Where Vascular Meets Neurodegenerative Disease

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Abstract**—**Vascular and neurodegenerative disease commonly cooccur in older persons. We review findings from the Rush Religious Orders Study and Memory and Aging Project. Both studies enroll subjects without diagnosed dementia, perform annual evaluations, and obtain autopsies proximate to death. We found that macroscopic infarcts are common, lower the threshold for cognitive impairment, and often coexist with Alzheimer's disease pathology. We also found that vascular pathology may be associated with memory impairment and may be difficult to distinguish from clinical Alzheimer's disease. Finally, because dementia in older persons often results from mixed pathology and the clinical phenotypes overlap, some risk factors may increase risk for clinical Alzheimer's disease through an increase in vascular pathology. **(*Stroke*. 2010;41[suppl 1]:S144-S146.)**

Key Words: Alzheimer's ■ cognitive impairment ■ dementia ■ epidemiology ■ neuropathology ■ risk factors ■ vascular cognitive impairment ■ VCI

Clinical–pathological studies have provided the framework for our present understanding of the pathogenesis of age-related dementia. In the early 20th century, most dementia was assumed to be secondary to cerebrovascular disease, specifically atherosclerosis-induced brain softening, whereas the contribution of Alzheimer's disease (AD) pathology was just beginning to evolve.[1] The past 4 decades have seen a near reversal in these assumptions, with AD considered the most common pathology and cerebrovascular pathology thought to account for a minority of age-related dementia. Whereas pathological criteria were developed and refined for AD,[2] specific criteria for the pathological diagnosis of vascular dementia were not realized. Recent years have shown a resurgence of interest in the role of vascular pathology in the pathogenesis of age-related dementia, with increasing recognition of mixed AD and infarct pathology.[3–5]

Knowledge regarding the pathological basis of dementia has been advanced by incorporating epidemiological techniques into clinical–pathological studies. These studies are shedding light on the role of vascular and mixed pathologies in age-related memory loss, mild cognitive impairment (MCI), and dementia. Clinical–pathological epidemiological studies enroll persons from the community, examine them prospectively, and include brain donation at death, thus enabling investigation of multiple specific pathologies in relation to cognition. This article reviews the findings on vascular and mixed pathologies from 2 such studies, the Rush Religious Orders Study and Memory and Aging Project. We will also show findings related to 4 risk factors: apolipoprotein (APO)Eε4, diabetes, depressive symptoms, and conscientiousness.

Methods

Subjects

The Religious Orders study enrolls older catholic clergy and the Memory and Aging Project enrolls older community-dwelling subjects without known dementia who agree to annual evaluations and organ donation. Currently, there are 528 deceased (497 autopsies) participants in the Religious Orders Study and 436 deceased (357 autopsies) in the Memory and Aging Project. In both studies, the average interval from last clinical evaluation to death is $<$8.5 months and the average age-at-death is $\approx$87 years. Subjects sign a consent form and an Anatomic Gift Act. Both studies were approved by the Rush University Medical Center Institutional Review Board.

Neuropsychologic Testing

Twenty-one neuropsychologic tests are performed yearly, and 19 tests (17 common to both cohorts) are used to create summary measures of 5 cognitive domains (episodic, semantic, and working memory, perceptual speed, and visuospatial ability) and overall cognition. The composite measures are created by converting each test to a z score and averaging the z scores.[6]

Clinical Evaluation and Diagnoses

An expert clinician reviews the clinical and neuropsychologic data and provides diagnoses of AD and other dementias.[7] MCI is diagnosed when there is cognitive impairment without a diagnosis of dementia.[8] After death, the clinician reviews all clinical data and provides a final diagnosis. APOEε4, diabetes, depressive symptoms, and conscientiousness were documented as previously described.[9–12]

Autopsy

The brain autopsy protocol is similar for both studies.[8] Brains are examined for infarcts and other pathologies. We used 1-cm slabs of brain fixed in 4% paraformaldehyde. Tissue blocks from the hippocampal, entorhinal, anterior cingulate, midfrontal, middle tempo-

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ral, and inferior parietal cortices and basal ganglia, thalamus, and midbrain are paraffin-embedded, cut into 6-micron sections, and stained with hematoxylin/eosin and modified Bielschowsky silver stain for assessment of vascular and AD pathology.

