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Clinical-Pathologic Correlations in Vascular Cognitive Impairment and Dementia

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Abstract

The most common causes of cognitive impairment and dementia are Alzheimer's disease (AD) and vascular brain injury (VBI), either independently, in combination, or in conjunction with other neurodegenerative disorders. The contribution of VBI to cognitive impairment and dementia, particularly in the context of AD pathology, has been examined extensively yet remains difficult to characterize due to conflicting results. Describing the relative contribution and mechanisms of VBI in dementia is important because of the profound impact of dementia on individuals, caregivers, families, and society, particularly the stability of health care systems with the rapidly increasing age of our population. Here we discuss relationships between pathologic processes of VBI and clinical expression of dementia, specific subtypes of VBI including microvascular brain injury, and what is currently known regarding contributions of VBI to the development and pathogenesis of the dementia syndrome.

1. Introduction

Cognitive impairment is identified as reduced performance in a variety of cognitive domains as typically measured with psychometric testing. Reduction in certain cognitive abilities is expected with increasing age. In some individuals, however, reduced cognitive function progresses beyond anticipated age-related cognitive decline resulting in a diagnosis of mild cognitive impairment (MCI) or dementia. Patients diagnosed with MCI exhibit impairments

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in one or more cognitive domains that do not substantially impact their usual activities; those diagnosed with MCI are significantly more likely to progress to dementia in subsequent years. A clinical diagnosis of dementia indicates more severe cognitive decline with concurrent impact on functional activities, such as managing financial matters, driving, and taking medications. In many people, dementia also is accompanied by behavioral and psychiatric changes. MCI and dementia are diagnoses that describe varying degrees of clinically apparent cognitive impairment; however, neither specifies a particular disease. Rather, each is a clinical syndrome, a collection of signs and symptoms that can be caused by multiple diseases either alone or in combination.

A diagnosis of MCI or dementia may be made on a given day, but the underlying neurodegenerative processes that ultimately result in a patient's cognitive impairment have been operating for years or decades. There are three hypothetical stages of chronic diseases: latency, in which pathophysiologic processes have started but there are no signs or symptoms; prodrome, in which the damage has progressed and there is some indication of the presence of disease (*e.g.*, MCI, which is conceived to be a prodromal state of dementia); and full expression, in which there is full clinical manifestation (*e.g.*, dementia). Although latency, prodrome, and full expression form a continuum for any chronic disease, in clinical practice there are exceptions to the theoretical progression from latency to MCI to dementia, potentially a result of poorly understood underlying pathologic processes.

Dementia is uncommon in individuals younger than 65 years of age; however, in this age range, the most common neurodegenerative causes are Alzheimer's disease (AD) and frontotemporal dementia [1–4]. Dementia in individuals older than 65 years of age is a major public health problem that causes substantial socioeconomic burden and threatens the stability of health care systems in the foreseeable future [5]. In individuals older than 65 years, the most common diseases contributing to the dementia syndrome are AD, vascular brain injury (VBI), and Lewy body disease (LBD) [6–8]. Importantly, in older individuals, some combination of these three diseases commonly co-exist, a condition referred to as co-morbidity. Based on genetic risk and biomarker data, the molecular drivers of these three diseases appear to be distinct, although they may interact with one another pathophysiologically.

Partial or full clinical expression of one or more of these underlying diseases leads to a variety of diagnoses based on clinical features: MCI or AD dementia in the case of AD, vascular cognitive impairment (VCI) in the case of VBI, Parkinson's disease (PD) with or without cognitive impairment or dementia with Lewy bodies (DLB) in the case of LBD, and mixed or multiple etiology dementia [9]. In this clinico-pathologic review, we focus on vascular contributions to cognitive impairment and dementia, either alone or in combination with other common chronic diseases.

2. Vascular disease and vascular brain injury

Vascular disease is a term that encompasses all of the pathophysiologic processes that target intrinsic components of blood vessels. Examples include atherosclerosis, arteriolosclerosis, thromboembolism, amyloidosis, vasculitis, vasospasm, malformation, aneurysm, and

dissection. In addition, some diseases impair cerebrovascular function without targeting components of the vessel wall. Examples of these are blood dyscrasias and coagulopathy. All of these vascular diseases can lead to cerebrovascular dysfunction and damage the brain; *i.e.*, VBI.

