Neurobiology of Aging 37 (2016) 1–11

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

# Brain pathologies in extreme old age

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ARTICLE INFO

*Article history:*
Received 14 August 2015
Received in revised form 28 September 2015
Accepted 8 October 2015
Available online 19 October 2015

*Keywords:*
KATP
TDP-43
Stroke
VCID
Arteriosclerosis
Lipohyalinosis
Synucleinopathy
NFT
Neuropathology
SUR2
Oldest-old
PART

ABSTRACT

With an emphasis on evolving concepts in the field, we evaluated neuropathologic data from very old research volunteers whose brain autopsies were performed at the University of Kentucky Alzheimer's Disease Center, incorporating data from the Georgia Centenarian Study ($n = 49$ cases included), Nun Study ($n = 17$), and University of Kentucky Alzheimer's Disease Center ($n = 11$) cohorts. Average age of death was 102.0 (range: 98–107) years overall. Alzheimer's disease pathology was not universal (62% with "moderate" or "frequent" neuritic amyloid plaque densities), whereas frontotemporal lobar degeneration was absent. By contrast, some hippocampal neurofibrillary tangles (including primary age-related tauopathy) were observed in every case. Lewy body pathology was seen in 16.9% of subjects and hippocampal sclerosis of aging in 20.8%. We describe anatomic distributions of pigment-laden macrophages, expanded Virchow-Robin spaces, and arteriolosclerosis among Georgia Centenarians. Moderate or severe arteriolosclerosis pathology, throughout the brain, was associated with both hippocampal sclerosis of aging pathology and an *ABCC9* gene variant. These results provide fresh insights into the complex cerebral multimorbidity, and a novel genetic risk factor, at the far end of the human aging spectrum.



## 1. Introduction

Among clinicians and researchers, there is an increasing appreciation of the heterogeneous nature of pathologies in the brains of persons who survive to extreme old age. The published literature includes multiple studies of centenarians that came to autopsy. Research subjects in those studies were characterized neuropathologically with regard to the presence and severities of Alzheimer's disease (AD), Lewy body diseases (LBD), hippocampal sclerosis of aging (HS-aging), cerebrovascular diseases (CVD), and other neuropathologic features (Giannakopoulos et al., 1993, 1995a, 1995b, 2008; Gold et al., 2000; Imhof et al., 2007; Itoh et al., 1998; Miller et al., 2010; Mizutani and Shimada, 1992; von Gunten et al., 2010). In addition to prior case series, there have been excellent reviews of the findings (Hof et al., 1996; Imhof et al., 2007; von Gunten et al., 2010). Both practical and theoretical challenges have been identified in terms of accurate clinical-pathologic correlation in centenarians (Ding et al., 2006a, 2006b; Garcia-Sierra et al., 2000;

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http://dx.doi.org/10.1016/j.neurobiolaging.2015.10.009

Gold et al., 2000; Jellinger and Attems, 2010b; Nelson et al., 2011b; Poon et al., 2007; Silver et al., 2002; Wang et al., 1999), and most of the autopsy series that focused on centenarians have been relatively small.

In addition to what can be learned from prior studies, there are some new ideas and pathologic designations based on an evolving understanding in the field, including increased appreciation of the complexities of human brain diseases. Awareness is growing that the medical conditions among extremely old individuals may be distinct in important ways from those that affect individuals in the 70- to 90-year age range (Arnold et al., 2010; Evert et al., 2003; Nelson et al., 2011a; Richmond et al., 2012). There also remain some controversial issues. For example, a hypothesis has been proffered that there is a "dissociation" between pathology and clinical outcomes among the "oldest old" (Imhof et al., 2007; Savva et al., 2009), but this hypothesis has also been countered (Nelson et al., 2012). Also, the pathologic condition characterized by predominantly subcortical/hippocampal neurofibrillary tangles (NFTs) without amyloid plaques in the elderly was recently termed primary age-related tauopathy (PART) (Crary et al., 2014). There have been arguments presented for and against the hypothesis that the pathologically defined PART cases should be considered a distinct condition or a subset of AD (Braak and Del Tredici, 2014; Duyckaerts et al., 2015; Jack, 2014; Jellinger et al., 2015). A salient consideration is whether PART inevitably progresses to full-blown AD. It has been shown that ~20% of individuals have PART pathology by their ninth decade (the remainder some degree of AD with amyloid plaques) (Braak et al., 2011); so, a centenarian group of comparable size with PART would seem to argue against the hypothesis that PART cases tend to progress inevitably to AD.

There also are diagnostic "border zones" that are awaiting clearer definitions, such as is the case for HS-aging and aging-related hippocampal TAR-DNA–binding protein-43 (TDP-43)–immunoreactive inclusions. These common pathologic features overlap with each other (Amador-Ortiz et al., 2007), and both have been associated with cognitive impairment in aging (Keage et al., 2014; Nelson et al., 2010a). However, there is no consensus-based diagnostic rubric or nomenclature. Studies before 2006 were necessarily unaware that TDP-43 pathology even existed (Neumann et al., 2006). It has been suggested that TDP-43 pathology seen in aged individuals may be a "forme fruste" (atypical, early, or otherwise diminished) manifestation of frontotemporal lobar degeneration (FTLD)–type pathogenetic changes (Dickson, 2009). Many nonagenarians (5%–30% in different autopsy series) have HS-aging with TDP-43 pathology (Kovacs et al., 2013; Leverenz et al., 2002; Nag et al., 2015; Nelson et al., 2011a, 2013; Zarow et al., 2012). It is interesting, therefore, to test whether there is any evidence of disease progression in the subsequent age group—is there an appreciable subset of centenarians with full-blown FTLD-TDP?

The goals of the present study were to obtain insights into the pathologies of extreme old age, emphasizing evolving and/or controversial concepts. To address these issues in a relatively large sample of research volunteers followed to autopsy, we here report data from the combined cohorts of the Georgia Centenarian Study (GCS, Poon et al., 1992), Nun Study (Snowdon et al., 1997; Tyas et al., 2007), and University of Kentucky Alzheimer's Disease Center (UK-ADC, Schmitt et al., 2012). The neuropathologic assessments were all performed and analyzed at the same research center (UK-ADC). We also examined the actuarial tables from the US Social Security Administration to frame the context of the study and to help convey the survival bias that relates to this group of individuals. We previously identified a single-nucleotide polymorphism (SNP) that was associated with risk for HS-aging pathology (Nelson et al., 2014, 2015), and here, we tested whether that gene variant (rs704178/rs704180 in the *ABCC9* gene) is associated with autopsy-confirmed HS-aging and brain arteriolosclerosis pathologies among individuals of extreme old age.

