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Brain pathologies in extreme old age

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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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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