VBI is a function of multiple variables. These include the etiologic factors discussed above, level of cerebrovasculature involved (artery, arteriole, capillary, vein), efficiency of anastomotic connections, anatomic idiosyncrasies of the circle of Willis, age, heritable factors, and environmental, dietary, and pharmaceutical exposures. VBI typically is categorized as either ischemic or hemorrhagic, with ischemic further subdivided into regional or global.

2.1. Regional VBI is Classified by Vasculature that Subserves Area of Injury

2.1.1 Arteries—The extracranial- and extraparenchymal-intracranial arteries that perfuse the brain are common sites of vascular occlusion. Thrombosis complicating atherosclerosis is a frequent means of occlusion of the larger arteries, whereas lodgment of emboli is the predominant mechanism of occlusion in the major branches of the circle of Willis, particularly at the trifurcation of the middle cerebral artery. VBI resulting from the occlusion of these blood vessels often leads to acute and significant stereotypical functional deficits that correspond to the particular region of brain damaged. This type of VBI is referred to as territorial infarction, as in the vascular territory of the middle cerebral artery.

2.1.2 Intraparenchymal Small Arteries and Arterioles—The intraparenchymal arteries and arterioles that arise from the arteries at the base of the brain are particularly susceptible to a spectrum of pathologic changes. In older patients, especially those with a history of hypertension, these vessels characteristically show tortuosity with intimal thickening, luminal stenosis, and medial cell loss with replacement by collagen. Damaged endothelial cells cannot oppose the insudation of plasma proteins, and the result is a swollen, acellular, and homogeneously eosinophilic blood vessel wall. Subsequently, eosinophilic material, mostly fibrin, seeps deeper and deeper into the vessel wall and may be accompanied by foam cells (fat-laden macrophages). The above-described changes in the vessel walls are collectively known as arteriolosclerosis or lipohyalinosis. These conditions are commonly associated with scattered perivascular monocytes, hemosiderin deposition, and dilatation of the perivascular space. The two classical forms of VBI that occur as a result of lipohyalinosis are lacunar infarcts and intracerebral hemorrhage.

2.1.3 Capillary Bed—Impairment of blood flow or occlusion of cerebral capillaries, often with involvement of small arterioles and venules, leads to regional ischemic damage characterized by petechial hemorrhages, perivascular myelin pallor, and small lesions often referred to as microinfarcts. These lesions are in fact difficult to distinguish definitively from microhemorrhages; for this reason we prefer the encompassing term microvascular lesion (MVL) when referring to pathologic change and microvascular brain injury (μVBI) when referring to the pathophysiologic process. Although they produce focal lesions, diseases affecting small blood vessels tend to be widespread and associated with global neurological dysfunction. Classic examples are thrombotic thrombocytopenic purpura, rickettsial

infections of the CNS, and fat or air emboli. Similar global functional impairment and dementia are associated with multiple cerebral MVLs observed in older adults with chronic hypertension and diabetes, but for whom the exact cause(s) are not known [10]. Recent advances in neuroimaging, especially 7T magnetic resonance imaging (MRI), have advanced our understanding of MVLs *in vivo* [11]; however, it must be stressed that despite more comprehensive assessment possible with MRI, the sensitivity to detect MVLs remains greater with microscopic examination, at least for the time being.

2.1.4 Veins—Venous sinus thrombosis is observed most frequently as a complication of systemic dehydration, hypercoagulable states, phlebitis, or secondary to compression or infiltration by an adjacent mass lesion. Venous thrombosis leads to stagnation of blood flow in the territories being drained, and eventually to conspicuously hemorrhagic infarcts that may involve the leptomeninges, cortex, and white matter. Finally, case reports highlight the potential for arteriovenous fistulae to masquerade as a progressive neurodegenerative disease, possibly as a result of functional changes secondary to altered cerebral blood flow. [12–14].

2.2. Global Ischemia

Cerebral perfusion pressure is a function of the difference between mean arterial pressure and intracranial pressure. Disease processes resulting in decreased mean arterial pressure or increased intracranial pressure may compromise cerebral blood flow and cause global ischemia. In its most extreme form, global ischemia culminates in total cerebral necrosis, a cause of “brain death”. In less extreme circumstances, *e.g.*, shock or cardiac arrest from which the patient is resuscitated, the pattern of VBI reflects an exaggerated or selective vulnerability of particular brain regions and cell types to ischemic injury.

