Published in final edited form as:

Acta Neuropathol. 2013 August ; 126(2): 161–177. doi:10.1007/s00401-013-1154-1.

Hippocampal sclerosis of aging, a prevalent and high-morbidity brain disease

Peter T. Nelson,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Division of Neuropathology, Department of Pathology, Sanders-Brown Center on Aging, University of Kentucky, Rm 311, Sanders-Brown Building 800 S. Limestone, Lexington, KY 40536-0230, USA

Charles D. Smith,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Department of Neurology, University of Kentucky, Lexington, KY 40536, USA

Erin L. Abner,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

Bernard J. Wilfred,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

Wang-Xia Wang,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

Janna H. Neltner,

Division of Neuropathology, Department of Pathology, Sanders-Brown Center on Aging, University of Kentucky, Rm 311, Sanders-Brown Building 800 S. Limestone, Lexington, KY 40536-0230, USA

Michael Baker,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

David W. Fardo,

Department of Biostatistics, University of Kentucky, Lexington, KY 40536, USA

Richard J. Kryscio,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Department of Biostatistics, University of Kentucky, Lexington, KY 40536, USA. Department of Statistics, University of Kentucky, Lexington, KY 40536, USA

Stephen W. Scheff,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Department of Anatomy and Neurobiology, University of Kentucky, Lexington, KY 40536, USA

Gregory A. Jicha,

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Department of Neurology, University of Kentucky, Lexington, KY 40536, USA

Kurt A. Jellinger,

Institute of Clinical Neurobiology, 1070 Vienna, Austria

Linda J. Van Eldik, and

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Department of Anatomy and Neurobiology, University of Kentucky, Lexington, KY 40536, USA

Frederick A. Schmitt

Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. Department of Neurology, University of Kentucky, Lexington, KY 40536, USA

Peter T. Nelson: pnels2@email.uky.edu

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; FTLT; 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, FTLN, 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 FTLN and TDP-43 pathology (FTLN-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 FTLT-TDP cases, both HS and aberrant hippocampal TDP-43 inclusions are observed. While overlapping pathologic features between FTLT and HS-Aging have been noted [14, 38], there are at least five key differences between HS-Aging and FTLT-TDP [5, 8, 20, 22, 65]: (1) FTLT-TDP tends to affect younger individuals (<65 years onset for FTLT-TDP versus >80 years onset for HS-Aging); (2) FTLT-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 FTLT-TDP which usually does not begin with an amnesic syndrome; (4) the genetic etiologies of FTLT-TDP are mostly known but those of HS-Aging remain to be determined (see below); and (5) FTLT-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 FTLT-TDP, so there may be fundamentally different underlying cause[s] in HS-Aging than FTLT-TDP. HS-Aging may not be classified optimally in close relation to FTLT-TDP unless, or until, further research supports a stronger link than is now known. The analogy to FTLT 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/FTLT can be caused by many different gene mutations as described below.

As with FTLT-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-A β , 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, FTLN, 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 word 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 TDP-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 FTL 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 FTL cases [39].

Moving outside the genes linked directly to FTL-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 FTL-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 astrogliosis with aberrant TDP-43 immunoreactivity. Important questions remain including ‘boundary issues’ with FTL and AD, and whether or not non-AD tauopathy or astrocytic changes contribute or co-occur pathogenetically. The amnesic 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.

Acknowledgments

We are deeply grateful to all of the study participants who make this research possible. The authors thank Sonya Anderson and Ela Patel for technical support; Greg Cooper, MD, Nancy Stiles, MD and Allison Caban-Holt, PhD for the clinical evaluations; and Daron Davis, MD for pathological evaluations. The corresponding author Peter Nelson, MD PhD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study funding: Research reported in this publication was supported by National Institutes of Health under award numbers P30 AG028383, R01 NR014189, R01 AG038651, TR000117, and S10 RR26489. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

References

1. Abdul HM, Sama MA, Furman JL, Mathis DM, Beckett TL, Weidner AM, Patel ES, Baig I, Murphy MP, LeVine H 3rd, Kraner SD, Norris CM. Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. *J Neurosci*. 2009; 29(41):12957–12969. 10.1523/JNEUROSCI.1064-09.2009. [PubMed: 19828810]
2. Ala TA, Beh GO, Frey WH 2nd. Pure hippocampal sclerosis: a rare cause of dementia mimicking Alzheimer's disease. *Neurology*. 2000; 54(4):843–848. [PubMed: 10690974]
3. Amador-Ortiz C, Ahmed Z, Zehr C, Dickson DW. Hippocampal sclerosis dementia differs from hippocampal sclerosis in frontal lobe degeneration. *Acta Neuropathol (Berl)*. 2007; 113(3):245–252. [PubMed: 17195931]
4. Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, Graff-Radford NR, Hutton ML, Dickson DW. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann Neurol*. 2007; 61(5):435–445. 10.1002/ana.21154. [PubMed: 17469117]
5. Armstrong RA, Cairns NJ. A morphometric study of the spatial patterns of TDP-43 immunoreactive neuronal inclusions in frontotemporal lobar degeneration (FTLD) with progranulin (GRN) mutation. *Histol Histopathol*. 2011; 26(2):185–190. [PubMed: 21154232]
6. Arnold SJ, Dugger BN, Beach TG. TDP-43 deposition in prospectively followed, cognitively normal elderly individuals: correlation with argyrophilic grains but not other concomitant pathologies. *Acta Neuropathol*. 2013 10.1007/s00401-013-1110-0.
7. Attems J, Jellinger KA. Hippocampal sclerosis in Alzheimer disease and other dementias. *Neurology*. 2006; 66(5):775. 10.1212/01.wnl.0000200959.50898.26. [PubMed: 16534130]
8. Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG, Burn DJ, Keir G, Lerner AJ, Mann DM, Perry R. Frontotemporal dementia in elderly individuals. *Arch Neurol*. 2012; 69(8):1052–1060. 10.1001/archneurol.2011.3323. [PubMed: 22529248]
9. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Shepherd 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. 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*. 2002; 16(4):203–212. [PubMed: 12468894]
10. Barkhof F, Polvikoski TM, van Straaten EC, Kalaria RN, Sulkava R, Aronen HJ, Niinisto L, Rastas S, Oinas M, Scheltens P, Erkinjuntti T. The significance of medial temporal lobe atrophy: a postmortem MRI study in the very old. *Neurology*. 2007; 69(15):1521–1527. 10.1212/01.wnl.0000277459.83543.99. [PubMed: 17923614]