Pathological Diagnoses and Measures

The pathological diagnosis of AD follows NIA-Reagan criteria.[2] To obtain continuous measures of AD pathology we count neuritic and diffuse plaques and neurofibrillary tangles from five brain regions and create a AD pathology global measure.[13] Macroscopic infarcts are confirmed by microscopy.[6] Cerebral amyloid angiopathy (CAA) is visualized using immunohistochemistry to β-amyloid (10D5; courtesy of ELAN) and a semiquantitative scale.[14]

Statistical Analyses

We used logistic or linear regression analyses to investigate the relation of neuropathology to cognitive status proximate to death. Risk factor analyses used pathology as the outcome or used mediation analyses. Depressive symptoms and conscientiousness included average scores from all years.[10–11] Analyses accounted for the effects of age, sex, and education.

Results

Macroscopic Infarcts, Cognitive Impairment, and Dementia

In autopsied participants of the Religious Orders Study, we found that macroscopic infarcts were common but often not clinically recognized.[6] Cerebral infarcts increased the odds of dementia and lowered cognition, especially perceptual speed but also memory function. Persons with multiple or a large volume of infarct(s) had the highest likelihood of dementia or cognitive impairment.

Macroscopic Infarcts, AD Pathology, and Dementia

Macroscopic infarcts commonly occur in the context of AD pathology. In the Religious Orders Study, we found that infarcts independently added to the likelihood of dementia without evidence of a synergistic (multiplicative) effect with AD pathology.[13] After accounting for AD pathology, infarcts were associated with all cognitive domains but had the strongest effect on perceptual speed.

Mixed Pathologies and Dementia

Few community-based studies have investigated the role of mixed pathologies in dementia. In the Memory and Aging Project, we found that in persons with dementia, more than half had mixed pathologies, most commonly AD with infarcts.[7] Persons with mixed compared to single pathologies were more likely to exhibit dementia.

Mixed Pathologies and Clinical AD

Given that AD is the most common dementia, we investigated the role of mixed pathologies in clinically diagnosed probable AD.[8] Using subjects from the Religious Orders Study and Memory and Aging Project, we found most persons with clinically diagnosed AD were confirmed to have pathological AD, but almost half had mixed pathology, most commonly mixed AD and infarct pathology. Thus, clinically diagnosed AD is pathologically heterogeneous disorder.

Infarct Pathology, Episodic Memory, and MCI

We investigated infarcts and AD pathology in persons with MCI and memory impairment.[8,15–16] In the Religious Orders Study, we found that persons with MCI had intermediate amount of AD pathology and infarcts.[15] In another study, AD pathology was the most common pathology in subjects with MCI, but they often had mixed AD and infarcts, or infarcts alone.[8] Finally, in the Memory and Aging Project, we found that subcortical infarcts were associated with lower episodic, semantic, and working memory after accounting for AD pathology.[16] These studies showed that the pathology underlying memory loss and MCI is heterogeneous; moreover, both AD and infarct pathology may be associated with memory impairment.

CAA and Cognitive Impairment

In the Religious Orders Study, we investigated CAA and cognitive domains.[14] CAA was very common and related to AD pathology. In analyses controlling for AD pathology and infarcts, we found that moderate to very severe CAA was associated with lower perceptual speed and episodic memory in persons with and without dementia. Further work will be needed to determine the mechanism.