## 2. Methods

All protocols were performed with institutional review board approval from the respective institutions. Patients who came to autopsy from the UK-ADC, Nun Study (Wolf et al., 1999), and GCS (Poon et al., 2007) cohorts were the basis for the study. Details of the UK-ADC, Nun Study, and GCS recruitment have been described elsewhere (Arnold et al., 2010; Gosche et al., 2002; Hensley et al., 2010; Nelson et al., 2007; Poon et al., 1992; Riley et al., 2002; Schmitt et al., 2001). Mental status testing (Schmitt et al., 2000) employed cognitive instruments that included the Mini-Mental State Examination (MMSE, Davey et al., 2013; Folstein et al., 1975).

Pathologic assessments were performed at the University of Kentucky on all the cases, and the methodology has been described in detail (Davis et al., 1999; Nelson et al., 2007, 2009a; Riley et al., 2002; Wolf et al., 1999). Braak NFT staging and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) quantification of neuritic amyloid plaques (NPs) were as described previously (Braak and Braak, 1991; Mirra, 1997). Lewy body pathologies were evaluated according to the consensus-based recommendations (McKeith et al., 2000, 2004). The neuropathologic criterion for HS-aging was neuron loss and gliosis in the hippocampal formation, not readily ascribable to another pathology such as neurofibrillary tangles or localizable infarction (Montine et al., 2012, Nelson et al., 2013). Aberrant TDP-43 immunohistochemistry was performed as described previously and refers to staining that is cytoplasmic, neuritic, or tangle like (Nelson et al., 2011b). For *ABCC9* SNP analyses, DNA was obtained from fresh (frozen) tissue and the SNP characterized as previously described (Nelson et al., 2014) using TaqMan-based SNP assays (Life Technologies). Otherwise, the results relate to the findings on available hematoxylin and eosin (H&E)–stained slides.

Semiquantitative assessment of the vascular pathologies was performed on all available H&E-stained slides for each of the GCS cohort's cases (22 different brain regions). These data were collected blinded to all clinical information and previous pathology diagnoses and were scored according to semiquantitative scoring methods. Virchow-Robin space alterations were graded based on 2 parameters: the severity around a given vessel and the degree of involvement of vessels throughout the section. The severity was graded on a 4-point scale, ranging from 0 to 3+. The degree of involvement was graded in quartiles (0, 1%–25%, 26%–50%, 51%–75%, and 76%–100%).

The presence of perivascular pigment-laden macrophages was also documented using H&E-stained sections. The entire slide in each section was examined (both gray and white matter) for the presence of perivascular macrophages. The number of vessels involved in both gray and white matter was combined to generate a single result. Up to 4 vessels were recorded individually; if the number of vessels involved was >4, the data were collapsed into a "≥5" category.

For statistical analyses of arteriolosclerosis pathology in the GCS data, data were imported into SAS/STAT, version 9.3. All arteriolosclerosis ratings in 22 brain regions were coded according to a 0–3 severity scale. Less than 4% of slides were missing in terms of H&E evaluation of arteriolosclerosis severity

**Table 1**
Cohorts with clinical and *APOE* information

| Cohorts | Overall ($n$) | Centenarians included ($n$) | Average age death (overall) | Age of death (range) | M/F | Average final MMSE ± SD | *APOE* ε4 allele/genotype |
|---|---|---|---|---|---|---|---|
| GCS | 49 | 41 | 102.0 | 98–107 | 6/43 | 13.7 ± 9.3 | 8/48 |
| Nun Study | 17 | 17 | 102.2 | 100–107 | 0/17 | 16.2 ± 8.9 | 1/17 |
| UK-ADC | 11 | 11 | 101.3 | 100–105 | 2/9 | 22.1 ± 6.5 | 2/11 |
| Total/overall | 77 | 69 | 102.0 | 98–107 | 8/69 | 15.4 ± 9.2 | 11/76 |

Key: APOE ε4, the proportion of genotyped cases that had 1 apolipoprotein E ε4 allele (no subject had 2 ε4 alleles); GCS, Georgia Centenarian Study; M/F, male/female; MMSE, Folstein Mini-Mental State Examination (Folstein et al., 1975); SD, standard deviation; UK-ADC, University of Kentucky Alzheimer's Disease Center.

(26 cases had complete data, 10 cases were missing 1 region, 10 cases were missing 2 regions, and 3 cases were missing 3 regions). For the comparisons we wished to perform (see subsequently), the main research questions related to the frequency of moderate-to-severe arteriolosclerosis in the sampled brain regions. The arteriolosclerosis ratings were recoded into dummy indicators for presence of at least moderate arteriolosclerosis versus absent or mild severity. Indicators for each case were summed to produce a count of brain regions with at least moderate arteriolosclerosis. The number of affected regions was scaled by the number of regions with nonmissing data. In separate models, we used Poisson regression to estimate the effect of TDP-43, HS-aging, and AD pathologies, and *ABCC9* genotype, on mean number of regions with at least moderate arteriosclerosis. In each model, pathology or genotype group was the only predictor.

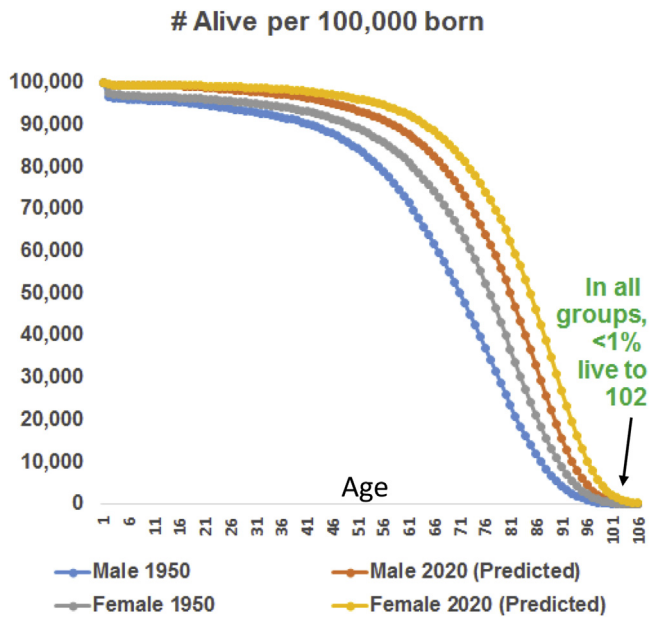


**Fig. 1.** Actuarial tables from the US Social Security Administration to depict the expected number of persons alive per 100,000. The 4 curves represent data from the year 1950 (male: blue and female: gray) and predicted the results for the year 2020 (male: orange and female yellow) in the United States. Note that although females live longer than males, the effect of the birth cohort is even stronger than gender. There is a dramatic increase in survival between the years 1950 and 2020. However, those reaching the age of 102 years in both groups—whether male or female—comprise <1% of individuals. These data indicate that social and medical changes are increasing survival for many, but centenarians will constitute the outer limits of human life span for the near future. The Web site to describe methodology is http://www.socialsecurity.gov/OACT/NOTES/as120/LifeTables_Body.html. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

