal TDP-43 pathology without frank "sclerosis".

What does the TDP-43 pathology in HS-Aging indicate? Aberrant immunohistochemical TDP-43 profiles are a pathologic landmark that signal both "reactive" (secondary to other pathogenetic factors) and toxic (primarily pathogenetic) changes. Focusing on the reactive aspect, TDP-43 pathology has been observed in human kindreds with numerous distinct genetic abnormalities (e.g., mutations in GRN, C9orf72, OPTN, VCP, ANG, ATXN2, UBQLN2, TMEM106B, and others [112]). The fact that mutations in the TDP-43 gene can alone induce a neurodegenerative disease phenotype with TDP-43 inclusions [111], along with other experimental observations [36, 59], confirms that TDP-43 inclusions are directly or indirectly toxic.

HS-Aging pathology has also been linked to non-AD tauopathy [4, 11, 53, 71], although this association is less strong and specific compared to TDP-43 pathology. Tau and TDP-43 pathologies have been proven to be sequelae of diverse primary genetic and environmental causes. For example, both tau and TDP-43 pathologies are observed in postencephalitic parkinsonism [63, 118]. Chronic traumatic encephalopathy (CTE) provides yet another demonstration of specific environmental stimuli that can lead to both tau- and TDP-43-immunopositive neuronal inclusions with associated neurological impairment [67, 97]. By definition, the cell loss in HS-Aging hippocampi is beyond that which would be expected by the AD-related changes alone, which in the hippocampus involves tau-positive neurofibrillary tangles. However, it has been noted that there are HS-Aging pathologic changes in some non-AD tauopathy cases and vice versa [4, 11, 53, 71]. There is also a growing appreciation of non-"canonical" tauopathic changes in advanced old age including cases with abundant glial tau or tau with atypical anatomical distribution [57]. Intriguingly, Arnold et al. [6] reported that TDP-43 pathology in nondemented aged individuals co-occurs with tau-positive argyrophilic grain pathology, perhaps indicating a preclinical state of disease progression. We also have observed that many cases with HS-Aging pathology show some tau pathology. In our experience, tauopathy seen in HS-Aging brains may diverge from the Braak staging continuum [17], with phospho-tau immunoreactivity in dentate granule cells, glial tau, and white matter tau changes. Here we provide data from a representative case with HS-Aging pathology (Figs. 2, 3); to the best of our knowledge, a systematic description of tauopathic changes in HS-Aging remains to be performed. This

highlights a broader need for more published information about HS-Aging, guided by the pathologic gold standard.

Epidemiology of HS-Aging

The prevalence and clinical correlates of HS-Aging pathology are of fundamental importance. Autopsy series have shown that 5–30 % of brains in advanced old age harbor HS-Aging pathology [25, 61, 80, 91, 123]. Differences in study design, including in pathologic methodology and demographics, contribute to the study-to-study variability in reported HS-Aging prevalence. Some studies reporting the low end of prevalence range may have many false negatives due to assessing only one side of the brain. Two other key factors influencing recognition of HS-Aging in autopsy cohorts are patient age and the date of the study. In some classic dementia clinical–pathological correlation studies [15, 95], research subjects had mostly died during their early 70s. HS-Aging is only infrequently observed at those ages, and the researchers were at that time blamelessly unaware of HS-Aging pathology (including TDP-43 pathology) as we now know it. Many of the published autopsy series included persons recruited for a dementia research clinic. Autopsy cohorts of this type are known to have skewed observations in clinical–pathological correlations: dementia clinic cohorts tend to oversample AD, FTLD, and unusual diseases, while undersampling aged cognitively intact individuals and persons with cerebrovascular pathologies [12, 21, 100].

We show data from The Nun Study (Fig. 5), a birth cohort followed from normal status with extremely high autopsy rate which lacked some of the biases of dementia clinic cohorts [73, 117]. Note that among the subjects who died beyond 90 years of age, the rate of severe AD pathology decreases, whereas the proportion of cases with HS-Aging pathology increases dramatically. For individuals past 95 years of age, the rate of pathologic observation for those two separate diseases is approximately the same. The appreciable late-life increase in risk for HS-Aging pathology indicates that this disease belongs in a category, like age-related macular degeneration and indolent prostate cancer [78, 96], that affects humans preferentially in their 90s rather than in their 70s.

The epidemiologic data indicate that HS-Aging pathology is prevalent and correlates with impaired cognition independently of AD pathology in advanced old age [77], which helps to explain the “dissociation” between AD pathology and cognitive status in the “oldest-old” [44, 80] (and see [16, 31]) The key consideration—that dementia is associated with HS-Aging pathology rather than pure AD pathology in many individuals past age 90—is directly relevant to clinical trials, biomarker analyses, and other dementia research studies. Unfortunately, most clinical series are blind to this phenomenon because people with HS-Aging pathology currently tend to be misdiagnosed during life as having AD (or only AD) [84]. It follows that there is a great need for novel methods to identify living patients with HS-Aging pathology.

Neurocognitive testing and neuroimaging findings linked to HS-Aging

An ideal HS-Aging diagnostic biomarker would identify individuals with HS-Aging pathology during a clinical window when therapies might work. The specific experimental goal is to recognize a particular feature or pattern that predicts HS-Aging pathology, versus AD pathology, with confidence. Neurocognitive testing and neuroimaging studies have begun to address this challenge.

