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The role of cerebrovascular disease when there is concomitant Alzheimer disease

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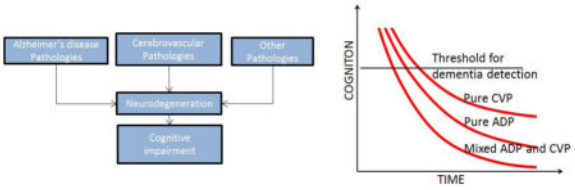
Abstract

Cerebrovascular Pathologies (CVP) are the most common co-existent pathologies observed in conjunction with Alzheimer disease. CVP rarely exists in isolation in later life, and CVP most likely plays a supporting role, rather than a sole leading role, in the pathogenesis of dementia. Our goal is to illustrate CVP's role using neuroimaging biomarkers. First, we discuss the frequency of CVP and present data from population-based Mayo Clinic Study of Aging. Here, we used a novel metric for identifying individuals with cerebrovascular imaging abnormalities (that we designate as "V+") and present the frequency of V−/V+ in the context of absence and presence of β-amyloid elevation (designated A−/A+). Next, we discuss the contribution of CVP to neurodegeneration and use hippocampal volume loss over time in a subset of participants categorized as A−V−, A−V+, A+V−, A+V+. Lastly, we discuss the contribution of CVP to cognitive impairment and conclude with the considerations for design of future studies.

Graphical Abstract



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Disclosures

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Introduction

Late onset dementia is usually a multi-factorial process wherein multiple, cumulative brain insults result in progressive cognitive impairment which ultimately leads to dementia. Cerebrovascular Pathologies (CVP) are the most common co-existent pathologies observed in conjunction with Alzheimer disease (AD)[1, 2]. The imaging hallmarks of CVP are white matter hyperintensities (WMH), lacunar infarcts, larger regional infarcts and cortical microbleeds. Both WMH and lacunar infarcts are believed to represent disease at the arteriolar level, and it is this type of CVP, that is thought to be close to, if not the main basis, for cognitive impairment in late life[3, 4]. WMH are not "pure" vascular lesions as they may also be related to neurodegenerative processes[5, 6], but it is nearly certain that ischemic and hypoxic changes cause WMH[7–10]. Lacunar infarcts are "pure" vascular lesions, of course, but their relevance may also lie in the extent that they are correlated with the presence of microinfarcts[11]. Even if microvascular disease is not the proximate cause of cognitive dysfunction in the setting of CVP, the burden of WMH and lacunar infarcts are reasonable biomarkers to estimate the "true" causal lesion.

Our goal is to review the role of CVP when there is concomitant AD using WMH and lacunar infarcts as biomarkers for CVP. Cortical microbleeds will not be considered here because despite their possible arteriolosclerotic basis, they are related to β-amyloid abnormalities[12–14]. We will first discuss the frequency of CVP in the elderly, the neurodegenerative changes associated with CVP, and the cognitive changes seen due to CVP. We will discuss these in in conjunction with a biomarker of Alzheimer's disease pathophysiology (ADP) because understanding the interrelationship between the two is critical for placing CVP in context. We have no evidence that non-AD degenerative processes have an interaction with CVP. Hence, other pathologies (pure Lewy body disease, hippocampal sclerosis etc.) will not be discussed here. We will conclude with a discussion of typical cognitive decline trajectories seen in etiologically pure dementias and etiologically combined dementias.

Frequency of Cerebrovascular Disease

Neuropathologically, CVP becomes evident in midlife and its frequency increases with age to about 60% by age 100[15]. Due to the lack of consistent criteria for diagnosing cerebrovascular disease relevant to cognitive impairment at autopsy and for the clinical diagnosis of vascular dementia, the proportion of persons with dementia and cerebrovascular disease varies between 10–40%[16]. At autopsy, pure vascular dementia due to "silent infarcts" is often rare and most cases are temporally related to overt, clinically-evident strokes[17]. The overall percentage of non-demented subjects with cerebrovascular disease, defined neuropathologically, is about a third of the elderly population[11, 18, 19]. Imaging evidence of WMH and infarcts also supports the claim that CVP increases steadily from midlife to later life[20–22].

In order to understand the prevalence of CVP in the elderly before the onset of cognitive impairment, we used a population based cohort of 457 cognitively normal Mayo Clinic Study of Aging (MCSA) participants (aged 70+)[23]. The basis for inclusion was the