## 3. Results

The research cohort comprised a sample of very old individuals ($n$ = 77 total) accrued by combining data from the GCS ($n$ = 49), Nun Study ($n$ = 17), and UK-ADC ($n$ = 11) autopsy cohorts (Table 1). Average overall age at death was 102.0 (range: 98–107 years; 8 cases were 98 or 99 years old at death). Many of the subjects were cognitively impaired before dying (average final MMSE score was 15.5 of 30, range 0–30). One individual had final MMSE score of 30, 5 individuals had final MMSE scores of 28, and each of these 6 brains had Braak NFT stages ≤III. The individual with final MMSE score of 30 was a woman who lived independently and had Braak NFT stage of II but no amyloid plaques. None of the research volunteers lacked any NFTs. For those with Braak NFT stages I–II, the average final MMSE score was 20.0 (standard deviation 7.4). By contrast, among those with Braak NFT stages V or VI ($n$ = 22), the average final MMSE score was 9.1 (standard deviation 8.6). The entire sample was skewed toward females (69/77 cases). See Supplementary Table 1 that contains detailed clinical and pathologic descriptions on each research subject.

To provide contextual information on the human aging spectrum in relation to the age of the individuals in the present study, we accessed actuarial data from the Social Security Administration (Fig. 1). These provide information from an authoritative source about the proportion of individuals expected to be alive from 100,000 births, and the "survival curves" include both past data and future predictions. As expected, females have longer life span than males. Using data referent to 2 dates, 1950 and 2020 projections, it is clear that a shift has been seen over time, favoring longer life span for both genders. That shift is more pronounced than the gender effect. However, even after that shift, <1% of individuals of both genders would be expected by the year 2020 to live beyond their 102nd birthday, which indicates that the present study sample reflects the very end of the human aging spectrum, at least for the near future.

Among the research volunteers included in the present study, AD-type changes—NFTs and NPs—were frequently seen. The pathologic stages defined by Braak and Braak (NFT stages) and

**Table 2**
AD-type pathologic changes, showing Braak NFT stages and CERAD NP grading, for the combined study cohort

| CERAD NP grading | Braak NFT stages | | | | | | | ND | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | I | II | III | IV | V | VI | | |
| None | 0 | 3 | 7 | 5 | 0 | 0 | 0 | 1 | 16 |
| Sparse | 0 | 0 | 4 | 1 | 2 | 3 | 2 | 1 | 13 |
| Moderate/severe | 0 | 2 | 10 | 8 | 8 | 12 | 5 | 3 | 48 |
| | | 5 | 21 | 14 | 10 | 15 | 7 | 5 | 77 |

Key: AD, Alzheimer's disease; ND, Braak staging was not performed, usually because of the presence of severe hippocampal sclerosis precluding reliable Braak staging; NFT, neurofibrillary tangle; NP, neuritic amyloid plaque.

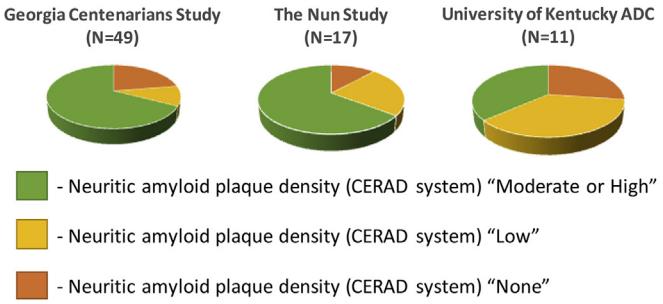


**Fig. 2.** Distribution of density of neuritic amyloid plaques (NPs), a defining pathologic hallmark of Alzheimer's disease (AD), in the 3 cohorts. Neuritic plaques are graded according to the CERAD system (Mirra, 1997). Note that in all the 3 autopsy cohorts—Georgia Centenarian Study (Poon et al., 1992), Nun Study (Snowdon et al., 1997; Tyas et al., 2007), and University of Kentucky Alzheimer's Disease Center (UK-ADC) (Schmitt et al., 2012)—there is a sizeable minority of individuals that have "low" or "none" NPs. These results seem to indicate that AD pathology, as operationalized by the presence of NPs, is not inevitable with brain aging.

CERAD neuritic plaque densities are shown in Table 2, and 5 cases were not given a Braak stage because of extensive HS-aging pathology. Further analyses revealed that there was some variation between the different research cohorts, but, in each, there was a substantial minority of individuals with no NPs (CERAD "none," Fig. 2). The variation between cohorts may reflect the small sample sizes in each cohort. Moreover, in the combined group, 37% of cases had either "none" or "sparse" NPs. Approximately 21% in the combined group had NFTs without NPs (i.e., PART), and there were no cases with amyloid plaques, but no NFTs, because all cases had some NFTs (Fig. 3).

Non-AD pathologies were predominantly LBD, HS-aging/TDP-43, and CVD. The DLB pathology was either "limbic type" (9/77, 12%) or "neocortical type" (4/77, 5%) (Table 3). Hippocampal sclerosis pathology was seen on H&E stain in 20.8% (16/77) of cases, with 12/15 (80%) cases tested immunohistochemically being positive for TDP-43 pathology in the hippocampal formation (Table 4). There were 9 cases (12% of the cohort) with hippocampal TDP-43 pathology but no HS seen by H&E stain, with the caveat that TDP-43 could not be assessed in 9 of the cases. The majority of

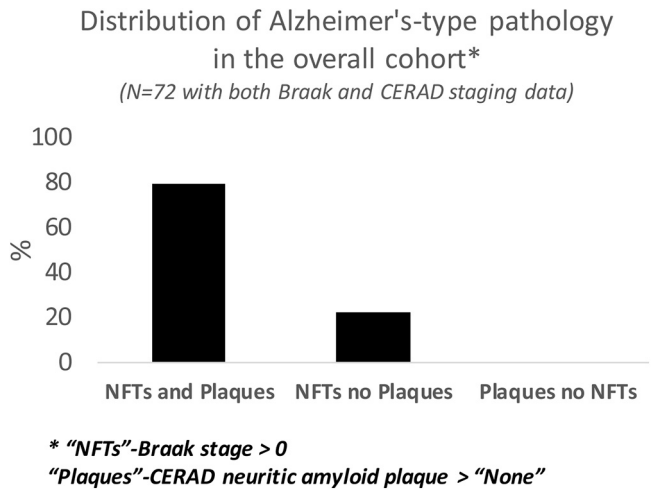


**Fig. 3.** The prevalence of 3 different pathologic combinations in the brains with both Braak staging and CERAD information. Note that some degree of Alzheimer's disease–type pathology (neurofibrillary tangle [NFT+]/neuritic amyloid plaque [NP+]) is quite prevalent (79%) of cases, followed by "NFT+/NP–" or primary age-related tauopathy cases (21%). By contrast, there were no "plaque-only" cases observed.