Although there is overlap in the clinical manifestations of HS-Aging and AD, careful analyses may identify distinctive behavioral and neurocognitive patterns reflecting differences in the underlying neuropathology. These studies require longitudinal cognitive

testing and state-of-the-art neuropathologic evaluations. For example, Dawe and colleagues [28] found that HS cases have relatively atrophic hippocampi and correlated impairment in episodic memory. Their data, albeit with low numbers of HS cases ($N = 4$), revealed statistically significant differences in global cognition between AD ($N = 40$) and AD plus HS ($N = 9$) when compared to control cases. However, global cognitive status in HS was also adversely affected. Studies have not yet quantified the impact of HS-Aging on complex cortical functions such as language, executive skills, and semantic memory early in the course of disease. Data suggest that commonly used clinical measures such as verbal fluency are not associated with hippocampal volume but rather correlate with frontal and temporal gray matter volumes in AD [29]. Therefore, it is reasonable to posit that there may be differences in the early presentation and clinical course of HS-Aging in contrast to other neurodegenerative disorders. To highlight this potential clinical marker, cognitive scores were explored in a large sample of HS-Aging cases and controls [80]. These analyses suggested that patients with relatively preserved verbal fluency (cortically dependent), despite profound world list delayed recall deficiency (hippocampal dependent), were at higher risk for having HS-Aging pathology. In Fig. 6, we show data on neurocognitive profiles of individuals who died with HS-Aging pathology, in comparison to a control group, at early stages in the disease including baseline. These changes were distinct from the pattern seen in individuals with AD pathology alone [80], although there has been recent insights into subtypes of AD which add another layer of complexity [49, 75, 76]. Further work is required to go beyond “group level” differences to identify markers that can distinguish individuals with HS-pathology with high sensitivity and specificity. We note that brains of many of the HS-Aging cases, as well as the controls, harbor AD pathology; it is not necessarily fruitful to specifically pursue “pure” HS-Aging cases if they are in the minority in a clinical context [2, 46, 123]. It is also unclear how the published studies that include patients with hippocampal atrophy linked to epilepsy (see [41]) should be integrated with the HS-Aging cognitive data literature. Another important question is the expected “natural history” of HS-Aging, and whether the expected end-stage clinical syndrome is similar to, or less severe, than AD. This remains to be definitively described through larger scale studies to define a neurocognitive pattern for HS-Aging and to differentiate HS-Aging from other neurodegenerative processes. Taking this into account, global dementia severity may be an important factor in the search for a clinical profile.

For research aimed at developing novel HS-Aging biomarkers, brain imaging adds a layer of study design complexity. Beyond the challenges related to autopsy cohorts (see above), there are additional potential sources of bias in neuroimaging studies (e.g., cardiac pacemakers precluding MRI). There are multifactorial “border area” problems: one must operationalize both HS-Aging and AD pathologies. This implies that the severity of plaque and/or tangle pathology threshold be quantified. Similarly, HS-Aging must also be carefully defined based on severity, bilateral presence in the brain, degree of TDP-43 pathology, as well as chronological age of the individual to distinguish HS-Aging from FTLD. It is also difficult to control for cognitive status since HS-Aging and AD are likely to have non-identical cognitive manifestations as described above. One must also take into account the clinical and pathologic variability introduced by other frequent comorbid pathologies including cerebrovascular pathology and α-synucleinopathies, and the importance of the stage(s) in the diseases’ multiyear course one chooses to study. We show here a subsample of cases who had MRIs at the UK-ADC with eventual autopsy-confirmed HS-Aging pathology (Fig. 7), underscoring the evolving appreciation that it is the rule, and not the exception, for older persons’ brains to harbor multiple disease processes [79, 87, 101, 123]. Finally, the technology used in both MRI studies, and the pathologic workups to which they are compared, are constantly changing, so an “apples-to-apples” comparison can be a challenge. Thus, because of many potential pitfalls, careful consideration of study design and implementation will be required to identify specific HS-Aging biomarkers.

At least partly because of the complexities described above, most of the published research on HS-Aging neuroimaging characteristics is subsumed in the far larger AD literature. An obvious fact is that hippocampal atrophy is pronounced in individuals with HS-Aging pathology [28, 122], so it would be inaccurate to describe MRI-detected hippocampal atrophy as a specific biomarker for AD. Detailed discussion on the topic of HS-Aging cases within AD-oriented studies is beyond the scope of this review.

Relatively few published studies featured research volunteers who underwent MRI at some point and also had autopsy evaluation to identify HS-Aging cases. Barkhof et al. [10] found that many cases with medial temporal atrophy lacked primary underlying AD pathology (in this study cohort, the sensitivity and specificity of severe atrophy for AD pathology was 63 and 69 %, respectively, which is consistent with the findings of Jack et al. [45]). Josephs et al. [51] reported that aberrant TDP-43 pathology in AD cases tended to be found in individuals with subsequent HS pathologically, although only 9/29 TPD-43(+) had pathologically verified HS. Overall, the TDP-43(+) cases were older, with more cognitive impairment, and more pronounced hippocampal atrophy than TDP-43(−) cases. In a report more focused on cases with HS-Aging per se, Zarow et al. [122] described that the atrophy and deformation of the hippocampus are considerably more severe in autopsy-confirmed HS-Aging than in AD. HS-Aging hippocampal atrophy was found to be frequently laterally asymmetric, and affected the hippocampus along the full rostral-caudal extent. Using postmortem MRI, Dawe et al. [28] also reported stronger correlation between hippocampal atrophy and HS-Aging pathology than AD pathology, and individuals with AD+HS pathologies had similar (greatly atrophic) hippocampi to HS alone. In summary, the radiographic findings to date essentially mirror the pathological observations, and the common thread has been to show that hippocampal atrophy is more severe in HS-Aging than AD. However, there has not been identification and independent validation of a neuroimaging “signature” that is specific for HS-Aging.