2.2.1 Arterial Border Zone Infarcts—Arterial border zone, or watershed, infarcts occur at the distal extreme of arterial territories, in regions of the brain and spinal cord where vascular territories overlap. When cerebral blood flow begins to ebb and the region of effective perfusion contracts, tissue in the border zone experiences the earliest and most profound ischemia and may progress to infarction. The brain regions most commonly affected in adults are those at the interface of the anterior and middle cerebral artery territories. Less severe injury with neuronal necrosis and astrogliosis, but without cavity formation, may also be seen with the same bilateral parasagittal distribution; this is termed granular atrophy.

2.2.2 Laminar Necrosis—Laminar necrosis occurs as a result of reduced cerebral perfusion pressure, which leads to markedly reduced blood flow in the capillary plexus of the deep gray matter. When complete, cystic degeneration of the deeper layers of the cerebral cortical gray may be observed grossly, characteristically following the gyrations of the cortical ribbon. Unlike arterial infarcts, in which the necrotic tissue extends to the pial surface, laminar necrosis is surrounded by viable, albeit gliotic, brain parenchyma.

2.3. Complete vs. incomplete infarction and overlap of pathological changes

VBI as a result of ischemia assumes one of three general forms depending on the severity of insult. The first is a complete infarct with necrosis of all tissue elements that ultimately, and uniquely in brain, yields a cavitated lesion. The second form of injury, incomplete infarction, occurs when ischemia is less severe and produces necrosis of only the more vulnerable cells, not all tissue elements. Incomplete infarction demonstrates that neurons and oligodendroglia are more vulnerable than other cell types to hypoxia/ischemia. Incomplete infarcts may exist apparently independent of complete infarcts; however, a zone of incomplete infarction typically surrounds the cavitated lesions of complete infarcts. For MVLs in cerebral cortex, complete lesions are microscopic cavities or parenchymal contraction around a central area of complete necrosis whereas incomplete lesions are marked by focal reduction in neuron density with gliosis that interrupt the otherwise orderly columnated and laminated organization. In white matter, MVLs may be complete cavitated lesions or incomplete lesions characterized by a microscopic focus of oligodendroglia loss, axonal degeneration, and gliosis. In global incomplete ischemia, selective loss of *cornu ammonis* pyramidal neurons of the hippocampus and cerebellar Purkinje cells occurs because these neurons are most vulnerable to the changes of ischemia. A third form of ischemic injury results in dysfunction but not necrosis of tissue elements, and at times may lead to gliosis but in other instances may leave no pathologic signature.

Finally, although using the level of vasculature as an approach to classification is useful in considering different types of VBI, it is crucial to emphasize that different types of VBI commonly co-exist in the same brain. This point is very important because it confounds interpretation of clinical-pathologic correlations. Thus, while the clinical-pathologic correlations presented above are a useful framework for understanding the complexity of VBI and its consequences to cognitive function and dementia, precise cause-and-effect relationships often are difficult to establish with certainty. This complexity is the reality of the aging human brain and will require clinical investigation of rare forms of VBI that occur in relative isolation and experimental approaches.

3. Cognitive impairment and dementia from VBI

Cognitive impairment and dementia may occur as a result of VBI exclusively or in conjunction with other pathologic processes that together contribute to the dementia syndrome [15]. Inherited diseases of the cerebrovasculature are perhaps the most clearly defined examples of VBI alone leading to cognitive impairment and dementia, whereas sporadic VBI is seen more often in association with comorbid diseases.

3.1. Genetic causes

3.1.1 Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)—Rare inherited diseases may lead to dementia in relatively young individuals. These diseases are important to consider because they demonstrate that cerebrovascular disease and VBI, in the absence of other disease processes, can cause cognitive impairment and dementia. The most common of these inherited diseases

is CADASIL, which is an autosomal dominant syndrome of stroke like episodes and leukoencephalopathy caused by mutations in the NOTCH3 gene [16].

CADASIL is characterized clinically by onset around 30 years of age with migraine headaches followed by transient ischemic attacks, ischemic VBI, cognitive decline, and eventually dementia. *NOTCH3* mutations in CADASIL were first reported in 1996 [16]. When mutated, NOTCH3, which is selectively expressed by vascular smooth muscle cells [17], is thought to result in degeneration of vascular smooth muscle cells and consequent impairment of vasomotor function [18].