**Table 3**
Lewy body pathologic changes in the cohorts, by LBD subtype (McKeith et al., 2004)

| Cohort | LBD | | | |
|---|---|---|---|---|
| | Overall (*n*) | Brainstem predominant type | Limbic type | Neocortical/ diffuse type |
| GCS | 49 | 0 | 7 | 3 |
| Nun Study | 17 | 0 | 1 | 0 |
| UK-ADC | 11 | 0 | 1 | 1 |
| Total/overall | 77 | 0 | 9 | 4 |

Key: GCS, Georgia Centenarian Study; LBD, Lewy body disease; UK-ADC, University of Kentucky Alzheimer's Disease Center.

individuals in the study had >1 subtype of comorbid pathology (Fig. 4). In this assessment, we operationalized different neuropathologic subtypes as "positive" if the case showed: Braak NFT stage >II (thus, either "intermediate severity" AD neuropathologic changes or PART), cerebral amyloid angiopathy (moderate or severe), arteriolosclerosis (moderate or severe), HS-aging or TDP-43 pathology, LBD, or large infarcts.

For further studies, related to cerebrovascular pathologies (Figs. 5 and 6 and Tables 5 and 6), we concentrated on a subset of the aged cohort, which had very uniform pathologic workup: the GCS study participants ($n = 49$), whose recruitment was described elsewhere (Arnold et al., 2010; Shaw et al., 2012). For these research participants, an identical panel of 22 different brain blocks were assessed evaluating both sides of the brain, followed by semi-quantitative counts of 3 pathologic features that were graded (blind to all other information, on a 0–3 scale) by a single neuropathologist (JHN): arteriolosclerosis, pigment-laden macrophages, and expanded Virchow-Robin spaces. The grading scheme is depicted in Fig. 5. The overall results of the cerebrovascular pathologic assessments in the GCS cohort are presented in Fig. 6, and the average degree of pathology scored in each of the brain regions is presented.

In addition to providing an opportunity to describe the brain distribution of arteriolosclerosis, pigment-laden macrophages, and expanded Virchow-Robin spaces, the scored data also provided an opportunity to test specific hypotheses. First, is brain arteriolosclerosis outside of the hippocampus associated with HS-aging pathology in the GCS, as previously shown in other cohorts (Neltner et al., 2014)? Second, does the *ABCC9* risk SNP previously linked to HS-aging (Nelson et al., 2014, 2015) also show association with brain arteriolosclerosis in this cohort? The results of these tests are shown in Tables 5 and 6. The GCS data provide support for the previous hypotheses. In comparing arteriolosclerosis ratings between cases with versus without HS-aging pathology, estimated mean number of regions with arteriolosclerosis for HS-aging+ cases = 8.67 (95% confidence interval [CI]: 6.60, 11.37) and for HS-aging– cases = 5.26 (4.61, 5.99), $p = 0.0011$. For cases with TDP-43 pathology, the estimated mean number of regions = 7.36 (95% CI: 6.07, 8.92), for TDP-43– cases = 5.38 (4.60, 6.29), $p = 0.0137$. By contrast, for cases with advanced AD pathology, mean number of arteriolosclerosis regions = 6.0 (95% CI: 4.88, 7.38) versus lacking that pathology = 5.53 (4.79, 6.38), $p = 0.52$. Extending the same analyses to *ABCC9* genotypes, comparing homozygous G_G versus (G_C or C_C), the estimated mean number of regions with arteriolosclerosis for G_G = 7.10 (95% CI: 5.63, 8.96) and for G_C and C_C = 5.20 (4.50, 6.01), $p = 0.026$. Leaving out the HS-aging cases, but performing the same analysis otherwise, the estimated mean number of regions for G_G = 7.13 (95% CI: 5.50, 9.24) and for G_C and C_C= 4.81 (4.11, 5.64), $p = 0.0114$. Finally, comparing just the homozygous cases (G_G vs. C_C), the estimated mean number of regions for G_G = 7.10 (95% CI: 5.63, 8.96) and for C_C = 4.11 (2.98, 5.67), $p = 0.007$.

**Table 4**
HS-aging, diagnosed on H&E stains, and TDP-43 immunoreactive pathology, by cohort to show combinations of pathology

| Cohort | Overall (*n*) | HS-aging (*n*) | TDP-43 assessed (*n*) | HS+/TDP+ (*n*) | HS+/TDP− (*n*) | HS−/TDP+ (*n*) |
|---|---|---|---|---|---|---|
| GCS | 49 | 6 | 43 | 6 | 0 | 8 |
| Nun Study | 17 | 6 | 17 | 4 | 2 | 0 |
| UK-ADC | 11 | 4 | 8 | 2 | 1 | 1 |
| Total | 77 | 16 | 68 | 12 | 3 | 9 |

Key: GCS, Georgia Centenarian Study; HS-aging, hippocampal sclerosis of aging; H&E, hematoxylin and eosin; TDP-43, TAR-DNA−binding protein-43; UK-ADC, University of Kentucky Alzheimer's Disease Center.

## 4. Discussion

We describe neuropathologic observations in a large sample of research subjects relative to prior studies in this age range. These data underscore both the complexity of brain pathologies in advanced old age and the evolving nature of the field studying them. Among these extremely old research subjects, AD-type pathology was not universal, whereas some degree of hippocampal NFTs (including PART cases) was seen in all cases. Both LBD and HS-aging pathologies were common, but by no means universal, among centenarians in this sample. By contrast, small-vessel CVD were very prevalent. Brains with widespread moderate or severe arteriolosclerosis pathology were relatively likely to also harbor HS-aging pathology (vs. those that lacked HS-aging pathology) and to be carriers of the rs704180 G_G genotype (in comparison with G_C and C_C carriers). To help frame the significance of these results, we presented data from the actuarial tables from the US Social Security Administration, indicating that <1% of Americans live to the age of this study cohort (average 102.0 years at death); so, these findings relate to the oldest portion of human aging.

There are some limitations to our study. The individuals derived from 3 separate cohorts (UK-ADC cohort is associated with a memory disorder clinic and the other 2 are population-based samples), rather than from a homogenous study cohort. Furthermore, all were evaluated over a course of many years, and in that time some of the methodologies of neuropathologic evaluations have changed. Specifically, contrary to recent consensus recommendations for AD neuropathologic diagnosis (Montine et al., 2012), there was no Thal staging (Thal et al., 2006) of Aβ immunohistochemistry available for most of the cases; so, this was left out of the study and represents a study limitation. It would have been challenging to perform Aβ immunohistochemistry on all the cases retrospectively. Furthermore, our evaluation of pigment-laden macrophages leaves open the question of whether all these cells have hemosiderin or some having other pigment (perhaps including lipofuscin). We have not found a perfect correlation between pigmented macrophages and the cells that are stained with Prussian blue on histology (data not shown). We also left unaddressed some of the other emerging concepts in neuropathology such as age-related astrocytic tauopathy (Ferrer et al., 2014). Although these considerations are important, there is also a positive trade-off because the methodology was relatively standardized, all being performed at the same institution. Even with that strength, the issues related to plaque and tangle quantification are complex (both technically and theoretically), and pathologic factors may not align perfectly with rigid classification schemes.