Factors that may cause or exacerbate HS-Aging

The etiologic mechanisms underlying HS-Aging are still essentially a mystery, but some clues and correlations have been reported. One of the first hypothetical etiological connections was between HS-Aging and cerebrovascular disease. The context—the aged human brain—is important to consider. “Cerebrovascular disease” is an umbrella term for a large number of different types of diseases [19, 50, 81, 113, 115], and practically all patients beyond age 90 have some morphologically discernible brain vascular pathologic changes in comparison to younger cohorts [35, 78, 79, 88]. As mentioned above, blood flow changes, reduced oxygenation, and glycemic fluctuations can profoundly damage the hippocampus through “acute excitotoxic mechanisms” [37, 48] without inducing TDP-43 pathology [60, 80]; this process seems different from what is observed in HS-Aging cases. However, there may be other cerebrovascular perturbation[s] that are etiologically linked with HS-Aging pathology. Dickson et al. [30], in a seminal autopsy series, found a relatively high tendency among 13 HS-Aging cases versus controls to have the specific pathologic diagnosis of arteriolosclerosis. Arteriolosclerosis is characterized by altered morphology of small blood vessel walls, particularly in arterioles. Jellinger observed that HS pathology with comorbid AD pathology is often seen in patients with coronary atherosclerosis, while “pure” HS is rare in older persons because of frequent co-morbidities [46]. As mentioned above, we also observe convoluted blood vessels in HS-Aging cases and there is possibly a pathogenetic link where chronic perturbations linked to arteriolosclerosis could directly lead to HS-Aging pathology, or there may be a common upstream cause of these two pathologies.

As with the links between HS-Aging pathology and cerebrovascular disease, the associations between specific genetic alleles and the risk for HS-Aging pathology require

further exploration. There has not been a published genome-wide, systematic study of genetic polymorphisms (genome-wide association studies or GWAS) that are linked to autopsy-confirmed HS-Aging. The disease may not be mono-allelic. In a study focusing on the FTLD risk gene GRN among AD cases, Dickson et al. [29] reported that a specific SNP (rs5848 T allele) in GRN correlates with increased HS risk. It has been confirmed that the rs5848 polymorphism is biologically important [32, 42, 52] and this genetic polymorphism may well explain a subset cases with HS-Aging pathology. Hexanucleotide expansion mutations in the C9ORF72 gene have been shown to induce hippocampal TDP-43 inclusions [74], with heterogeneous clinical and pathological presentations albeit more related to FTD-type clinical manifestations, so C9ORF72 also is a candidate for HS-Aging pathogenetically. In a RNA deep sequencing study, with small group sizes, no differences were detected when small RNAs were compared between pathologically verified HS-Aging, AD, DLB, and FTLD cases [39].

Moving outside the genes linked directly to FTLD-TDP, and also beyond the solid endophenotype of pathologically confirmed HS-Aging, a number of researchers have used MRI-detected hippocampal atrophy as an endophenotype for correlation with genetic polymorphisms in human GWAS. Although these MRI phenotypes do not yet discriminate HS-Aging from other causes of hippocampal atrophy (such as AD), this study design may provide new directions that are directly relevant to HS-Aging pathogenesis. In Table 3, we show a list of studies and the genes implicated in GWAS that use hippocampal atrophy as an endophenotype. These studies have drawn on overlapping research subjects, particularly from the AD Neuroimaging Initiative [ADNI] cohort [85], so they are not actually independent of each other and Table 3 is not a “meta-analysis”. A fundamentally important consideration in these studies—relevant for all studies related to HS-Aging—is the age of the research volunteers. Note that most of the research volunteers in the MRI/GWAS, in ADNI and other large clinical studies, had case/control diagnoses while in their middle 70s. This age range would be too young to capture most cases with HS-Aging pathology in an autopsy sample. While the same calculation does not necessarily apply to an (in vivo) imaging study, we await future studies that use essentially the same research methods but focus upon older research subjects.

Finally, the impacts of environmental factors should be considered as potential disease modifiers. Specifically, TDP-43 pathology may be seen in the brains of individuals who suffered chronic brain trauma such as CTE [54, 67]. This phenomenon, combined with the advanced age of many affected individuals, lead us to speculate that HS-Aging may be, at least in part, a manifestation of long-term brain “wear-and-tear”. We conclude that, as with the many different gene polymorphisms that lead to FTLD-TDP [112], and diverse chemical pathways that can induce TDP-43 perturbations in cultured cells [59], there could be numerous different genetic and environmental factors that contribute to the process that manifests as HS-Aging pathology in elderly persons’ brains.

Summary

HS-Aging is a prevalent, high-morbidity brain disease that affects people in old age. Currently, HS-Aging is primarily defined by neuropathological observations including hippocampal neuron loss and astrocytosis with aberrant TDP-43 immunoreactivity. Important questions remain including ‘boundary issues’ with FTLD and AD, and whether or not non-AD tauopathy or astrocytic changes contribute or co-occur pathogenetically. The amnestic changes of HS-Aging tend to be conflated clinically with AD in aged patients, which, given the high prevalence of HS-Aging pathology, presumably hinders or confounds analyses of AD clinical trials. However, the specific neurocognitive characteristics of HS-Aging, particularly as a potential method to help differentiate the disease from AD, have

seen recent progress, highlighting the relative preservation of verbal fluency in HS-Aging patients. Radiographic and genomic changes are at this point in the early stages of providing specific clinical biomarkers for HS-Aging, and many questions remain in terms of the underlying pathogenesis of the disease. Ultimately, the epidemiology of the disease may be driven by demographic trends: there is predicted to be dramatic increases in the number of humans who live beyond 90 years of age (Fig. 5), and so HS-Aging—if no therapeutic strategy is devised—will constitute an ever increasing public health problem. Further work in the area of HS-Aging should be recognized as a priority for research and clinical care on the scale of what the National Alzheimer Project Act (NAPA) has done for AD.

