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Where Vascular meets Neurodegenerative Disease

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Abstract

Vascular and neurodegenerative disease commonly co-occur 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 (AD) pathology. We also found that vascular pathology may be associated with memory impairment and may be difficult to distinguish from clinical AD. Finally, because dementia in older persons often results from mixed pathology and the clinical phenotypes overlap, some risk factors may increase risk for clinical AD through an increase in vascular pathology.

Introduction

Clinical-pathologic studies have provided the framework for our current understanding of the pathogenesis of age-related dementia. In the early twentieth 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 four decades has 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. While pathologic criteria were developed and refined for Alzheimer's disease,² specific criteria for the pathologic 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 pathologic basis of dementia has been advanced by incorporating epidemiologic techniques into clinical-pathologic 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-pathologic epidemiologic 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 paper reviews the findings on vascular and mixed pathologies from two such studies, the Rush Religious Orders Study and Memory and Aging project. We will also show findings related to four risk factors: Apolipoprotein E (APOE) $\epsilon 4$, diabetes, depressive symptoms and conscientiousness.

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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 about 87 years. Subjects sign a consent form and an Anatomical Gift Act. Both studies were approved by the Rush University Medical Center IRB.

Neuropsychologic testing

Twenty-one neuropsychologic tests are performed yearly and nineteen tests (17 common to both cohorts) are used to create summary measures of five 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. APOE ϵ 4, 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 temporal, and inferior parietal cortices, and basal ganglia, thalamus, and midbrain are paraffin-embedded, cut into 6-micron sections, and stained with Hematoxylin and Eosin and modified Bielschowsky silver stain for assessment of vascular and AD pathology.

Pathologic diagnoses and measures

The pathologic 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 beta-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 employed mediation analyses. Depressive symptoms and conscientiousness included average scores from all years.^{10–11} Analyses accounted for the effects of age, sex, or 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, over 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 Religious Orders Study and Memory and Aging Project, we found most persons with clinically-diagnosed AD were confirmed to have pathologic 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 APOE ϵ 4 allele is a risk factor for clinical AD. We and others have found that the ϵ 4 allele is related to the accumulation of amyloid.¹⁷ In another study we found that persons with the ϵ 4 genotype also have an increased likelihood of cerebral infarcts.¹² Therefore, while the ϵ 4

genotype is related to clinical AD primarily through AD pathology, infarcts may also contribute to the likelihood of dementia in persons with an $\epsilon 4$ 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 pathology¹⁰ 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-pathologic studies from the Rush Religious Orders Study and Memory and Aging project, community-based epidemiologic 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 pathologic 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. Since 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 APOE $\epsilon 4$ 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 post-mortem 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-pathologic studies suggest 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 healthy life styles. While this homogeneity may increase power by decreasing inter-subject 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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References

1. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiol Aging* 1998 May-Jun;19:173–89. [PubMed: 9661992]
2. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging* 1997;18:S1–2. [PubMed: 9330978]
3. Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study (MRC CFAS). Pathologic correlates of late onset dementia in a multicentre, community based population in England and Wales. *Lancet* 2001;357:169–75. [PubMed: 11213093]
4. White L, Small BJ, Petrovitch H, Ross GW, Masaki K, Abbott RD, Hardman J, Davis D, Nelson J, Markesbery W. Recent clinical-pathologic research on the causes of dementia in later life: update from the Honolulu-Asia Aging Study. *J Geriatr Psychiatry Neurol* 2005;18:224–7. [PubMed: 16306244]
5. 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;62:406–13. [PubMed: 17879383]
6. Schneider, Wilson RS, Cochran EJ, Bienias JL, Evans DA, Bennett DA. Relation of cerebral infarctions to dementia and cognitive function in older persons. *Neurology* 2003;60:1082–1089. [PubMed: 12682310]
7. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed Brain Pathologies Account for Most Dementia Cases in Community-Dwelling Older Persons. *Neurology* 2007 Dec 11;69:2197–204. [PubMed: 17568013]
8. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol* 2009 Aug;66:200–8. [PubMed: 19743450]
9. Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, Bennett DA. Diabetes is related to cerebral infarction but not to AD pathology in older persons. *Neurology* 2006 Dec 12;67:1960–5. [PubMed: 17159101]
10. Wilson RS, Schneider JA, Bienias JL, Arnold SE, Evans DA, Bennett DA. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. *Neurology* 2003 Oct 28;61:1102–7. [PubMed: 14581672]
11. Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Arch Gen Psychiatry* 2007 Oct;64:1204–12. [PubMed: 17909133]

12. Schneider JA, Bienias JL, Wilson RS, Berry-Kravis E, Evans DA, Bennett DA. Apolipoprotein E ϵ 4 increases the odds of chronic cerebral infarctions detected at autopsy. *Stroke* 2005;36:954–959. [PubMed: 15774818]
13. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer's disease pathology. *Neurology* 2004;62:1148–1156. [PubMed: 15079015]
14. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral Amyloid Angiopathy Pathology and Cognitive Domains in Older Persons. *Annals of Neurology*. 2010 in press.
15. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology* 2005 Mar 8;64:834–41. [PubMed: 15753419]
16. Schneider JA, Boyle PA, Arvanitakis Z, Bienias JL, Bennett DA. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Ann Neurol* 2007 Jul;62:59–66. [PubMed: 17503514]
17. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Berry-Kravis, Arnold SE. Amyloid mediates the association of apolipoprotein E ϵ 4 Allele to cognitive function in older persons. *Journal of Neurology, Neurosurgery, and Psychiatry* 2005 Sep;76:1194–9.
18. Bennett DA, Wilson RS, Schneider JA, Bienias JL, Arnold SE. Cerebral infarctions and the relationship of depression symptoms to level of cognitive functioning in older persons. *Am J Geriatr Psychiatry* 2004 Mar–Apr;12:211–9. [PubMed: 15010350]