11. 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. Hippocampal sclerosis dementia with tauopathy. *Brain Pathol.* 2003; 13(3):263–278. [PubMed: 12946017]
12. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology.* 2006; 66(12):1837–1844. [PubMed: 16801647]
13. Bis JC, DeCarli C, Smith AV, van der Lijn F, Crivello F, Fornage M, Debette S, Shulman JM, Schmidt H, Srikanth V, Schuur M, Yu L, Choi SH, Sigurdsson S, Verhaaren BF, DeStefano AL, Lambert JC, Jack CR Jr, Struchalin M, Stankovich J, Ibrahim-Verbaas CA, Fleischman D, Zijdenbos A, den Heijer T, Mazoyer B, Coker LH, Enzinger C, Danoy P, Amin N, Arfanakis K, van Buchem MA, de Bruijn RF, Beiser A, Dufouil C, Huang J, Cavalieri M, Thomson R, Niessen WJ, Chibnik LB, Gislason GK, Hofman A, Pikula A, Amouyel P, Freeman KB, Phan TG, Oostra BA, Stein JL, Medland SE, Vasquez AA, Hibar DP, Wright MJ, Franke B, Martin NG, Thompson PM, Nalls MA, Uitterlinden AG, Au R, Elbaz A, Beare RJ, van Swieten JC, Lopez OL, Harris TB, Chouraki V, Breteler MM, De Jager PL, Becker JT, Vernooij MW, Knopman D, Fazekas F, Wolf PA, van der Lugt A, Gudnason V, Longstreth WT Jr, Brown MA, Bennett DA, van Duijn CM, Mosley TH, Schmidt R, Tzourio C, Launer LJ, Ikram MA, Seshadri S. Enhancing Neuro Imaging Genetics through Meta-Analysis C; Cohorts for H, Aging Research in Genomic Epidemiology C. Common variants at 12q14 and 12q24 are associated with hippocampal volume. *Nature genetics.* 2012; 44 (5):545–551. 10.1038/ng.2237. [PubMed: 22504421]
14. Blass DM, Hatanpaa KJ, Brandt J, Rao V, Steinberg M, Troncoso JC, Rabins PV. Dementia in hippocampal sclerosis resembles frontotemporal dementia more than Alzheimer disease. *Neurology.* 2004; 63(3):492–497. pii: 63/3/492. [PubMed: 15304580]
15. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry.* 1968; 114(512):797–811. [PubMed: 5662937]
16. Boyle PA, Wilson RS, Yu L, Barr AM, Honer WG, Schneider JA, Bennett DA. Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Ann Neurol.* 2013 10.1002/ana.23964.
17. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991; 82(4):239–259. [PubMed: 1759558]
18. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol.* 2011; 70(11):960–969. 10.1097/NEN.0b013e318232a379. [PubMed: 22002422]
19. Buchman AS, Yu L, Boyle PA, Levine SR, Nag S, Schneider JA, Bennett DA. Microvascular brain pathology and late-life motor impairment. *Neurology.* 2013; 80(8):712–718. 10.1212/WNL.0b013e3182825116. [PubMed: 23365057]
20. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL 3rd, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann DM. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol (Berl).* 2007; 114(1):5–22. [PubMed: 17579875]
21. Carr SA, Davis R, Spencer D, Smart M, Hudson J, Freeman S, Cooper GE, Schmitt FA, Markesbery WR, Danner D, Jicha GA. Comparison of recruitment efforts targeted at primary care physicians versus the community at large for participation in Alzheimer disease clinical trials. *Alzheimer disease and associated disorders.* 24(2):165–170. 10.1097/WAD.0b013e3181aba927. [PubMed: 19571728]
22. Chen-Plotkin AS, Martinez-Lage M, Sleiman PM, Hu W, Greene R, Wood EM, Bing S, Grossman M, Schellenberg GD, Hatanpaa KJ, Weiner MF, White CL 3rd, Brooks WS, Halliday GM, Kril JJ, Gearing M, Beach TG, Graff-Radford NR, Dickson DW, Rademakers R, Boeve BF, Pickering-Brown SM, Snowden J, van Swieten JC, Heutink P, Seelaar H, Murrell JR, Ghetti B, Spina S, Grafman J, Kaye JA, Woltjer RL, Mesulam M, Bigio E, Llado A, Miller BL, Alzualde A, Moreno F, Rohrer JD, Mackenzie IR, Feldman HH, Hamilton RL, Cruts M, Engelborghs S, De Deyn PP, Van Broeckhoven C, Bird TD, Cairns NJ, Goate A, Frosch MP, Riederer PF, Bogdanovic N, Lee