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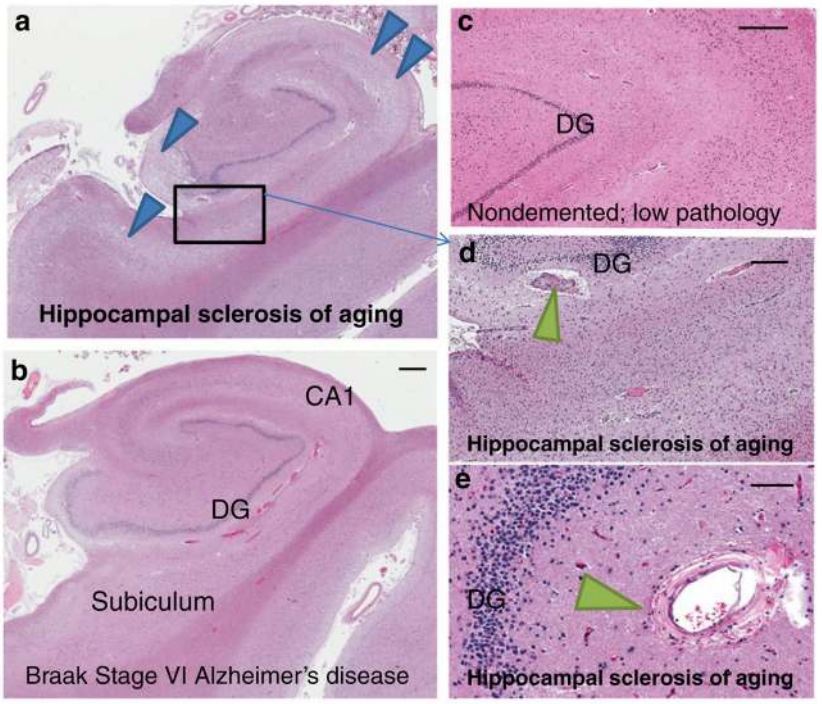


Fig. 1.

Histopathology of HS-Aging: hematoxylin and eosin (H&E) findings. **a** Low-power photomicrograph of hippocampal formation of a woman who died at 88 years of age with dementia and HS-Aging pathology. Even at low power one can appreciate that the hippocampus has atrophy and areas of neuropil rarefaction (*blue arrows*) in dentate granule area, CA1, and subiculum. **b** For comparison sake, the brain of a man who died at age 77 with dementia and end-stage (Braak VI) AD, with dentate granules (*DG*), *CA1*, and subiculum labeled. Note that even in AD the hippocampus (at the same scale as in **a**) is somewhat larger and without the neuropil rarefaction. **c** In individuals with neither AD nor HS-Aging, such as this 71-year-old cognitively intact male, with Braak stage I pathology, the hippocampal neuropil appears homogenously *pink* and nondisrupted on an H&E stain. **d** Other features of HS-Aging are shown in this medium-power photomicrograph of the boxed area from **a**. Even at this magnification, the disruption of the normal hippocampal architecture can be observed, along with thickened medium-sized blood vessel (*green arrow*). **e** At higher magnification, from the hippocampus of a woman who died with dementia at age 91 with HS-Aging pathology, this blood vessel profile (*green arrow*) shows the arteriolosclerosis and thickened multilumen blood vessel profiles that can accompany HS-Aging pathology. *Scale bars* **a**–**c** =1 mm, **d** =500 μm, **e** =150 μm

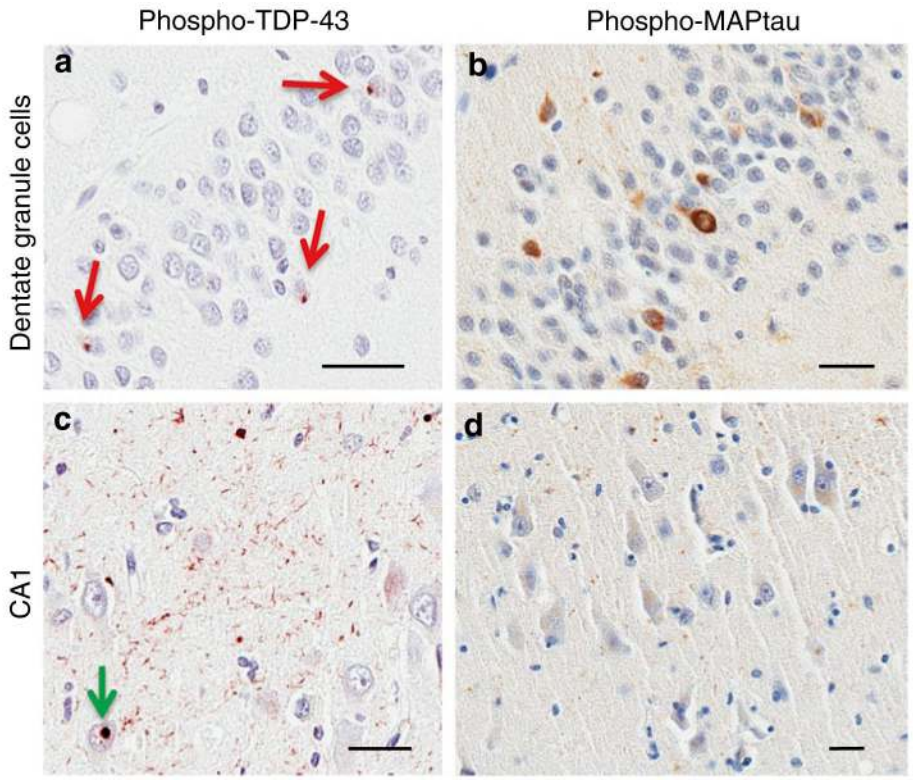


Fig. 2.