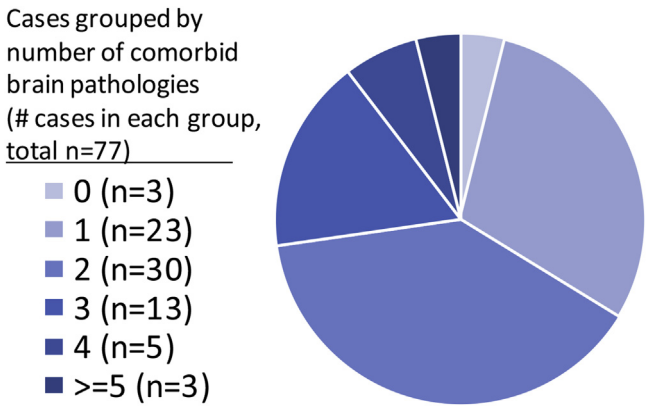


**Fig. 4.** The majority of individuals had >1 subtype of comorbid brain pathologies. For the overall study cohort ($n = 77$), the individuals were binned according to the number of different subtypes of pathology in the brain—Braak neurofibrillary tangle stage >II, cerebral amyloid angiopathy, arteriolosclerosis, hippocampal sclerosis of aging or TAR-DNA binding protein-43 pathology, Lewy body disease, or large infarcts. For example, there were 30 cases with 2 different comorbid pathologies noted, 23 cases with only 1 noted, and so forth. Note that more than half of the included subjects' brains harbored >1 of these pathologic features.

More theoretically, an assumption is that centenarians provide insights into mechanisms related to "aging," but the concept of aging is not universally defined in a biologic sense, beyond chronologic persistence. Any study of centenarians involves a strong survival bias so that many of the individuals that have been removed from consideration (by death or by otherwise not participating as a research volunteer) may have manifested aging in different ways. A specific example of such a potential source of bias is that women, who live longer than men on average (Fig. 1), also are less likely to develop neocortical LBD (Nelson et al., 2010b), which may help explain the relative lack of Lewy body pathology (no Parkinson's disease patients) in this sample that is almost 90% female. Additional factors may cause or exacerbate parkinsonism in older individuals (Buchman et al., 2012; Hack et al., 2012). Finally, there is a possibility that future efforts will enable people to live longer (Christensen et al., 2009), perhaps even much longer, so that the age of 102 years may not represent the true "final stage" of human longevity. Whereas this theoretically may be true, we note that, as of November 2014, in the entire world, there were only estimated to be 300–450 individuals over the age of 110 years (only 79 validated at that time, see Robert and Fulop, 2014 and http://www.grg.org/Adams/E.HTM), of >7,000,000,000 alive, so the potential for widespread life span attainment much beyond that is theoretical indeed.

Despite the potential challenges, there are important insights that can be gained by studying centenarians. Prior studies have yielded excellent information in this area, although some controversies and questions remain. One clear implication of the present study is that AD (the malignant plaque and tangle disease) is not inevitable in advanced old age although it is the most frequent and highly impactful neurodegenerative condition in this group. This result agrees with a prior study in a large extremely high-quality autopsy sample that found ~20% of centenarian cases lack Aβ by immunohistochemistry (Thal Aβ stage 0) (Braak et al., 2011). It is intriguing that the *APOE* ε4 genotype in the present sample (only 11 individuals out of 76 tested were ε4 allele carriers) is lower than