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availability of usable Pittsburgh compound B positron emission tomography (PIB-PET) imaging from which amyloid load was ascertained and FLAIR MR imaging from which grading of WMH and enumerating of lacunar infarcts was completed[24]. We classified participants as being on the amyloid pathway (A+) if they had a global cortical Aβ load of ≥1.5 Standard uptake value ratio. The criteria for abnormal vascular pathway (V+) were based on a combination of infarcts and WMH burden. Either one infarct or a WMH load ≥ 1.11% of total intracranial volume was necessary for a designation of V+. We derived the WMH value using an independent subsample of 1,082 non-demented individuals (869 cognitively normal, 213 with mild cognitive impairment) from the MCSA[24]. We assumed that while the effect of an infarct on cognition can vary based on the size and location of the infarct, the presence of a large cortical infarct or a subcortical infarct was sufficient to indicate the presence of relevant CVP (V+). Next, we estimated how much WMH (as a percentage of total intracranial volume (TIV)) would cause the same annual rate of cognitive decline as seen by an infarct. The resultant WMH cutpoint was 1.11%. The extent of WMH/TIV% load corresponding to 1.1 is shown in Figure 1. We noted that the cutpoint for V+ resulted in assigning about one third of our population to a V+ designation. That level is about the same as estimates from the neuropathological literature for similar age non-demented cohorts[25]. The cutpoint value therefore reflects “some” CVP and enables us to describe the imaging correlates of CVP. We recognize that the cutpoint values are probably far below a threshold needed to produce pure vascular dementia, but the development of an algorithm to quantitate imaging evidence of CVP with WMH and infarcts to assign a CVP positivity criteria to our participants. We believe the criteria represent only a first step, and intend to refine and expand the criteria in the future.

Figure 2 shows the frequency of vascular positivity and amyloid positivity in cognitively normal individuals across the age spectrum between 70 and 90 years derived from a cross-sectional analysis. The percentage with neither AVP nor CVP (A−V− group) was 73% at age 70 and dropped to 24% by age 90. Individuals with only CVP (A−V+) monotonically increased with age from 15% at age 70 to 36% at age 90. Participants with both ADP and CVP pathologies (A+V+) had an estimate of 0 at age 70 but steadily increased to 30% by age 90. Vascular-disease-positive individuals (A+V+ and A−V+) started at 15% at age 70 and steadily increased to 66% by age 90. The prevalence of participants with A+V− peaked at around age 80 and then steadily declined at higher ages. A plausible explanation was that persons who were A+V− transition to the A+V+ category. The observations of monotonic nature of vascular positivity (combined A−V+ and A+V+) and non-monotonic nature of amyloid positivity (combined A+V− and A+V+) which peaked around age 85 years but slightly decreased in the oldest old was similar to the frequency curves based on amalgamation of published neuropathological literature[15]. An important observation here is that there are still V+ individuals at older ages who were cognitively normal suggesting that the presence of vascular disease alone in most cases may not be sufficient to cause cognitive impairment.

While CVP and ADP coexist in the older age ranges, similar to what has been seen in neuropathological studies[1], our observations show that at younger age the overlap is less. Beyond age 90 years, however, the proportion of A+ cases who are also V+ suggests that

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cerebrovascular disease cannot be ignored. These data provide a population-based antemortem view of the coexistence of ADP and CVP.

Contribution of Cerebrovascular Pathologies to Neurodegeneration

CVP is associated with neurodegeneration. While extensive WMH can drive widespread cortical thinning and ventricular expansion[26–28], regional WMH load may also be relevant. For example frontal WMH may have a greater impact on frontal lobe thinning[28–31]. On the other hand, locations of the infarctions also have a direct impact on region specific neurodegeneration[32]. Imaging studies show substantial white matter integrity loss (as measured by diffusion tensor imaging) in cerebrovascular disease[33, 34]. A recent study, for example, showed that increased vascular burden may lead to subtle attentional network dysfunction, through impaired frontal-parietal and frontal interhemispheric connectivity[35].

In a subset of participants from the Mayo Clinic Study of Aging (303 cognitively normal individuals with baseline vascular imaging ratings, PET-derived β-amyloid levels and at least two serial structural MRI scans), we gauged the impact of A+ or V+ status on hippocampal atrophy, which in turn is a direct marker of neurodegeneration. Figure 3 shows the differences in slopes of hippocampal volume by group. We found that there was significantly more hippocampal volume loss in participants due to amyloid positivity than vascular positivity. A+V− subjects had more significant volume loss than A−V− as well as A−V+ subjects ($p<0.05$) suggesting that the effect of ADP may be greater on hippocampal volume in comparison to the effect of CVP on hippocampal volume early in the disease process. Thus, using hippocampal volume as a proxy for neurodegeneration, V+ status did not have any impact. To the extent that hippocampal volume changes are likely to precede episodic memory loss associated with ADP, our observations fail to support a role for CVP for a cognitively relevant biomarker of neurodegeneration. On the other hand, there are many other mechanisms by which CVP could influence cognition, such as brain volume loss in other regions and disconnection of cortical regions due to white matter integrity loss[36]. Nonetheless, at least as far as hippocampal volume in cognitively normal persons, CVP was neither additive nor interactive with an ADP process. Our data do not support the claim that CVP interacts with ADP at the structural imaging level in the hippocampus.