- VM, Trojanowski JQ, Van Deerlin VM. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. *Arch Neurol*. 2011; 68(4):488–497. 10.1001/archneurol.2011.53. [PubMed: 21482928]
23. Clark AW, White CL 3rd, Manz HJ, Parhad IM, Curry B, Whitehouse PJ, Lehmann J, Coyle JT. Primary degenerative dementia without Alzheimer pathology. *Canad J Neuro Sci Le J Canad Des Sci Neurolog*. 1986; 13(4 Suppl):462–470.
 24. Corey-Bloom J, Sabbagh MN, Bondi MW, Hansen L, Alford MF, Masliah E, Thal LJ. Hippocampal sclerosis contributes to dementia in the elderly. *Neurology*. 1997; 48(1):154–160. [PubMed: 9008511]
 25. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: the 90+ study. *Curr Alzheimer Res*. 2012; 9(6):709–717. [PubMed: 22471863]
 26. Cuenco KT, Friedland R, Baldwin CT, Guo J, Vardarajan B, Lunetta KL, Cupples LA, Green RC, DeCarli C, Farrer LA, Group MS. Association of TTR polymorphisms with hippocampal atrophy in Alzheimer disease families. *Neurobiol Aging*. 2011; 32(2):249–256. 10.1016/j.neurobiolaging.2009.02.014. [PubMed: 19328595]
 27. Davidson YS, Raby S, Foulds PG, Robinson A, Thompson JC, Sikkink S, Yusuf I, Amin H, DuPlessis D, Troakes C, Al-Sarraj S, Sloan C, Esiri MM, Prasher VP, Allsop D, Neary D, Pickering-Brown SM, Snowden JS, Mann DM. TDP-43 pathological changes in early onset familial and sporadic Alzheimer's disease, late onset Alzheimer's disease and Down's syndrome: association with age, hippocampal sclerosis and clinical phenotype. *Acta Neuropathol*. 2011; 122(6):703–713. 10.1007/s00401-011-0879-y. [PubMed: 21968532]
 28. Dawe RJ, Bennett DA, Schneider JA, Arfanakis K. Neuropathologic correlates of hippocampal atrophy in the elderly: a clinical, pathologic, postmortem MRI study. *PloS one*. 2011; 6(10):e26286. 10.1371/journal.pone.0026286. [PubMed: 22043314]
 29. Dickson DW, Baker M, Rademakers R. Common variant in GRN is a genetic risk factor for hippocampal sclerosis in the elderly. *Neurodegener Dis*. 7(1–3):170–174. 10.1159/000289231. [PubMed: 20197700]
 30. Dickson DW, Davies P, Bevona C, Van Hoeven KH, Factor SM, Grober E, Aronson MK, Crystal HA. Hippocampal sclerosis: a common pathological feature of dementia in very old (> or = 80 years of age) humans. *Acta Neuropathol*. 1994; 88(3):212–221. [PubMed: 7810292]
 31. Erten-Lyons D, Dodge HH, Woltjer R, Silbert LC, Howieson DB, Kramer P, Kaye JA. Neuropathologic basis of age-associated brain atrophy. *JAMA neurol*. 2013; 70(5):616–622. 10.1001/jamaneurol.2013.1957. [PubMed: 23552688]
 32. Fenoglio C, Galimberti D, Cortini F, Kauwe JS, Cruchaga C, Venturelli E, Villa C, Serpente M, Scalabrini D, Mayo K, Piccio LM, Clerici F, Albani D, Mariani C, Forloni G, Bresolin N, Goate AM, Scarpini E. Rs5848 variant influences GRN mRNA levels in brain and peripheral mononuclear cells in patients with Alzheimer's disease. *J Alzheimers Dis*. 2009; 18(3):603–612. 10.3233/JAD-2009-1170. [PubMed: 19625741]
 33. Furman JL, Sama DM, Gant JC, Beckett TL, Murphy MP, Bachstetter AD, Van Eldik LJ, Norris CM. Targeting astrocytes ameliorates neurologic changes in a mouse model of Alzheimer's disease. *J Neurosci*. 2012; 32(46):16129–16140. 10.1523/JNEUROSCI.2323-12.2012. [PubMed: 23152597]
 34. Furney SJ, Simmons A, Breen G, Pedrosio I, Lunnon K, Proitsi P, Hodges A, Powell J, Wahlund LO, Kloszewska I, Mecocci P, Soininen H, Tsolaki M, Vellas B, Spenger C, Lathrop M, Shen L, Kim S, Saykin AJ, Weiner MW, Lovestone S. Alzheimer's Disease Neuroimaging I, AddNeuroMed C. Genome-wide association with MRI atrophy measures as a quantitative trait locus for Alzheimer's disease. *Mol Psychiatry*. 2011; 16(11):1130–1138. 10.1038/mp.2010.123. [PubMed: 21116278]
 35. Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HB. Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. *Lancet*. 2000; 356(9230):628–634. 10.1016/S0140-6736(00)02604-0. [PubMed: 10968435]
 36. Gendron TF, Josephs KA, Petrucelli L. Review: transactive response DNA-binding protein 43 (TDP-43): mechanisms of neurodegeneration. *Neuropathol Appl Neurobiol*. 2010; 36(2):97–112. 10.1111/j.1365-2990.2010.01060.x. [PubMed: 20202122]