The anatomic distribution of arteriole involvement in CADASIL is diffuse; however the CNS is predominantly affected, particularly the leptomeninges, deep white matter, basal ganglia, thalamus, pons and spinal cord. CADASIL-specific vascular changes include the deposition of granular basophilic medial deposits, granular osmiophilic material deposition (on electron microscopy), accumulation of the extracellular domain of NOTCH3, degeneration of medial smooth muscle cells, and fibrous arteriolar wall thickening with luminal stenosis (Figure 1). VBI from CADASIL commonly includes lacunes and leukoencephalopathy.

CADASIL is considered the archetype of pure vascular subcortical dementia, but the cerebral cortex is likely involved as well. Although not uniform, radiographic evidence strongly favors cerebral cortical involvement in CADASIL [19,20] with apoptotic neurons [21] and MVLs [22] in the cerebral cortex. Interestingly, apoptotic neurons are predominately in layers 3–5 of cerebral cortex without topographical correlation with cerebral MVLs. Instead, cerebral cortical apoptotic neurons appear to have close topographical relationships with axonal changes in the subcortical white matter, suggesting that cerebral cortical neuron death may be secondary to axonal changes in the underlying subcortical white matter via axonal retrograde degeneration or deafferentation. Thus, chronic alterations in small vessel function caused by a specific mutation lead to extensive cerebral degeneration and dementia.

3.1.2 Other Inherited Forms—CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy) is a rare entity caused by mutations in high-temperature requirement A serine peptidase 1 (HTRA1) [23] with a similar clinical phenotype as CADASIL but with more apparent memory impairment [18,24,25]; MRI studies of CARASIL demonstrate widespread white matter injury and cortical atrophy with characteristic late stage T2 hyperintense lesions from pons to middle cerebellar peduncles [26]. CARASIL affects the same small vessels as CADASIL, but without the characteristic accumulation of basophilic material or granular osmiophilic material. The histopathologic features of vessels in CARASIL do not appear to be specific to the disease and are primarily characterized by advanced arteriosclerotic changes. White matter is involved by diffuse ischemic changes that spare U fibers [27]

Cerebral amyloid angiopathy (CAA) is characterized by amyloid β deposits within the wall of arterioles and small arteries in the brain and leptomeninges [28], and is strongly associated with cerebral cortical microhemorrhage [29], and spontaneous lobar hemorrhage

in the elderly [30]. Familial CAA is caused by a variety of mutations in the amyloid precursor protein (APP) gene, and is usually, but not always, accompanied by pathologic changes of AD [31]. Patients with hereditary cerebral hemorrhage with amyloidosis-Dutch type consistently have severe CAA in association with minimal neurofibrillary degeneration; however, the amount of CAA, as quantified by computerized morphometry, is associated with the presence of dementia and not neurofibrillary degeneration, senile plaque density, or age [32]. These findings suggest that CAA in isolation may be sufficient to cause dementia, and may have implications for AD. Indeed, one autopsy study showed that 83% of AD patients had at least mild CAA, and 26% had moderate to severe CAA affecting more than one region of cerebral cortex [33]. CAA, particularly the familial type, is associated with VBI, especially micro and lobar hemorrhages but also ischemic injury [34]. Beyond the complexity of multiple types of VBI, familial CAA provides potentially valuable insights into AD pathogenesis, because mutations in the APP gene result in varying levels of AD pathologic change and CAA [35]. There is a strong *APOE* ε4 allele dose-dependent increased risk of CAA and AD, with much overlap but also important differences in the composition of Aβ deposits in these diseases [36–38].

3.2. Sporadic VBI

The vast majority of VBI is “sporadic,” meaning there may be multiple genetic and environmental risk factors of varying strengths, but no known genetic cause or clear environmental stressor. Assessment of the extent to which sporadic VBI contributes to cognitive impairment and dementia has been hindered by three issues: (i) common co-morbidity of VBI with other causes of cognitive impairment and dementia in older adults, particularly AD, (ii) co-existence of multiple types of VBI in the same brain, and (iii) lack of a clear, standardized and widely accepted protocol for pathologic evaluation.

3.2.1 Co-morbidity of sporadic VBI with other common causes of cognitive impairment and dementia—Most knowledge about the contribution of sporadic VBI to cognitive impairment and dementia has come from community- and population-based studies of brain aging that do not select for specific neurodegenerative diseases [39].