Histopathology of HS-Aging: Phospho-TDP-43 and phospho-tau immunohistochemical findings. Observations in brain sections from the same case are as shown in composite in Fig. 3. These sections (dentate granule cells, **a**, **b**; *CA1*, **c**, **d**) have been stained with hematoxylin (stain nuclei and some cell *contour blue*) and counter-stained with brown chromagen. Sections **a** and **c** are stained for phospho-TDP-43 (clone 1D3, Millipore). Note that in the dentate granule cells, there are immunoreactive inclusions in cell bodies (*red arrows*), whereas there are prominent neuritic (narrow non-tapering nerve cell processes) TDP-43+ staining in the CA1 area, in addition to some cellular staining (intranuclear inclusion, *green arrow*). Phospho-tau staining (PHF-1, a gift from Dr Peter Davies) has features that do not map well onto Braak staging. For example, there are relatively numerous phospho-tau-positive dentate granule inclusions, whereas *CA1* shows very little phospho-tau immunoreactivity. *Scale bars* **a**, **b** =30 μm; **c**, **d** =50 μm

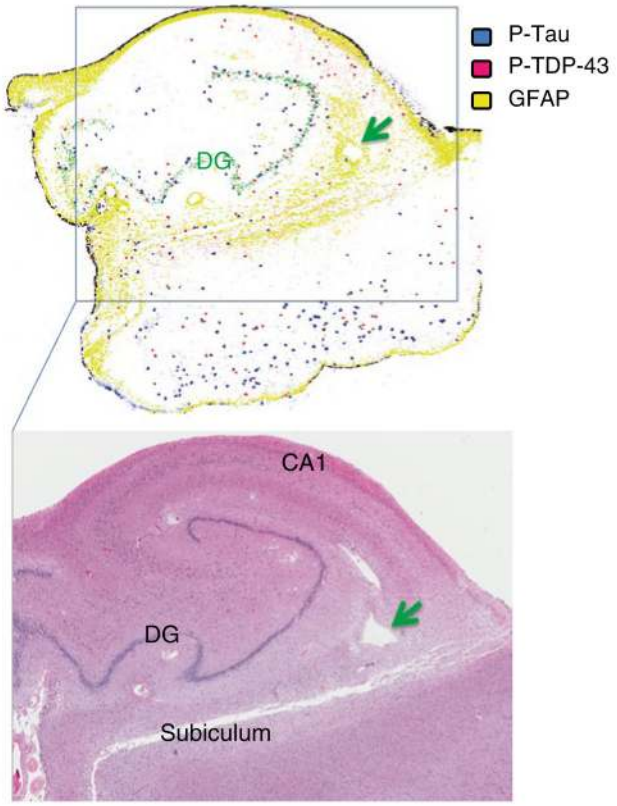
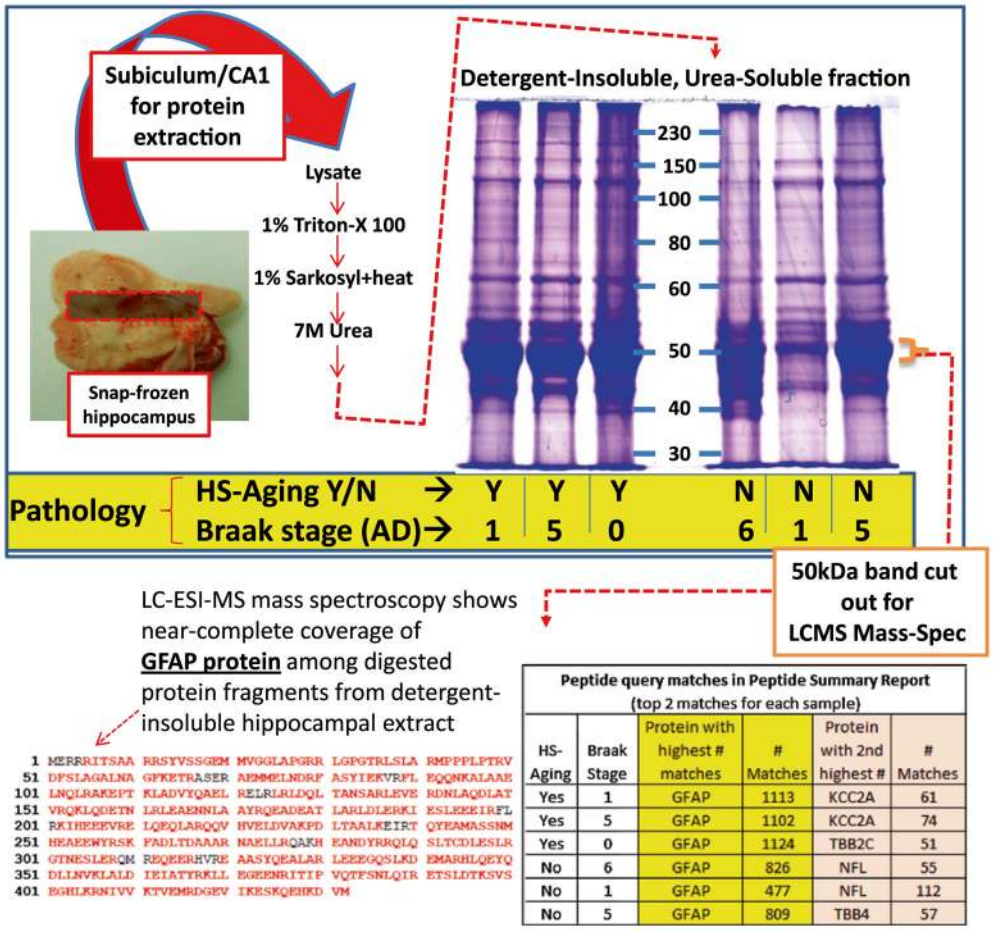


Fig. 3.