37. Gold G, Kovari E, Hof PR, Bouras C, Giannakopoulos P. Sorting out the clinical consequences of ischemic lesions in brain aging: a clinicopathological approach. *J Neurol Sci.* 2007; 257(1–2):17–22. S0022-510X(07)00045-7. [PubMed: 17321551]
38. Hatanpaa KJ, Blass DM, Pletnikova O, Crain BJ, Bigio EH, Hedreen JC, White CL 3rd, Troncoso JC. Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia. *Neurology.* 2004; 63(3):538–542. 63/3/538. [PubMed: 15304590]
39. Hebert SS, Wang WX, Zhu Q, Nelson PT. A study of small RNAs from cerebral neocortex of pathology-verified Alzheimer's disease, dementia with lewy bodies, hippocampal sclerosis, frontotemporal lobar dementia, and non-demented human controls. *J Alzheimers Dis.* 2013 10.3233/JAD-122350.
40. Herskowitz JH, Seyfried NT, Duong DM, Xia Q, Rees HD, Gearing M, Peng J, Lah JJ, Levey AI. Phosphoproteomic analysis reveals site-specific changes in GFAP and NDRG2 phosphorylation in frontotemporal lobar degeneration. *J Proteome Res.* 2010; 9(12):6368–6379. 10.1021/pr100666c. [PubMed: 20886841]
41. Hlobil U, Rathore C, Alexander A, Sarma S, Radhakrishnan K. Impaired facial emotion recognition in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS): side and age at onset matters. *Epilepsy Res.* 2008; 80(2–3):150–157. 10.1016/j.epilepsyres.2008.03.018. [PubMed: 18468867]
42. Hsiung GY, Fok A, Feldman HH, Rademakers R, Mackenzie IR. rs5848 polymorphism and serum progranulin level. *J Neurol Sci.* 2011; 300(1–2):28–32. 10.1016/j.jns.2010.10.009. [PubMed: 21047645]
43. Igaz LM, Kwong LK, Chen-Plotkin A, Winton MJ, Unger TL, Xu Y, Neumann M, Trojanowski JQ, Lee VM. Expression of TDP-43 C-terminal Fragments in Vitro Recapitulates Pathological Features of TDP-43 Proteinopathies. *J Biol Chem.* 2009; 284(13):8516–8524. 10.1074/jbc.M809462200. [PubMed: 19164285]
44. Imhof A, Kovari E, von Gunten A, Gold G, Rivara CB, Herrmann FR, Hof PR, Bouras C, Giannakopoulos P. Morphological substrates of cognitive decline in nonagenarians and centenarians: A new paradigm? *J Neurol Sci.* 2007
45. Jack CR Jr, Dickson DW, Parisi JE, Xu YC, Cha RH, O'Brien PC, Edland SD, Smith GE, Boeve BF, Tangalos EG, Kokmen E, Petersen RC. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology.* 2002; 58(5):750–757. [PubMed: 11889239]
46. Jellinger K. Pure hippocampal sclerosis: a rare cause of dementia mimicking Alzheimer's disease. *Neurology.* 2000; 55(5):739–740. [PubMed: 10980757]
47. Jellinger KA. Hippocampal sclerosis: a common pathological feature of dementia in very old humans. *Acta Neuropathol.* 1994; 88(6):599. [PubMed: 7879610]
48. Jellinger KA. Vascular-ischemic dementia: an update. *J Neural Transm Suppl.* 2002; 62:1–23. [PubMed: 12456046]
49. Jellinger KA. Complex tauopathies versus tangle predominant dementia. *Acta Neuropathol.* 2011; 122(4):515. 10.1007/s00401-011-0868-1. (author reply 517). [PubMed: 21932121]
50. Jellinger KA, Attems J. Prevalence and pathology of vascular dementia in the oldest-old. *J Alzheimers Dis.* 2010 C8P71311K1937840.
51. Josephs KA, Whitwell JL, Knopman DS, Hu WT, Stroh DA, Baker M, Rademakers R, Boeve BF, Parisi JE, Smith GE, Ivnik RJ, Petersen RC, Jack CR Jr, Dickson DW. Abnormal TDP-43 immunoreactivity in AD modifies clinicopathologic and radiologic phenotype. *Neurology.* 2008; 70(19 Pt 2):1850–1857. 10.1212/01.wnl.0000304041.09418.b1. [PubMed: 18401022]
52. Kamalainen A, Viswanathan J, Natunen T, Helisalmi S, Kauppinen T, Pikkariainen M, Pursiheimo JP, Alafuzoff I, Kivipelto M, Haapasalo A, Soininen H, Herukka SK, Hiltunen M. GRN variant rs5848 reduces plasma and brain levels of granulin in Alzheimer's disease patients. *J Alzheimers Dis.* 2013; 33(1):23–27. 10.3233/JAD-2012-120946. [PubMed: 22890097]
53. King A, Al-Sarraj S, Troakes C, Smith BN, Maekawa S, Iovino M, Spillantini MG, Shaw CE. Mixed tau, TDP-43 and p62 pathology in FTL associated with a C9ORF72 repeat expansion and p.Ala239Thr MAPT (tau) variant. *Acta Neuropathol.* 2013; 125(2):303–310. 10.1007/s00401-012-1050-0. [PubMed: 23053136]