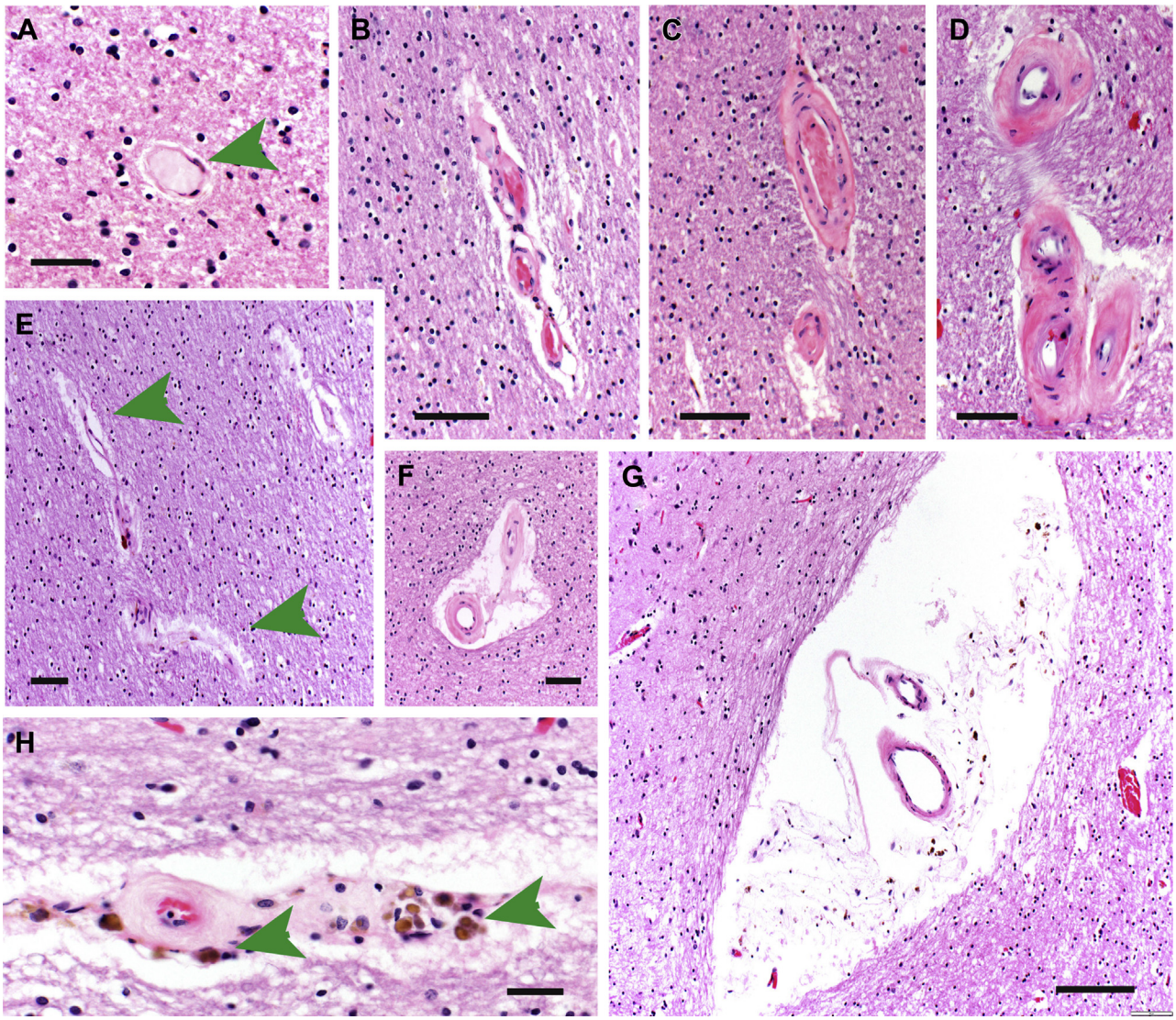


**Fig. 5.** Cerebrovascular disease pathologies as scored using semiquantitative measurements. Photomicrographs depicting frontal cortex (Brodmann area 9) white matter are shown (A–H). Normal white matter vessel (A), compared with mild (B), moderate (C), and severe arteriolosclerosis (D). Virchow-Robin space spectrum ranges from 1+ (E), 2+ (F), and to 3+ (G). Pigment laden macrophages (H) are also present in the perivascular spaces. (A–G) ×10 magnification (bar: 100 μm) and (H) ×20 magnification (bar: 50 μm). In the panel (A), the arrowhead indicates the blood vessel and in the panels (E) and (H), the arrowheads indicate 1+ expanded Virchow-Robin spaces and the pigment laden macrophages, respectively.

most populations (Singh et al., 2006), possibly indicating a survival effect as suggested previously (Jicha et al., 2008, but see Corrada et al., 2013). Clearly, some degree of hippocampal NFTs develop even in the absence of amyloid plaques, albeit an attenuated distribution (Crary et al., 2014; Jellinger et al., 2015; Nelson et al., 2009b). Relative to slightly younger cohorts, the overall proportion of AD and PART cases seems to be stable in advanced old age, supporting the hypothesis that PART pathology is not necessarily destined to progress to full-blown AD. By contrast, in this cohort there were no "plaque-only" cases because all brains had some hippocampal NFTs.

Our study also provides further support for the prevalence of non-AD pathologies in advanced old age (Attems et al., 2014; Brenowitz et al., 2015; Corrada et al., 2012; Dickson, 2009; Erten-Lyons et al., 2013; Jellinger and Attems, 2010a, 2010b; Jicha et al., 2012; Kawas et al., 2015; Kovacs et al., 2013; Magaki et al., 2014; Serrano-Pozo et al., 2013; Sonnen et al., 2011; Toledo et al., 2013). Here, we found extensive co-occurrence of CVD, AD, HS-aging, and alpha-synucleinopathy, and as expected, most brains contained >1 subtype of pathology. These common cerebral multimorbidities help to explain the apparent "dissociation" between clinical and pathologic parameters in correlation analyses that only focus on a single subtype of pathology (Nelson et al., 2012; Scheff et al., 2014). Any determination of specific relationships between cognition and pathology in extreme old age requires either culling out for analysis the rare cases of "pure" (single pathology) examples of that pathologic subtype or formulating multiple variable approaches that require large cohorts, carefully-applied statistical models, and numerous—preferably nonordinal—quantitative pathologic parameters. The present study, assessing the numerous pathologies of the oldest old among relatively few research subjects, lacked adequate statistical power to accomplish robust clinical-pathologic correlation.

In terms of pathologies with established impact on cognition, there is an emerging appreciation of the strong impact of HS-aging and TDP-43 pathologies (Nelson et al., 2010a, 2013). As shown