This area of investigation was initiated with the landmark publication from the Nun Study [40], and followed by important validation from the Oxford Project to Investigate Memory and Ageing [41] and the Honolulu-Asia Aging Study (HAAS) [42]. Investigators from the Adult Changes in Thought (ACT) Study validated the contribution of VBI to the risk of dementia and the use of screening sections of cerebral cortex for the enumeration of cerebral MVLs as an efficient means of staging the extent of μVBI [8]. Using this approach, ACT Study investigators estimated that the population-attributable risk for dementia in a typical urban/suburban population in the US was 45% for AD and 33% for μVBI. Subsequently, several other groups have reproduced these core results in studies from around the world [43–47].

To further investigate this issue of co-morbid diseases contributing to cognitive impairment, we developed a summary measure to represent individual co-morbidity called the summary neuropathology score. This method converts consensus neuropathologic criteria for AD

neuropathologic change, LBD, and μVBI into numerical scores of 0, 1, 2, or 3 and further sums these values for a maximum possible score of 9 [48]. Although there are limitations to this approach, the goal of the summary score is to graphically represent co-morbidity among individuals. The summary neuropathology score for each of 336 consecutively enrolled individuals from the ACT Study with available brain autopsy data is plotted in Figure 2, segregated into three groups based on cognitive and functional status. The first group encompasses higher cognitive performance individuals categorized as “not dementia,” with results on the Cognitive Abilities Screening Instrument (CASI), a screening measure of global cognitive function, of 91/100 or higher (upper four quintiles of ACT cohort [48]) within two years of death (n=107, average ± SD age at death 84 ± 7 years). The lower cognitive performance group is categorized as “not dementia,” but with performance on the CASI of 90 or lower (lowest quintile of ACT cohort) within two years of death (n=71, average ± SD age at death 88 ± 7 years). Individuals in the third group were diagnosed with “dementia” prior to death during a clinical diagnostic consensus conference, using DSM-III-R criteria (n=158, average ± SD age at death 89 ± 6 years). Interestingly, this individual approach to the pathologic data shows that in the high cognitive function group, only 3% of individuals had no evidence of any of these three diseases; the remaining 97% had pathological evidence of at least one disease. No one in the “not dementia, low CASI” group was free of disease. Co-morbidity varies widely among individuals in all three groups with the general trends from latency to dementia being: increased severity of AD neuropathologic changes, and increased frequency and severity for μVBI and LBD (Table 1).

Figure 3 graphs the cumulative frequency distribution of the summary neuropathology scores for the same three functional groups. Drawing a line at a summary score of 3, which represents high level of any one disease or a combination of low or moderate levels of multiple diseases, clearly distinguishes latent and dementia groups. Those with latent disease(s) have a summary score of 3 or less in approximately 80% of individuals, while only 30% of those with dementia have a summary score this low. The extremes of this graph are interesting to consider. How do approximately one-third of individuals with dementia have a summary score of 3 or less? Perhaps this represents individuals who are especially vulnerable to clinical expression of dementia from one or more of these diseases, or perhaps this is a result of one or more unknown processes. Additionally, how do approximately one-fifth of high functioning adults have summary scores of 4 or more? This very interesting group presumably has a larger functional reserve or some form of resilience making them resistant to the pathophysiologic process or clinical expression of cognitive impairment or dementia.

APOE alleles are known to influence one’s vulnerability to pathophysiologic process of AD; therefore, we explored a potential relationship of *APOE* alleles with μVBI (Figure 3B). The number of MVLs in consensus cerebral screening sections from individuals in the three functional groups was compared across the *APOE* genotypes ε2/ε3, ε3/ε3, or ε3/ε4. Functional group was highly significantly associated with number of MVLs ($P < 0.0001$) but not with *APOE* genotype, nor was there a significant interaction between these two variables. The high cognitive function group had the best representation across these three *APOE* genotypes. When focusing on this group (Figure 3C), there is a numerical trend toward higher number of MVLs in *APOE* ε2/ε3 > *APOE* ε3/ε3 > *APOE* ε3/ε4; however, this

is not statistically significant. These results are consistent with the hypothesis that lower levels of MVLs are sufficient to cause impairment for people with the *APOE* ε4 allele, compared with people with the *APOE* ε3 allele, and lower levels of MVLs are sufficient to cause impairment for people with the *APOE* ε3 allele, compared with people with the *APOE* ε2 allele. For comparison, the same individuals were evaluated for cerebral cortical concentration of Aβ42 and these results were significantly different ($P < 0.0001$). Together, this analysis indicates that μVBI is strongly associated with cognitive function but not with *APOE* genotype, and suggests the possibility that APOE genotype may impact the threshold of brain insults necessary to culminate in a diagnosis of dementia.