Not All Risk Factors for Clinical AD Are Related to AD Pathology

The APOEε4 allele is a risk factor for clinical AD. We and others have found that the ε4 allele is related to the accumulation of amyloid.[17] In another study we found that persons with the ε4 genotype also have an increased likelihood of cerebral infarcts.[12] Therefore, although the ε4 genotype is related to clinical AD primarily through AD pathology, infarcts may also contribute to the likelihood of dementia in persons with an ε4 allele.

Persons with diabetes have an increased likelihood of dementia, including clinical AD. In the Religious Orders Study, we investigated the relationship between diabetes and age-related pathologies.[9] Diabetes was not related to the amount of amyloid or tangles but was related to macroscopic infarcts. Thus, diabetes appears to increase the likelihood of clinical AD through an increase in cerebral infarcts.

Depression is a risk factor for clinical AD and dementia. In the Religious Orders Study, depressive symptoms increased risk of clinical AD but were not related to AD pathology[10] or macroscopic infarcts.[18] These studies suggest that depression works through an alternative mechanism to increase risk of AD.

Finally, in the Religious Orders Study, conscientiousness (the inclination to control impulses and be goal directed) is related to a lower risk of clinical AD.[11] Conscientious was not related to pathology, but did modify the association of pathology with cognition. Unexpectedly, persons with infarcts and high conscientiousness had lower cognition. The mechanism is unclear, but may be related to unidentified susceptibility factors.

Summary

Clinical–pathological studies from the Rush Religious Orders Study and Memory and Aging Project, community-based epidemiological studies of dementia, add to a growing body of literature that underscore the important role of vascular and AD pathology in older persons. There are several important implications.

First, the underlying pathology of clinically diagnosed dementia and probable AD is heterogeneous. Indeed, most persons with dementia and nearly half of those with probable AD have mixed pathologies, most commonly AD and infarcts. These infarcts are not benign but add to the likelihood of cognitive impairment and lower the threshold for clinical AD and dementia.

Second, vascular and AD phenotypes overlap, such that the pathological basis for dementia may not be easily extricated when there are mixed pathologies. Indeed, we found that macroscopic infarcts and amyloid angiopathy have prominent effects on perceptual speed but may also affect episodic memory, the phenotypic hallmark of clinical AD. Thus, the use of cognitive profiles to distinguish AD from vascular cognitive impairment may be limited.

Finally, our data urge caution when attributing a risk factor for clinical AD to amyloid or tangle accumulation. Because vascular pathology contributes to the AD phenotype, some risk factors for clinical AD are likely to be risk factors for vascular pathology. For instance, we found that diabetes, a risk factor for clinical AD, is related to infarcts but not AD pathology. Furthermore, the APOEε4 genotype, which is strongly related to AD pathology, is also related to infarcts and, therefore, may increase risk of dementia via an additional mechanism. Given the heterogeneity underlying the clinical diagnosis of AD and dementia, determining mechanisms by which genetic, environmental, and medical factors increase risk of dementia will benefit from either antemortem or postmortem indicators of burden of specific pathologies.

There are other common vascular pathologies in the brains of older persons, including microscopic infarct, microbleeds, lipohyalinosis, and white matter changes. There is accumulating evidence that some of these factors may play a role in age-related cognitive impairment. In particular, literature from community-based clinical–pathological studies suggests that microinfarcts are important.[3–5] In future studies, it will be important to measure additional vascular pathologies to further elucidate the role of vascular and AD changes in the spectrum of clinical AD and dementia.

These studies have limitations. Participants from the Religious Orders Study are highly educated, have excellent access to medical care, and have healthy lifestyles. Although this homogeneity may increase power by decreasing intersubject heterogeneity, the participants may not be representative of the population. The Memory and Aging Project cohort is more diverse and representative of the population. Finally, subjects who agree to autopsy may be different from those who do not agree. This potential bias is mitigated by the high autopsy rates. In the future, it may be possible to conduct similar analyses in vivo using structural MRI for vascular disease and PET amyloid imaging for AD pathology.

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Disclosures

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