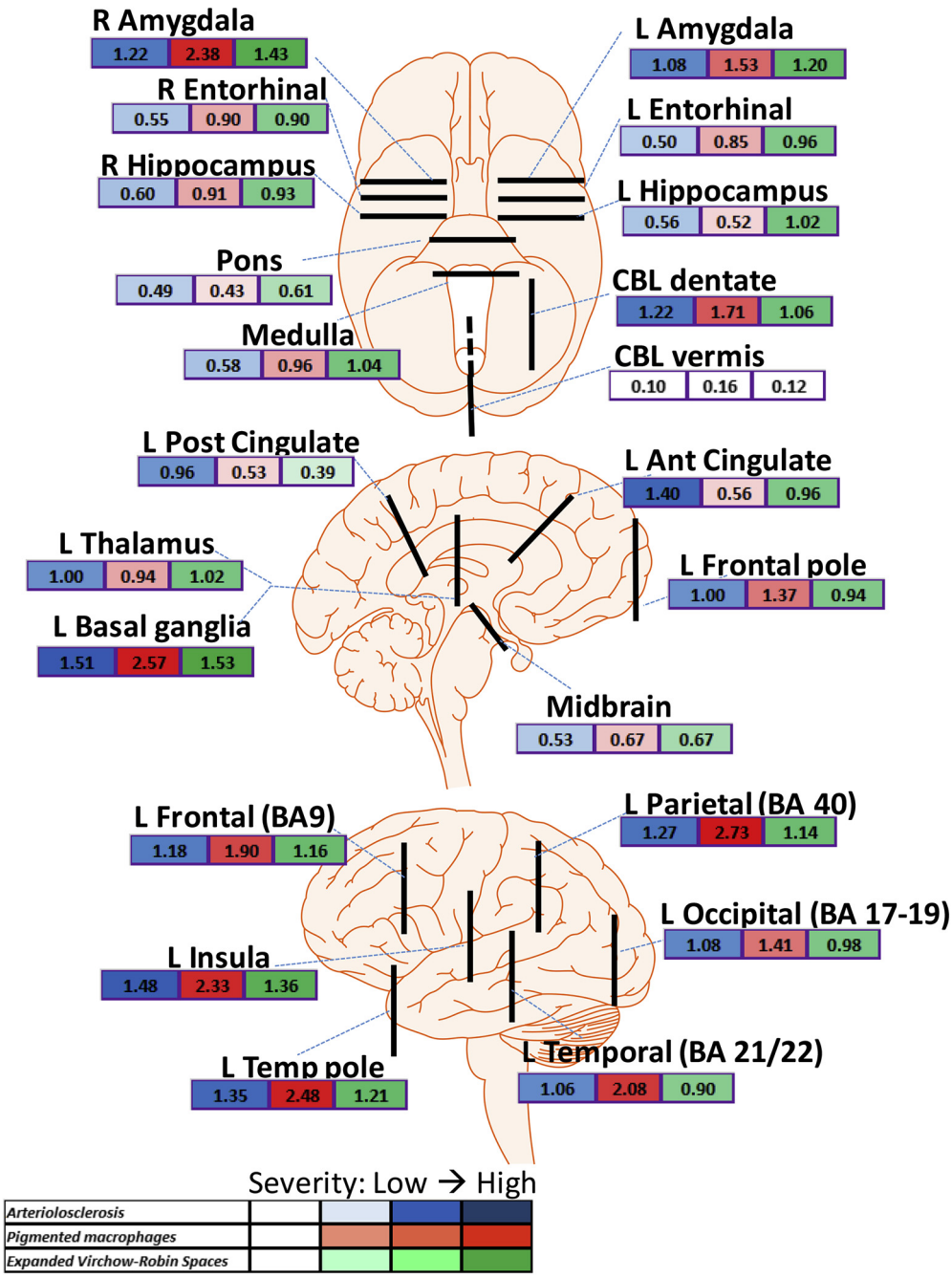


**Fig. 6.** Cerebrovascular disease pathologies in 22 brain areas. A convenience sample of 49 cases of the Georgia Centenarian Study were scored using semiquantitative measurements. The schematic shows (from top to bottom) the ventral surface, medial aspect, and lateral brain convexity to help visualize the neuroanatomic locations. Separate data are shown for arteriolosclerosis (blue), extravascular pigmented macrophages (red), and expanded Virchow-Robin spaces (green). Each was scored on a 4-tier (0–3) scale, from low to high severity, in each case. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

previously (Amador-Ortiz et al., 2007; Nelson et al., 2011b), most cases with HS-aging pathology also showed TDP-43 pathology (79% of HS-aging cases in the current cohort were TDP-43+). Although we showed previously that HS-aging pathology increases in advanced old age (as opposed to the prevalence of AD, cerebral amyloid angiopathy, or DLB pathologies, which level off or even decreases) (Brenowitz et al., 2014, 2015; Nelson et al., 2011a, 2011b), the present study indicates that HS-aging pathology and TDP-43 pathology that frequently coexists with HS-aging are by no means universal among centenarians. If hippocampal TDP-43 were an early manifestation of a disease process that would ultimately lead to full-blown FTLD-TDP, then there should be an appreciable subset of very old people with an overall pathologic status that resembles FTLD-TDP with extremely widespread TDP-43 pathology. This does not appear to be the case. However, there may well be pathogenetic overlap between aging-related hippocampal TDP-43 pathology and FTLD-TDP as underscored by genetic data presented in other studies (Aoki et al., 2015; Fenoglio et al., 2009; Murray et al., 2014; Nelson et al., 2015; Rademakers et al., 2008; Rutherford et al., 2012).

Where HS-aging and FTLD may differ relates to the potential impact of arteriolosclerosis on the brains of individuals in advanced

**Table 5**
Average arteriolosclerosis scores from all 22 brain regions analyzed from the Georgia Centenarians, stratifying separately by HS-aging (HS+/−), TDP-43 (TDP+/−), and Alzheimer's disease (AD+/−) pathologies

| | HS+ ($n = 6$) | HS− ($n = 43$) | TDP+ ($n = 14$) | TDP− ($n = 35$) | AD+ ($n = 14$) | AD− ($n = 35$) |
|---|---|---|---|---|---|---|
| Counted neocortical NFTs[a], average | 24.4 | 8.1 | 16.2 | 7.6 | 29.0 | 2.5 |
| Average arteriolosclerosis score | | | | | | |
| Lt frontal pole | 1.40 | 0.93 | 1.09 | 0.96 | 1.00 | 1.00 |
| Lt frontal cortex (BA 9) | 1.33 | 1.16 | 1.43 | 1.09 | 1.29 | 0.93 |
| Lt sup/mid temporal cortex (BA 21/22) | 1.50 | 1.00 | 1.43 | 0.91 | 1.03 | 1.15 |
| Lt hippocampus | 0.83 | 0.52 | 0.57 | 0.56 | 0.56 | 0.57 |
| Rt hippocampus | 1.33 | 0.49 | 0.71 | 0.55 | 0.55 | 0.71 |
| Lt entorhinal cortex | 1.00 | 0.43 | 0.71 | 0.41 | 0.41 | 0.71 |
| Rt entorhinal cortex | 0.67 | 0.53 | 0.43 | 0.60 | 0.54 | 0.57 |
| Lt amygdala | 1.50 | 1.02 | 1.07 | 1.09 | 1.11 | 1.00 |
| Rt amygdala | 2.00 | 1.12 | 1.33 | 1.18 | 1.22 | 1.20 |
| Lt parietal cortex (BA 39/40) | 1.33 | 1.26 | 1.50 | 1.17 | 1.14 | 1.57 |
| Lt occipital cortex (BA 17/18) | 1.17 | 1.07 | 1.21 | 1.03 | 1.09 | 1.07 |
| Lt basal ganglia | 1.67 | 1.49 | 1.57 | 1.49 | 1.49 | 1.57 |
| Midbrain | 0.67 | 0.51 | 0.50 | 0.54 | 0.54 | 0.50 |
| Pons | 1.00 | 0.42 | 0.79 | 0.37 | 0.46 | 0.57 |
| Medulla oblongata | 1.00 | 0.53 | 0.62 | 0.57 | 0.71 | 0.29 |
| Dentate (deep cerebellar) nucleus | 1.33 | 1.21 | 1.29 | 1.20 | 1.23 | 1.21 |
| Cerebellar vermis | 0.33 | 0.07 | 0.14 | 0.09 | 0.14 | 0.00 |
| Lt temporal pole | 1.17 | 1.38 | 1.69 | 1.23 | 1.20 | 1.77 |
| Lt thalamus | 1.17 | 0.98 | 0.93 | 1.03 | 1.00 | 1.00 |
| Lt anterior cingulate | 2.00 | 1.31 | 1.86 | 1.21 | 1.29 | 1.64 |
| Lt posterior cingulate | 1.50 | 0.88 | 1.07 | 0.91 | 0.91 | 1.07 |
| Lt insula | 1.60 | 1.46 | 1.69 | 1.39 | 1.37 | 1.71 |
| Overall arteriolosclerosis average | 1.25 | 0.90 | 1.07 | 0.89 | 0.92 | 0.99 |
| $p$ Value[b] | 0.0011 | | 0.014 | | 0.52 | |

Key: BA, Brodmann area; HS-aging, hippocampal sclerosis of aging; Lt, left; mid, middle; NFT, neurofibrillary tangle; Rt, right; sup, superior; TDP-43, TAR-DNA–binding protein-43.
[a] Neocortical NFT counts refer to summed NFTs counted from frontal, temporal, parietal, and occipital cortices in each case, as previously described (Nelson et al., 2007).
[b] Statistics refer to comparisons between pathology groups for mean number of brain regions with presence of at least moderate arteriolosclerosis versus absent or mild severity (see Section 2).