3.2.2 Co-existence of multiple types of VBI in the same brain—The overall unadjusted odds ratio for dementia from μVBI determined in the above referenced population- and community-based studies was approximately 2.3 [10]. It is important to stress that μVBI most commonly is co-morbid not only with neuropathologic changes of AD, including CAA, but also with other forms of VBI, primarily territorial infarcts and lacunes. All forms of VBI have the potential to cause some degree of cognitive impairment or dementia [49]. Most, but not all [50], studies have highlighted an independent contribution by μVBI; some even have concluded that μVBI and not larger forms of VBI are associated with risk for dementia [8,42,51–53]. These results should not be surprising because the propensity of μVBI to present with global cognitive impairment has been known for decades from diseases that target cerebral capillaries, *e.g.*, thrombotic thrombocytopenic purpura (TTP), rickettsial infection, fat emboli, and air emboli. Overall, these results demonstrate that VBI, both μVBI and larger infarcts, can significantly increase the clinical expression of dementia.

3.2.3 Consensus neuropathologic guidelines for VBI in cognitive impairment and dementia—One likely contributor to the variation in results from the studies cited above is inconsistent protocols for the sampling and evaluation of tissue. Indeed, the HAAS and ACT Study, which used the same protocols, independently have reached nearly identical results despite investigation of two very different populations [8,42]. This approach now forms the basis of tissue-based assessment of VBI, territorial infarcts, lacunes, and μVBI, in the context of dementia, and was adapted by a consensus panel of neuropathologists convened by the National Institutes on Aging and the Alzheimer's Association (NIA-AA) [54,55]. Briefly, the NIA-AA guidelines recommend the sampling of six regions of cerebrum followed by histologic assessment of H&E-stained slides. Other approaches exist and each has advantages and limitations. The strengths of the NIA-AA guidelines are that they are accessible to all pathology laboratories, and with time will generate a large consensus database on the contribution of multiple forms of VBI to cognitive impairment and dementia in older individuals.

4. Conclusion

The contributions of vascular disease and VBI to the development of cognitive impairment and dementia are varied and complex but clinically meaningful in older individuals. Inherited vascular diseases demonstrate that vascular dysfunction alone can cause dementia. The more common sporadic VBI, especially μVBI, in many older individuals interacts with

AD and perhaps other neurodegenerative processes, and less commonly has an exclusive causal role in dementia. The easily accessible NIA-AA guidelines provide a neuropathologic consensus for both the sampling and evaluation of tissue for VBI. A major challenge is to bring greater clarity to which type of VBI interacts with what specific pathophysiologic process of neurodegeneration to produce cognitive decline and dementia. One approach to meeting this challenge will be more detailed and technically sophisticated clinical-pathologic correlations, but success also will require advances in experimental models, like ones for VBI and AD. Recognition of the important contributions of VBI to brain health should guide public health strategies and medical management to diminish this common, yet treatable, contributor to cognitive impairment and dementia in the elderly.

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Highlights

- Different vascular diseases lead to different types of vascular brain injury
- Cognitive impairment and dementia may occur from vascular brain injury alone
- Vascular brain injury commonly is present in with Alzheimer's disease