54. King A, Sweeney F, Bodi I, Troakes C, Maekawa S, Al-Sarraj S. Abnormal TDP-43 expression is identified in the neo-cortex in cases of dementia pugilistica, but is mainly confined to the limbic system when identified in high and moderate stages of Alzheimer's disease. *Neuropathology*. 2010; 30(4):408–419. 10.1111/j.1440-1789.2009.01085.x. [PubMed: 20102526]
55. Kohannim, O.; Hibar, DP.; Jahanshad, N.; Stein, JL.; Hua, X.; Toga, AW.; Jack, CR., Jr; Weiner, MW.; Thompson, PM. the Alzheimer's Disease Neuroimaging I. Predicting Temporal Lobe Volume on Mri from Genotypes Using L(1)-L(2) Regularized Regression. *Proceedings/IEEE International Symposium on Biomedical Imaging: from nano to macro IEEE International Symposium on Biomedical Imaging*; 2012. p. 1160-1163. 10.1109/ISBI.2012.6235766
56. Kohannim O, Hibar DP, Stein JL, Jahanshad N, Hua X, Rajagopalan P, Toga AW, Jack CR Jr, Weiner MW, de Zubicaray GI, McMahon KL, Hansell NK, Martin NG, Wright MJ, Thompson PM. Alzheimer's Disease Neuroimaging I. Discovery and replication of gene influences on brain structure using LASSO regression. *Frontiers Neurosci*. 2012; 6:115. 10.3389/fn.ins.2012.00115.
57. Kovacs GG, Molnar K, Laszlo L, Strobel T, Botond G, Honigschnabl S, Reiner-Concin A, Palkovits M, Fischer P, Budka H. A peculiar constellation of tau pathology defines a subset of dementia in the elderly. *Acta Neuropathol*. 2011; 122(2):205–222. 10.1007/s00401-011-0819-x. [PubMed: 21437732]
58. Kraybill ML, Larson EB, Tsuang DW, Teri L, McCormick WC, Bowen JD, Kukull WA, Leverenz JB, Cherrier MM. Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology*. 2005; 64(12):2069–2073. 64/12/2069. [PubMed: 15985574]
59. Lee EB, Lee VM, Trojanowski JQ. Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration. *Nat Rev Neurosci*. 2012; 13(1):38–50. 10.1038/nrn3121. [PubMed: 22127299]
60. Lee EB, Lee VM, Trojanowski JQ, Neumann M. TDP-43 immunoreactivity in anoxic, ischemic and neoplastic lesions of the central nervous system. *Acta Neuropathol*. 2008; 115(3):305–311. 10.1007/s00401-007-0331-5. [PubMed: 18087705]
61. Leverenz JB, Agustin CM, Tsuang D, Peskind ER, Edland SD, Nochlin D, DiGiacomo L, Bowen JD, McCormick WC, Teri L, Raskind MA, Kukull WA, Larson EB. Clinical and neuropathological characteristics of hippocampal sclerosis: a community-based study. *Arch Neurol*. 2002; 59(7):1099–1106. noc10247. [PubMed: 12117357]
62. Leverenz JB, Lipton AM. Clinical aspects of hippocampal sclerosis. *Handb Clin Neurol*. 2008; 89:565–567. S0072-9752(07)01252-3. [PubMed: 18631778]
63. Ling H, Holton JL, Lees AJ, Revesz T. TDP-43 pathology is present in most post-encephalitic Parkinsonism brains. *Neuropathol Appl Neurobiol*. 2013 10.1111/nan.12067.
64. Lippa CF, Fujiwara H, Mann DM, Giasson B, Baba M, Schmidt ML, Nee LE, O'Connell B, Pollen DA, St George-Hyslop P, Ghetti B, Nochlin D, Bird TD, Cairns NJ, Lee VM, Iwatsubo T, Trojanowski JQ. Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. *Am J Pathol*. 1998; 153(5):1365–1370. [PubMed: 9811326]
65. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJ, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DM. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol*. 2010; 119(1):1–4. 10.1007/s00401-009-0612-2. [PubMed: 19924424]
66. Martinez A, Carmona M, Portero-Otin M, Naudi A, Pamplona R, Ferrer I. Type-dependent oxidative damage in frontotemporal lobar degeneration: cortical astrocytes are targets of oxidative damage. *J Neuropathol Exp Neurol*. 2008; 67(12):1122–1136. 10.1097/NEN.0b013e31818e06f3. [PubMed: 19018247]
67. McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW, Perl DP, Hedley-Whyte ET, Price B, Sullivan C, Morin P, Lee HS, Kubilus CA, Daneshvar DH, Wulff M, Budson AE. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2010; 69(9):918–929. 10.1097/NEN.0b013e3181ee7d85. [PubMed: 20720505]
68. Meda SA, Koran ME, Pryweller JR, Vega JN, Thornton-Wells TA. Alzheimer's Disease Neuroimaging I. Genetic interactions associated with 12-month atrophy in hippocampus and