Histopathology of HS-Aging: Composite low-power figure depicts the distribution of pathology localized with multiple pathological immunomarkers. Sections were analyzed from the brain of a man who died cognitively impaired at age 92 years; autopsy showed HS-Aging and Braak stage II pathologies. An Aperio ScanScope XT with Genie™ image recognition software was used to highlight the positive immunoreactivity. The *top portion* shows the composite results of three nearly consecutive sections stained for phospho-tau (*blue*), phospho-TDP-43 (*red*); and GFAP (*yellow*). Labeled are dentate granule cell layer (*DG*, shown in *green* in *top portion*), *CA1*, and subiculum (*bottom*). *Green arrows* show same abnormally enlarged Virchow-Robin space on both *top* and *bottom* figures. This representative case shows that HS-Aging brains have a multifaceted pathological picture that includes TDP-43 pathology, astrocytosis, tauopathy, and vascular profiles that are aberrant in comparison to that which would be observed in younger control individuals. Future work is required to identify the truly specific, and clinical disease-driving, feature(s) of HS-Aging pathology



Peptide query matches in Peptide Summary Report (top 2 matches for each sample)

HS-Aging	Braak Stage	Protein with highest # matches	# Matches	Protein with 2nd highest #	# Matches
Yes	1	GFAP	1113	KCC2A	61
Yes	5	GFAP	1102	KCC2A	74
Yes	0	GFAP	1124	TBB2C	51
No	6	GFAP	826	NFL	55
No	1	GFAP	477	NFL	112
No	5	GFAP	809	TBB4	57

Fig. 4.

Human subiculum affected by HS-Aging pathology contains abundant detergent-insoluble glial fibrillary acidic protein (*GFAP*). For this experiment, tissue was isolated from subiculum of six different cases, three HS-Aging and three controls. The tissue was processed as previously described [43, 82] to isolate detergent-insoluble protein using a method that ultimately solubilizes proteins with 7 M urea. Coomassie Blue stained urea-polyacrylamide gel from the detergent-insoluble extract shows a ~50 kDa band that is accentuated in HS-Aging cases (*three leftward lanes* on the gel). Individual 50 kDa gel bands were excised for each of the six cases and the gel fragments were submitted separately for liquid chromatography–electrospray ionization mass spectrometric (LC-ESI-MS) proteomic analysis. Gel pieces were digested with trypsin, and LC-ESI-MS performed using a ThermoFinnigan LTQ. Resulting MS spectra were searched against human proteins in the Swiss-Prot database using the Mascot search engine (Matrix Science). In both the HS-Aging and control cases, the overwhelming proportion of this 50 kDa band was GFAP. Shown at the *bottom right* of the figure are the two proteins in this size range with the most peptide query matched reads, for each of the six samples. With caveats appropriate for comparison between two experimental groups comprising only three samples each, the cases with HS-Aging pathology had larger amount of GFAP peptide fragments, covering almost the entire span of the protein, than the controls ($P < 0.03$)

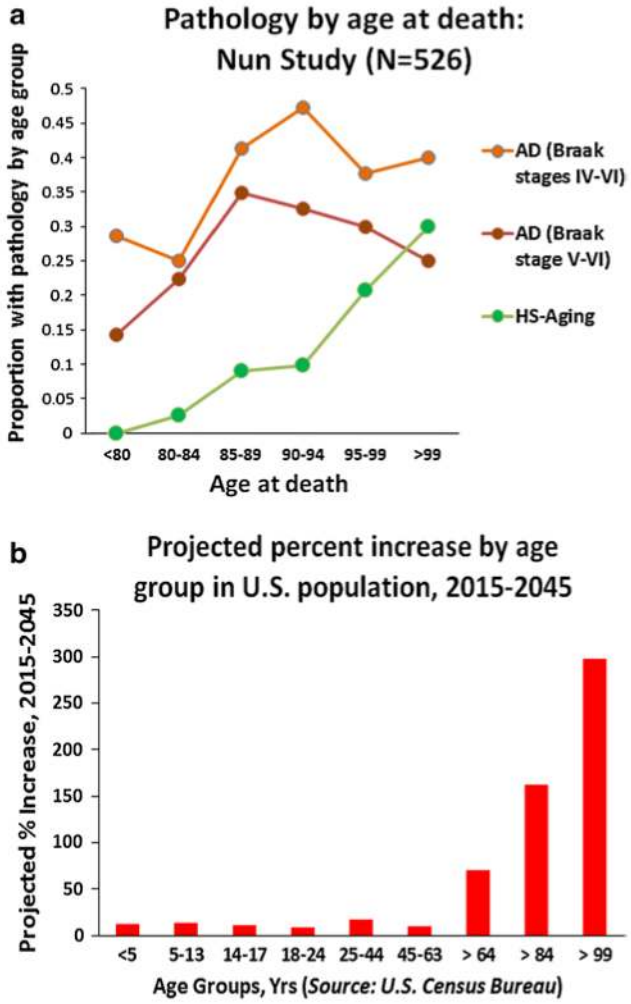


Fig. 5.