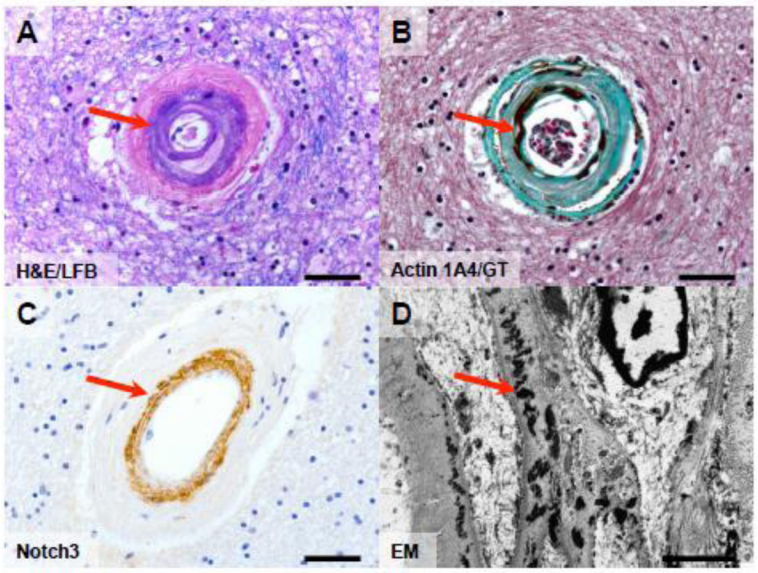

Figure 1. Pathologic changes in CADASIL

(A) Deposition of granular basophilic material within the vascular media (arrow) that can be observed on hematoxylin and eosin/luxol fast blue stained sections of cerebral cortical white matter. **(B)** In concert, smooth muscle breakdown (highlighted by brown smooth muscle actin immunohistochemistry (arrow) is present in conjunction with arterelosclerosis as demonstrated by increased collagen (green staining from Gomori trichrome). **(C)** Immunohistochemistry for Notch 3 extracellular domain highlights medial deposition (arrow) in sclerotic subcortical white matter arterioles, **(D)** which corresponds to granular osmiophilic material deposits identified ultrastructurally.

Scale bars in A–C = 100 microns; scale bar in D = 2 microns. H&E/LFB, hematoxylin and eosin/Luxol fast blue; GT, Gomori trichrome; EM, electron microscopy.

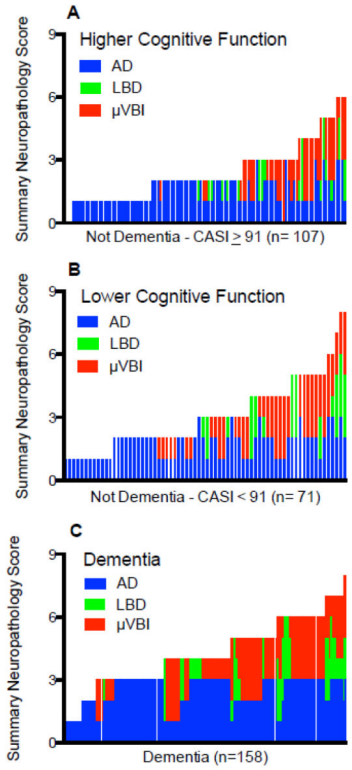

Figure 2. Distribution of individual summary neuropathology scores for three functional groups in the ACT Study

(A) Higher cognitive function: categorization of "not dementia" and performance on the CASI of 91 or higher(upper four quintiles of ACT cohort) within 2 years of death (n=107), **(B)** Lower cognitive function: categorization of "not dementia" and performance on the CASI of 90 or lower (lowest quintile of ACT cohort) within 2 years of death (n=71), and **(C)** Dementia: diagnosis of "dementia" (n=158). Diagnosis of "dementia" was made according to DSM-IV criteria. Each bar is the summary neuropathology score for an individual, which converts consensus neuropathologic results into numerical scores of 0, 1, 2, or 3 and then sums these values for AD neuropathologic change (AD), LBD, and μVBI for a maximum score of 9. For AD neuropathologic change (blue), consensus grades of "not AD," "low AD neuropathologic change," "moderate AD neuropathologic change," and "high AD neuropathologic change" were converted to 0, 1, 2, and 3, respectively. For μVBI, the number of microvascular lesions observed by consensus protocol were grouped as 0 for no MVL, 1 for 1 MVL, 2 for two MVLs, and 3 for three or more MVLs. For LBD, 0 is for no LB observed, 1 for LB in the substantia nigra or locus ceruleus, 2 for LB in the limbic system, and 3 for cerebral cortical LB in consensus tissue sections.