- entorhinal cortex in Alzheimer's Disease Neuroimaging Initiative. *Neurobiol Aging*. 2013; 34(5): 1518, e9–1518.e1518. 10.1016/j.neurobiolaging.2012.09.020. [PubMed: 23107432]
69. Meda SA, Narayanan B, Liu J, Perrone-Bizzozero NI, Stevens MC, Calhoun VD, Glahn DC, Shen L, Risacher SL, Saykin AJ, Pearlson GD. A large scale multivariate parallel ICA method reveals novel imaging-genetic relationships for Alzheimer's disease in the ADNI cohort. *Neuroimage*. 2012; 60(3):1608–1621. 10.1016/j.neuroimage.2011.12.076. [PubMed: 22245343]
 70. Melville SA, Buross J, Parrado AR, Vardarajan B, Logue MW, Shen L, Risacher SL, Kim S, Jun G, DeCarli C, Lunetta KL, Baldwin CT, Saykin AJ, Farrer LA. Alzheimer's Disease Neuroimaging I. Multiple loci influencing hippocampal degeneration identified by genome scan. *Ann Neurol*. 2012; 72(1):65–75. 10.1002/ana.23644. [PubMed: 22745009]
 71. Miki Y, Mori F, Hori E, Kaimori M, Wakabayashi K. Hippocampal sclerosis with four-repeat tau-positive round inclusions in the dentate gyrus: a new type of four-repeat tauopathy. *Acta Neuropathol*. 2009; 117(6):713–718. 10.1007/s00401-009-0531-2. [PubMed: 19360425]
 72. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT. National institute on aging-Alzheimer's association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012; 123(1):1–11. 10.1007/s00401-011-0910-3. [PubMed: 22101365]
 73. Mortimer JA. The Nun Study: risk factors for pathology and clinical-pathologic correlations. *Curr Alzheimer Res*. 2012; 9(6):621–627. [PubMed: 22471869]
 74. Murray ME, DeJesus-Hernandez M, Rutherford NJ, Baker M, Duara R, Graff-Radford NR, Wszolek ZK, Ferman TJ, Josephs KA, Boylan KB, Rademakers R, Dickson DW. Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in C9ORF72. *Acta Neuropathol*. 2011; 122(6):673–690. 10.1007/s00401-011-0907-y. [PubMed: 22083254]
 75. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol*. 2011; 10(9):785–796. S1474-4422(11)70156-9. [PubMed: 21802369]
 76. Nelson PT, Abner EL, Schmitt FA, Kryscio RJ, Jicha GA, Santacruz K, Smith CD, Patel E, Markesbery WR. Brains with medial temporal lobe neurofibrillary tangles but no neuritic amyloid plaques are a diagnostic dilemma but may have pathogenetic aspects distinct from Alzheimer disease. *J Neuropathol Exp Neurol*. 2009; 68(7):774–784. 10.1097/NEN.0b013e3181aacbe9. [PubMed: 19535994]
 77. Nelson PT, Abner EL, Schmitt FA, Kryscio RJ, Jicha GA, Smith CD, Davis DG, Poduska JW, Patel E, Mendiondo MS, Markesbery WR. Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. *Brain Pathol*. 2010; 20(1):66–79. 10.1111/j.1750-3639.2008.00244.x. [PubMed: 19021630]
 78. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, Abner EL, Smith CD, Van Eldik LJ, Kryscio RJ, Scheff SW. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol*. 2011; 121(5):571–587. 10.1007/s00401-011-0826-y. [PubMed: 21516511]
 79. Nelson PT, Jicha GA, Schmitt FA, Liu H, Davis DG, Mendiondo MS, Abner EL, Markesbery WR. Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles "do count" when staging disease severity. *J Neuropathol Exp Neurol*. 2007; 66(12):1136–1146. [PubMed: 18090922]
 80. Nelson PT, Schmitt FA, Lin Y, Abner EL, Jicha GA, Patel E, Thomason PC, Neltner JH, Smith CD, Santacruz KS, Sonnen JA, Poon LW, Gearing M, Green RC, Woodard JL, Van Eldik LJ, Kryscio RJ. Hippocampal sclerosis in advanced age: clinical and pathological features. *Brain*. 2011; 134(Pt 5):1506–1518. 10.1093/brain/awr053. [PubMed: 21596774]
 81. Nelson PT, Smith CD, Abner EA, Schmitt FA, Scheff SW, Davis GJ, Keller JN, Jicha GA, Davis D, Wang-Xia W, Hartman A, Katz DG, Markesbery WR. Human cerebral neuropathology of Type 2 diabetes mellitus. *Biochim Biophys Acta*. 2009; 1792(5):454–469. 10.1016/j.bbdis.2008.08.005. [PubMed: 18789386]