Data related to HS-Aging epidemiology underscore the large, and increasing, public health impact of HS-Aging. Data from The Nun Study [73, 110] among research subjects with pathologic data ($N = 526$). The proportion of individuals with moderate or severe Alzheimer's disease (AD; moderate or severe neuritic amyloid plaque pathology and Braak stages using two different threshold cutoffs, Braak IV and above and Braak V and above) are compared to the proportion of individuals with HS-Aging pathology. Note that a significant number of patients had both pathologies as would be expected. This is a birth cohort that had been followed for many years, incorporating a full spectrum of cognitive impairment, without many of the biases that are linked to dementia clinics, thus insights into the population-level epidemiology. Median age of this cohort is >90 years of age at death. **b** The late-life increase in HS-Aging pathology can be viewed in context of projected demographic increases in numbers of very old persons predicted by the U.S. Census Bureau. Source: http://www.census.gov/population/projections/data/national/2012/summarytables.html

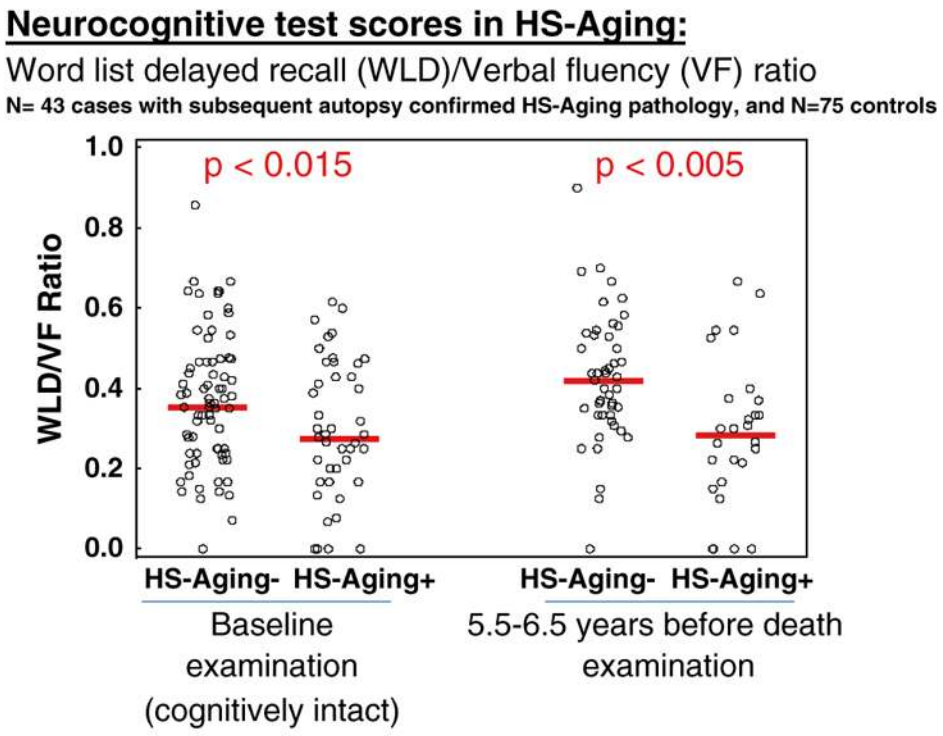


Fig. 6.

Neurocognitive changes provide a clinical feature that distinguishes cases with eventual HS-Aging pathology versus controls. Each data point represents an individual research volunteer. *N* = 43 HS-Aging cases, and *N* = 75 controls, matched for age, gender, education level, and APOE status with each of those parameters used as covariate. These 118 participants had a total of 966 yearly longitudinal assessments for an average of 8.2 assessments per participant. All were followed from nondemented cognitive state at baseline. Plots show the distribution of values for the ratios of test scores of word list delay (*WLD*): verbal fluency (*VF*) at baseline and at an examination 5.5–6.5 years prior to the patients' death. The timepoint of ~6 years prior to death was selected because this usually was after symptom onset but before end-stage disease. All statistical analyses were performed using SAS/STAT® 9.2 software. This figure is adapted from PT Nelson et al. [76] Brain, published by Oxford University Press, and is reproduced with permission

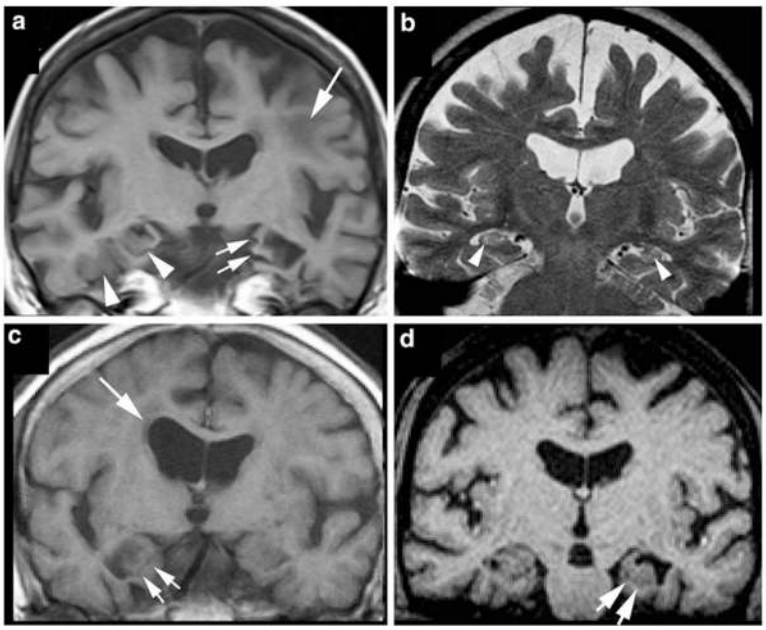


Fig. 7.