**Table 6**
Average arteriolosclerosis scores from all 22 brain regions analyzed from the Georgia Centenarians ($n = 45$ with genetic information available), stratifying by *ABCC9* rs704178 genotype

| | *ABCC9* rs704178 genotype | | |
|---|---|---|---|
| | C_C ($n = 9$) | G_C ($n = 26$) | G_G ($n = 10$) |
| No. of cases with HS-aging pathology | 0 | 3 | 2 |
| Average arteriolosclerosis score | | | |
| Lt frontal pole | 0.80 | 1.05 | 0.86 |
| Lt frontal cortex (BA 9) | 1.00 | 1.27 | 1.00 |
| Lt sup/mid temporal cortex (BA 21/22) | 0.78 | 1.16 | 1.00 |
| Lt hippocampus | 0.50 | 0.54 | 0.50 |
| Rt hippocampus | 0.38 | 0.58 | 0.78 |
| Lt entorhinal cortex | 0.44 | 0.48 | 0.50 |
| Rt entorhinal cortex | 0.11 | 0.65 | 0.60 |
| Lt amygdala | 0.67 | 1.23 | 1.10 |
| Rt amygdala | 0.80 | 1.20 | 1.50 |
| Lt parietal cortex (BA 39/40) | 1.00 | 1.35 | 1.40 |
| Lt occipital cortex (BA 17/18) | 0.67 | 1.38 | 0.80 |
| Lt basal ganglia | 1.56 | 1.38 | 1.90 |
| Midbrain | 0.56 | 0.42 | 0.60 |
| Pons | 0.33 | 0.42 | 0.60 |
| Medulla oblongata | 0.67 | 0.44 | 0.80 |
| Dentate (deep cerebellar) nucleus | 1.00 | 1.23 | 1.50 |
| Cerebellar vermis | 0.22 | 0.00 | 0.10 |
| Lt temporal pole | 1.13 | 1.35 | 1.50 |
| Lt thalamus | 1.00 | 1.46 | 1.67 |
| Lt anterior cingulate | 0.56 | 1.04 | 1.10 |
| Lt posterior cingulate | 0.89 | 0.92 | 1.20 |
| Lt insula | 1.44 | 1.36 | 1.88 |
| Overall arteriosclerosis average | 0.75 | 0.95 | 1.04 |
| $p$ Value[a], GG versus (GC + CC) | | 0.026 | |
| $p$ Value[a], GG versus (GC + CC) without HS-aging cases | | 0.011 | |
| $p$ Value[a], + versus − cases | | 0.007 | |

Key: BA, Brodmann area; HS-aging, hippocampal sclerosis of aging; Lt, left; mid, middle; NFT, neurofibrillary tangle; Rt, right; sup, superior; TDP-43, TAR-DNA–binding protein-43.
[a] Statistics refer to comparisons between genotype groups for mean number of brain regions with presence of at least moderate arteriolosclerosis versus absent or mild severity (see Section 2).

old age. We previously showed that arteriolosclerosis outside of the hippocampus is increased in persons with comorbid HS-aging pathology versus controls (Neltner et al., 2014). Furthermore, an *ABCC9* SNP is associated with risk for HS-aging pathology (Nelson et al., 2014, 2015), and the present study indicates that the same SNP is also a risk factor for brain arteriolosclerosis (additional work is being performed in our laboratory to test this hypothesis). Acute vascular injury does not induce HS-aging or TDP-43 pathologies (Lee et al., 2008), but chronic vascular injury may do so. As an analogous concept, acute brain trauma does not result in TDP-43 pathology (Johnson et al., 2011), but chronic brain trauma often does (King et al., 2010; Saing et al., 2012; Smith et al., 2013). Our data indicate that a disproportionate subset of cases with (presumably chronic) brain arteriolosclerosis develop HS-aging pathology (Neltner et al., 2014), both linked to *ABCC9* gene variants. Importantly, the cases included in the present study were not also used in Neltner et al. (2014); so, this is a validation of the prior report indicating that HS-aging is just one manifestation of a "whole brain" disease with arteriolosclerosis widespread outside of the hippocampus. We also note that the association between HS-aging and brain arteriolosclerosis pathologies in advanced old age aligns well with results of prior studies (Chui et al., 2006; Dickson et al., 1994; Jellinger, 2007; Pantoni et al., 1996; Snowdon et al., 1997; White, 2009). Collectively, these findings indicate that HS-aging pathology may be the manifestation of a disease with attributes that are seen in both cerebrovascular and neurodegenerative conditions.

Finally, the present study addressed some cerebrovascular neuropathologic features that are not standardized in terms of universally applied neuropathologic guidelines: pigment-laden macrophages, expanded Virchow-Robin spaces, and arteriolosclerosis. For the purposes of the present study, these results are purely descriptive. The data are presented to help convey how the various CVD subtypes are distributed in the brains of individuals in this cohort. We were struck that some areas of the brain that are not necessarily frequently associated with CVD (e.g., insula cortex) showed a very high burden of small vessel pathology in this sample. Furthermore, it would appear that microscopic extravasation of blood is common among centenarians because many cerebral cortical areas showed pigmented macrophages near blood vessels. These changes may help explain the prior discovered alterations in small blood vessel profiles (Imhof et al., 2007). Future work is required to better understand the cerebrovascular pathologies in the oldest-old.

We conclude that the study of extremely old individuals' brains provides scientific insights into brain diseases and aging in general. FTLD seems to mainly manifest in younger individuals. We have not seen a case that lacks some degree of hippocampal NFTs unless the hippocampus was obliterated by sclerotic changes. Yet we confirm prior studies (Garcia-Sierra et al., 2000; Gold et al., 2000; Imhof et al., 2007; Itoh et al., 1998; Mizutani and Shimada, 1992) that indicate variability in the severity of this pathology in centenarians. Because none of these other neurodegenerative disease pathologies (AD, FTLD, HS-aging, or LBD) is universal among centenarians, our data can be interpreted optimistically to support the hypothesis that the "neurodegenerative diseases" can be addressed by future therapeutic strategies to counteract the genetic and environmental factors (many probably as yet unknown) that lead to these pathologies. However, there are aspects of aging that are more likely to be an inevitable manifestation of the human genetic blueprint. The aged brain, as with other organs, seems to be often afflicted with small blood vessel degenerative changes. Presumably, there are some risk factors (hypertension) that can exacerbate blood vessel pathology among individuals of all ages. However, it remains to be determined whether cerebral small blood vessel changes in extreme old age can be therapeutically eliminated.

## Disclosure statement

The authors have no conflicts of interest to disclose.

## Acknowledgements

We are deeply grateful to all the study volunteers. We thank Sonya Anderson for technical support and Greg Cooper, MD, Nancy Stiles, MD, and Allison Caban-Holt, PhD, for the clinical evaluations. This study was supported by National Institutes of Health grants R01 NS061933, R01 AG19241, P01 AG17553, P30 AG028383, and U01 AG016976.

## Appendix A. Supplementary data

Supplementary data related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2015.10.009.

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