82. Neumann M, Kwong LK, Lee EB, Kremmer E, Flatley A, Xu Y, Forman MS, Troost D, Kretschmar HA, Trojanowski JQ, Lee VM. Phosphorylation of S409/410 of TDP-43 is a consistent feature in all sporadic and familial forms of TDP-43 proteinopathies. *Acta Neuropathol.* 2009; 117(2):137–149. 10.1007/s00401-008-0477-9. [PubMed: 19125255]
83. Norris CM, Kadish I, Blalock EM, Chen KC, Thibault V, Porter NM, Landfield PW, Kraner SD. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. *J Neurosci.* 2005; 25(18):4649–4658. 25/18/4649. [PubMed: 15872113]
84. Pao WC, Dickson DW, Crook JE, Finch NA, Rademakers R, Graff-Radford NR. Hippocampal Sclerosis in the Elderly: genetic and Pathologic Findings Some Mimicking AlzheimerDisease Clinically. *Alzheimer Dis Assoc disord.* 2011 10.1097/WAD.0b013e31820f8f50.
85. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR Jr, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW. Alzheimer's disease neuroimaging initiative (ADNI): clinical characterization. *Neurology.* 2010; 74(3):201–209. 10.1212/WNL.0b013e3181cb3e25. [PubMed: 20042704]
86. Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H, Kokmen E. Neuropathologic features of amnesic mild cognitive impairment. *Arch Neurol.* 2006; 63(5):665–672. 10.1001/archneur.63.5.665. [PubMed: 16682536]
87. Petrovitch H, Ross GW, He Q, Uyehara-Lock J, Markesbery W, Davis D, Nelson J, Masaki K, Launer L, White LR. Characterization of Japanese-American men with a single neo-cortical AD lesion type. *Neurobiol Aging.* 2007 10.1016/j.neurobiolaging.2007.03.026.
88. Polvikoski TM, van Straaten EC, Barkhof F, Sulkava R, Aronen HJ, Niinisto L, Oinas M, Scheltens P, Erkinjuntti T, Kalaria RN. Frontal lobe white matter hyperintensities and neurofibrillary pathology in the oldest old. *Neurology.* 2010; 75(23):2071–2078. 10.1212/WNL.0b013e318200d6f9. [PubMed: 21048201]
89. Potkin SG, Guffanti G, Lakatos A, Turner JA, Kruggel F, Fallon JH, Saykin AJ, Orro A, Lupoli S, Salvi E, Weiner M, Macciardi F. Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease. *PLoS ONE.* 2009; 4(8):e6501. 10.1371/journal.pone.0006501. [PubMed: 19668339]
90. Probst A, Taylor KI, Tolnay M. Hippocampal sclerosis dementia: a reappraisal. *Acta Neuropathol.* 2007; 114(4):335–345. 10.1007/s00401-007-0262-1. [PubMed: 17639426]
91. Rauramaa T, Pikkarainen M, Englund E, Ince PG, Jellinger K, Paetau A, Alafuzoff I. TAR-DNA binding protein-43 and alterations in the hippocampus. *J Neural Transm.* 2011 10.1007/s00702-010-0574-5.
92. Rauramaa T, Pikkarainen M, Englund E, Ince PG, Jellinger K, Paetau A, Alafuzoff I. Consensus recommendations on pathologic changes in the hippocampus: a postmortem multi-center inter-rater study. *J Neuropathol Exp Neurol.* 2013; 72(6):452–461. 10.1097/NEN.0b013e318292492a. [PubMed: 23656988]
93. Robinson JL, Geser F, Corrada MM, Berlau DJ, Arnold SE, Lee VM, Kawas CH, Trojanowski JQ. Neocortical and hippocampal amyloid-beta and tau measures associate with dementia in the oldest-old. *Brain.* 2011; 134(Pt 12):3708–3715. 10.1093/brain/awr308. [PubMed: 22120149]
94. Rosenberg CK, Pericak-Vance MA, Saunders AM, Gilbert JR, Gaskell PC, Hulette CM. Lewy body and Alzheimer pathology in a family with the amyloid-beta precursor protein APP717 gene mutation. *Acta Neuropathol.* 2000; 100(2):145–152. [PubMed: 10963361]
95. Roth M, Tomlinson BE, Blessed G. Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects. *Nature.* 1966; 209(5018):109–110. [PubMed: 5927229]
96. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology.* 2012; 119(3):571–580. 10.1016/j.ophtha.2011.09.027. [PubMed: 22176800]
97. Saing T, Dick MC, Nelson PT, Kim RC, Cribbs DH, Head E. Frontal cortex neuropathology in dementia Pugilistica. *J Neurotrauma.* 2011 10.1089/neu.2011.1957.