Magnetic resonance images (MRIs) from individuals with eventual autopsy diagnosis of HS-Aging. This group of coronal MRIs from four individuals illustrates that HS-Aging pathology is often associated with co-morbid brain diseases. **a** A 96-year-old female patient with an acute stroke shortly before autopsy. Shown on the T1-weighted image are signs of acute cortical swelling in the medial and inferior right temporal lobe due to a right posterior cerebral artery stroke (*arrowheads*), subcortical white matter hypointensity from prior ischemia (*arrow*), and marked left hippocampal atrophy (*double arrow*). Extensive vascular disease, hippocampal sclerosis, and Alzheimer's disease (Braak stage V) were found at autopsy. **b** T2-weighted image from 80-year-old female patient demonstrates atrophy and abnormally increased signal in the hippocampi (*arrowheads*). Autopsy 16 years later demonstrated AD pathology, Braak stage VI, and HS. **c** HS with Braak stage III pathology and stroke were found at autopsy 7 years after this scan demonstrates asymmetric right medial temporal atrophy (*double arrows*) and dilation of the right frontal horn (*arrow*), **d** T1-weighted scan from 86-year-old woman with slowly progressive memory loss and stroke demonstrates asymmetric left medial temporal atrophy (*double arrows*). Autopsy confirmed HS-Aging pathology

Table 1

Prior studies of direct relevance to hippocampal sclerosis of aging (HS-Aging)

References	HS-Aging (*N*)	Average death age, cases	Total (*N*)	Notes and key contributions
[23]	3	N/A	22	HS cases were among non-AD dementia cases
[30]	13	89	81	HS linked to both advanced aging and arteriolosclerosis
[47]	5	78	67	HS linked to dementia, but not to CVD
[108, 119]	12	N/A	12	HS not linked to APOE genotype
[24]	8	78.5	8	Probably includes FTLD, anoxic, and HS-Aging cases
[7, 46]	28	AD/HS: 85; other +HS: 78	1,000	"Pure" HS is rare; HS + AD is linked to atherosclerotic coronary artery disease
[2]	7 ("pure")	71	1,771	"Pure" HS is relatively rare, linked to CVD/anoxia
[9]	50	73	382	"Pure" HS cases in this series tended to be older
[114, 115]	41	N/A	443	HS is linked to AD, dementia, and infarcts
[61, 62]	16	85	134	HS is prevalent, not APOE linked in community sample
[11]	14	82	14	High rate of tauopathy/AGs in HS cases
[14, 38]	19	78	N/A	HS dementia linked with FTLD but series almost certainly include true FTLD cases
[121]	9	86	28	Neuronal loss in CA2 as well as CA1 in HS
[86]	2	90	15	HS pathology frequently seen in MCI (both with AGs)
[3]	8	84	18	HS in aged persons differs from FTLD-linked HS
[4]	21	83	188	TDP-43+ in 71 % of HS-Aging, ~23 % of "pure" AD
[28]	13	88 (pure)	100	HS-Aging has strong independent impact on cognition and hippocampal atrophy
[90]	10	88	10	TDP-43 pathology in only 3/10 HS cases; mostly tau pathology seen in other cases
[120]	31	83	130	HS often in mixed pathology cases; unilateral 50 %; 93 % of HS-Aging+ are TDP-43+
[77, 80]	106	91	1,100	Defines cognitive impact of HS-Aging, with prevalence that approximates severe AD in advanced old age
[84]	28	83	205	Patients with HS-Aging pathology are usually diagnosed clinically with AD
[122, 123]	11	84	43	HS cases showed prior severe MRI hippocampal atrophy
[27]	5 ("pure")	89 (pure)	235	HS and TDP-43 pathology correlate with or without AD
[27, 93]	17	98	41	HS-Aging pathology correlates with dementia
[25]	11	N/A	104	HS-Aging pathology correlates with dementia
[92]	~27	78	260	(Younger) HS cases of many different etiologies

AD Alzheimer's disease, *AG* argyrophilic grains, *APOE* apolipoprotein E, *CVD* cerebrovascular disease, *FTLD* frontotemporal lobar degeneration, *HS* hippocampal sclerosis, *MCI* mild cognitive impairment, *N/A* not applicable

Table 2

Synopsis of differences and overlap between Hs-Aging and other related brain diseases

Disease	Mesial temporal sclerosis	Clinical syndrome(S)			Age range (most cases)	Location of aberrant TDP-43 in brain	Genes
		Early amnesia	Aphasia/semantic	Behavior variant			
Epilepsy	Y				Usually <40	None	Many
Vascular insufficiency	Y	Y			Any age	None	N/A
FTLD-TDP	Y		Y	Y	40–75	Very widespread	GRN, VCP, C9orf72
AD	Y	Y			60–100	Not part of “classic” AD	APOE, PSEN1, PSEN2, APP
HS-Aging	Y	Y			>85	Hippocampus and amygdala	(?)

Table 3

Studies using hippocampal volume as GWAS endophenotype

Reference	Years	Average Age of "AD" or affected population	Genes linked to hippocampal atrophy in MRI-based GWAS
[89]	2009	75	S100A5, SCAMP1-LHFPL2, ARSB, EFNA5, IKZF1-AC020743.7, MAGI2, MAL2, PRUNE2, RP11, ETS1, ARID2-SFRS2IP, CNAD1, FRMD6, C20orf132, RPN2, ZBP1, FDPSP
[102]	2010	76	EPHA4, APOE, TP63, NXPH1, UBE2D1
[104]	2010	76	ZNF326, UTP20
[26]	2011	73	TTR
[34]	2011	75	ZNF292, PICALM
[70]	2012	75	SLC1A7, LPHN2, F5/SELP, ATF3, GCFC2, STXBP5L, NKAIN2, VPS13B, TLE1, PICALM, LHFP, DLGAP1, APOE, COL18A1
[105]	2012	75	TESC, HMGA2, DDR2
[55, 56]	2012	75	MACROD2, SORCS2, GRIN2B, GALNTL4, NRXN3, AK130123,MAGI2, NPAS3, RBFOX1, AY229892, ZMAT4, STAGS3L2, GAS7, ADARB2, GABRG3, CDH4, CLSTN2, CDH13, GALNTL6, GALNTL6, PRKAG2, CHODL
[13]	2012	Multiple cohorts	MSRB3-WIF1, HRK-FBXW8, DPP4, ASTN2
[68, 69]	2013	76	Complex patterns of genes with hypothesized interactions

Highly overlapping sample attainment in these studies