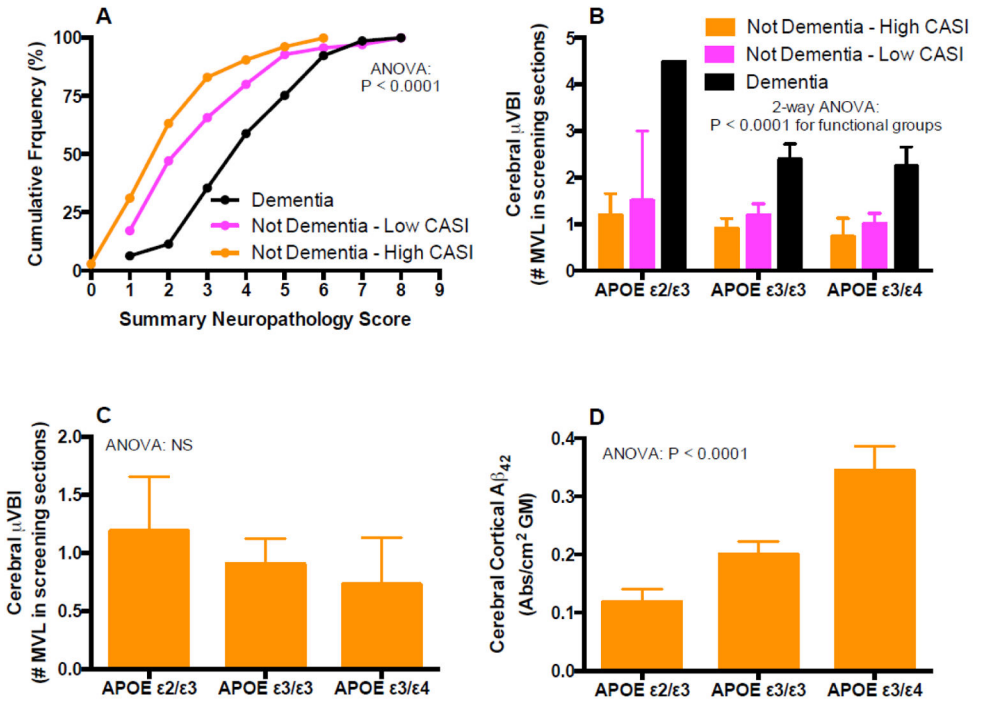

Figure 3. µVBI in the ACT Study

(A) The cumulative frequency distribution of summary neuropathology scores for the same three functional groups as described in Figure 2. ANOVA had $P < 0.0001$ and corrected repeat comparisons had $P < 0.05$ for every paired comparison. **(B)** Plot of the number of MVLs in consensus screening sections from the subset of individuals in panel A with the corresponding *APOE* genotypes. Data are mean ± SEM except for the APOE 2/3 "Not dementia Low CASI" group (n=2) and *APOE* 2/3 "Dementia" group (n=8) which plot only the mean because of small sample sizes. Two-way ANOVA for the entire data set of only *APOE* 3/3 and *APOE* 3/4 had $P < 0.0001$ for cognitive function or dementia group, but was not significant for *APOE* genotype or interaction. **(C)** Plot of the number of MVLs in consensus screening sections or **(D)** concentration of cerebral cortical $A\beta_{42}$ from ACT participants categorized with "not dementia" and performance on the CASI of 91 or higher (upper four quintiles of ACT cohort) within 2 years of death and who have *APOE* genotypes 2/3 (n=16), 3/3 (n=51), or 3/4 (n=22). ANOVA was not significant (NS) for number of MVLs but had $P < 0.0001$ for cerebral cortical concentration of $A\beta_{42}$.

Table 1

Neuropathologic burden of disease

Prevalence and severity of neuropathologic burden of disease among 336 ACT study participants with consecutive brain autopsy stratified into three functional groups: (i) high functioning individuals categorized within 2 years of death as “not dementia” and with performance on the CASI of 91 or higher (n=107, average ± SD age at death 84 ± 7 years), (ii) individuals categorized within 2 years of death as “not dementia” and with performance on the CASI of 90 or lower (n=71, average ± SD age at death 88 ± 7 years), and (iii) individuals diagnosed with “dementia” (n=158, average ± SD age at death 89 ± 6 years). Data are percentages of individuals with any neuropathologic change or the highest level of Alzheimer’s disease (AD)neuropathologic change, microvascular brain injury (μVBI), or Lewy body disease (LBD).

	Prevalence among 336 consecutive ACT brain autopsies (%)					
	Any Pathologic Change			**Highest Level Pathologic Change**		
	High CASI	**Low CASI**	**Dementia**	**High CASI**	**Low CASI**	**Dementia**
AD	97	100	100	7	10	56
μVBI	32	49	61	11	14	31
LBD	15	17	24	1	8	7