98. Schmitt FA, Nelson PT, Abner E, Scheff S, Jicha GA, Smith C, Cooper G, Mendiondo M, Danner DD, Van Eldik LJ, Caban-Holt A, Lovell MA, Kryscio RJ. University of Kentucky Sanders-Brown healthy brain aging volunteers: donor characteristics, procedures and neuropathology. *Curr Alzheimer Res.* 2012; 9(6):724–733. [PubMed: 22471862]
99. Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis.* 2009 10.3233/JAD-2009-1227.
100. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007; 69(24):2197–2204. 10.1212/01.wnl.0000271090.28148.24. [PubMed: 17568013]
101. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol.* 2009; 66(2):200–208. 10.1002/ana.21706. [PubMed: 19743450]
102. Shen L, Kim S, Risacher SL, Nho K, Swaminathan S, West JD, Foroud T, Pankratz N, Moore JH, Sloan CD, Huentelman MJ, Craig DW, DeChairo BM, Potkin SG, Jack CR Jr, Weiner MW, Saykin AJ. Alzheimer's Disease Neuroimaging I. Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: A study of the ADNI cohort. *Neuroimage.* 2010; 53(3):1051–1063. 10.1016/j.neuroimage.2010.01.042. [PubMed: 20100581]
103. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol.* 2007; 62(4):406–413. 10.1002/ana.21208. [PubMed: 17879383]
104. Stein JL, Hua X, Morra JH, Lee S, Hibar DP, Ho AJ, Leow AD, Toga AW, Sul JH, Kang HM, Eskin E, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen AN, Corneveaux JJ, Stephan DA, Webster J, DeChairo BM, Potkin SG, Jack CR Jr, Weiner MW, Thompson PM. Alzheimer's Disease Neuroimaging I. Genome-wide analysis reveals novel genes influencing temporal lobe structure with relevance to neurodegeneration in Alzheimer's disease. *Neuroimage.* 2010; 51(2):542–554. 10.1016/j.neuroimage.2010.02.068. [PubMed: 20197096]
105. Stein JL, Medland SE, Vasquez AA, et al. Identification of common variants associated with human hippocampal and intracranial volumes. *Nature Genet.* 2012; 44 (5):552–561. 10.1038/ng.2250. [PubMed: 22504417]
106. Thompson WL, Van Eldik LJ. Inflammatory cytokines stimulate the chemokines CCL2/MCP-1 and CCL7/MCP-3 through NFkB and MAPK dependent pathways in rat astrocytes [corrected]. *Brain Res.* 2009; 1287:47–57. 10.1016/j.brainres.2009.06.081. [PubMed: 19577550]
107. Tremblay C, St-Amour I, Schneider J, Bennett DA, Calon F. Accumulation of transactive response DNA binding protein 43 in mild cognitive impairment and Alzheimer disease. *J Neuropathol Exp Neurol.* 2011; 70(9):788–798. 10.1097/NEN.0b013e31822c62cf. [PubMed: 21865887]
108. Troncoso JC, Kawas CH, Chang CK, Folstein MF, Hedreen JC. Lack of association of the apoE4 allele with hippocampal sclerosis dementia. *Neurosci Lett.* 1996; 204(1–2):138–140. 0304-3940(96)12331-4. [PubMed: 8929997]
109. Tschanz JT, Treiber K, Norton MC, Welsh-Bohmer KA, Toone L, Zandi PP, Szekely CA, Lyketsos C, Breitner JC. A population study of Alzheimer's disease: findings from the Cache County Study on Memory, Health, and Aging. *Care Manag J.* 2005; 6(2):107–114. [PubMed: 16544872]
110. Tyas SL, Snowdon DA, Desrosiers MF, Riley KP, Markesbery WR. Healthy ageing in the Nun Study: definition and neuropathologic correlates. *Age Ageing.* 2007; 36(6):650–655. afm120. [PubMed: 17906306]
111. Van Deerlin VM, Leverenz JB, Bekris LM, Bird TD, Yuan W, Elman LB, Clay D, Wood EM, Chen-Plotkin AS, Martinez-Lage M, Steinbart E, McCluskey L, Grossman M, Neumann M, Wu IL, Yang WS, Kalb R, Galasko DR, Montine TJ, Trojanowski JQ, Lee VM, Schellenberg GD, Yu CE. TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. *Lancet Neurol.* 2008; 7(5):409–416. 10.1016/S1474-4422(08)70071-1. [PubMed: 18396105]

112. Van Langenhove T, van der Zee J, Van Broeckhoven C. The molecular basis of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum. *Ann Med*. 2012; 44(8):817–828. 10.3109/07853890.2012.665471. [PubMed: 22420316]
113. Vinters HV. Cerebrovascular disease—practical issues in surgical and autopsy pathology. *Current Topics Pathol Ergebnisse der Pathologie*. 2001; 95:51–99.
114. White L. Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia aging study. *J Alzheimers Dis*. 2009; 18(3):713–725. UV586J3644H2V552. [PubMed: 19661625]
115. White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross GW, Masaki K, Launer L, Markesbery WR. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. *Ann N Y Acad Sci*. 2002; 977:9–23. [PubMed: 12480729]
116. Wilson AC, Dugger BN, Dickson DW, Wang DS. TDP-43 in aging and Alzheimer's disease: a review. *Int J Clin Exp Pathol*. 2011; 4(2):147–155. [PubMed: 21326809]
117. Wolf DS, Gearing M, Snowdon DA, Mori H, Markesbery WR, Mirra SS. Progression of regional neuropathology in Alzheimer disease and normal elderly: findings from the Nun study. *Alzheimer Dis Assoc Disord*. 1999; 13(4):226–231. [PubMed: 10609672]
118. Wong KT, Allen IV, McQuaid S, McConnell R. An immunohistochemical study of neurofibrillary tangle formation in post-encephalitic Parkinsonism. *Clin Neuropathol*. 1996; 15(1):22–25. [PubMed: 8998852]
119. Zabar Y, Carson KA, Troncoso JC, Kawas CH. Dementia due to hippocampal sclerosis: clinical features and comparison to Alzheimer's Disease. *Neurology*. 1998; 50(4 Suppl 4):A59–A60.
120. Zarow C, Sitzer TE, Chui HC. Understanding hippocampal sclerosis in the elderly: epidemiology, characterization, and diagnostic issues. *Current Neurol Neurosci Reports*. 2008; 8(5):363–370.
121. Zarow C, Vinters HV, Ellis WG, Weiner MW, Mungas D, White L, Chui HC. Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. *Ann Neurol*. 2005; 57(6):896–903. 10.1002/ana.20503. [PubMed: 15929035]
122. Zarow C, Wang L, Chui HC, Weiner MW, Csernansky JG. MRI shows more severe hippocampal atrophy and shape deformation in hippocampal sclerosis than in Alzheimer's disease. *Int J Alzheimers Dis*. 2011; 2011:483972. 10.4061/2011/483972. [PubMed: 21547227]
123. Zarow C, Weiner MW, Ellis WG, Chui HC. Prevalence, laterality, and comorbidity of hippocampal sclerosis in an autopsy sample. *Brain Behav*. 2012; 2(4):435–442. 10.1002/brb3.66. [PubMed: 22950047]

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 homogeneously *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 μ m; **c, d** = 50 μ m

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, astrogliosis, 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

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/su/mmarytables.html>

Neurocognitive test scores in HS-Aging:

Word list delayed recall (WLD)/Verbal fluency (VF) ratio

N= 43 cases with subsequent autopsy confirmed HS-Aging pathology, and N=75 controls

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