Contribution of Cerebrovascular Pathologies to Cognitive Impairment

In the MCSA, we found that ADP and CVP both affect longitudinal cognitive trajectories adversely and are the major drivers of age related cognitive decline in the elderly[24]. Specifically we found that for a prototypical 79-year-old participant (the mean age in the study), the predicted annual rate of global cognitive z-score decline was −0.02 if the subject had neither CVP nor ADP (A−V−), −0.07 if the subject had CVP (A−V+), −0.08 if the subject had ADP (A+V−), and −0.13 if the subject had both CVP and ADP (A+V+). The latter is statistically the sum of the independent effect of ADP and CVP .and there was no evidence for an interaction between CVP and ADP. Other biomarker studies have also found that the effect of CVP and ADP was approximately additive on cognitive performance i.e. the effect of CVP and ADP on cognition is the sum of the independent effects of CVP and ADP[37–41]. Several pathology studies have also found that vascular risk factors may

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independently contribute to the risk of dementia by increasing the burden of CVP but do not directly influence the burden of ADP [40, 42–44].

In Figure 4, we summarize the typical cognitive decline trajectories that may be expected in combined etiology dementia (A+V+) individuals in comparison to subjects with pure ADP (A+V−) and persons with pure CVP (A−V+). As illustrated in Figure 4A, for the same amount of amyloid burden and vascular burden, the time to dementia for persons with pure ADP is shorter and rate of cognitive decline is faster than those with pure CVP. The presence of both ADP and CVP significantly lowers the time to onset of dementia and increases the rate of cognitive decline in comparison to the presence of ADP or CVP alone. In Figure 4A, we made a simplistic assumption that both pathologies start almost at the same time and evolve in parallel which is rarely the case. In Figure 4B, we present a scenario where CVP may start at a later time after the onset of AD. In Figure 4C, we present a scenario where a single strategic infarct causes significant impact on cognitive performance shown by a step function followed shortly by the onset of ADP which further worsens cognition. The threshold shown in the figure indicates the cognition threshold for dementia detection.

Design of Future Studies

It is important to account for cerebrovascular disease while studying other dementing diseases because it has an impact on the expression of cognitive impairment. Intervention trials on different dementia populations may lend different results due to the difference in vascular disease burden. We recognize that including cerebrovascular imaging will make presentations that focus on Alzheimer's or Lewy Body diseases more complicated, but burden of CVP should be accounted for.

Studies need to be better designed to accommodate and understand multi-etiology dementias because they represent at least a substantial minority of dementia cases and perhaps a majority over age 90 years. Multicenter studies such as the Alzheimer's Disease Neuroimaging Initiative exclude participants with severe vascular disease which might limit the generalizability of some studies from that cohort, especially ones that make claims about cerebrovascular lesions.

In AD, the latest diagnostic formulations (NIA-AA and International Working Group criteria) have proposed the incorporation of AD-related biomarker based cutoffs for diagnosis[45, 46]. The field is rapidly moving towards the use of cut-points for operationalization of biomarker-based clinical diagnostic criteria for dementia. While there is an impetus to standardize criteria for clinical diagnosis, pathological diagnosis, and neuroimaging image interpretation and reporting in vascular cognitive impairment.[47, 48], there are still no widely accepted criteria for determining biomarker positivity for cerebrovascular disease. Given multiple different hallmarks of CVP based on neuroimaging, there is a need to develop methodologies, such as we described here, that provide a consolidated measure for cerebrovascular disease and thus allow us to classify subjects as positive or negative for CVP. Our attempt described here and in a prior publication[24] is a preliminary one that requires further refinement and validation. This will not only accelerate our understanding of CVP in the context of late life dementia but also provide a single

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metric that can be used to account for CVP while studying other neurodegenerative and age-related illnesses.

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Highlights

- We used a novel metric for identifying individuals with CVD imaging abnormalities.
- We estimated prevalence of CVD and amyloid in a cognitively normal elderly sample.
- Greater hippocampal volume loss due to amyloid elevation than vascular abnormalities.
- Faster rate of cognitive decline in individuals with both amyloid and CVD abnormalities than alone.

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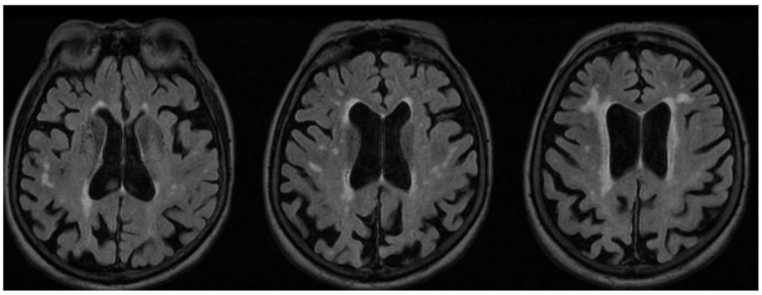

Figure 1.
Illustration of the extent and distribution of white matter hyperintensities on a FLAIR MRI observed in an 80 year old female at the cutpoint of 1.1 % WMH of TIV. From a figure shown in[24].

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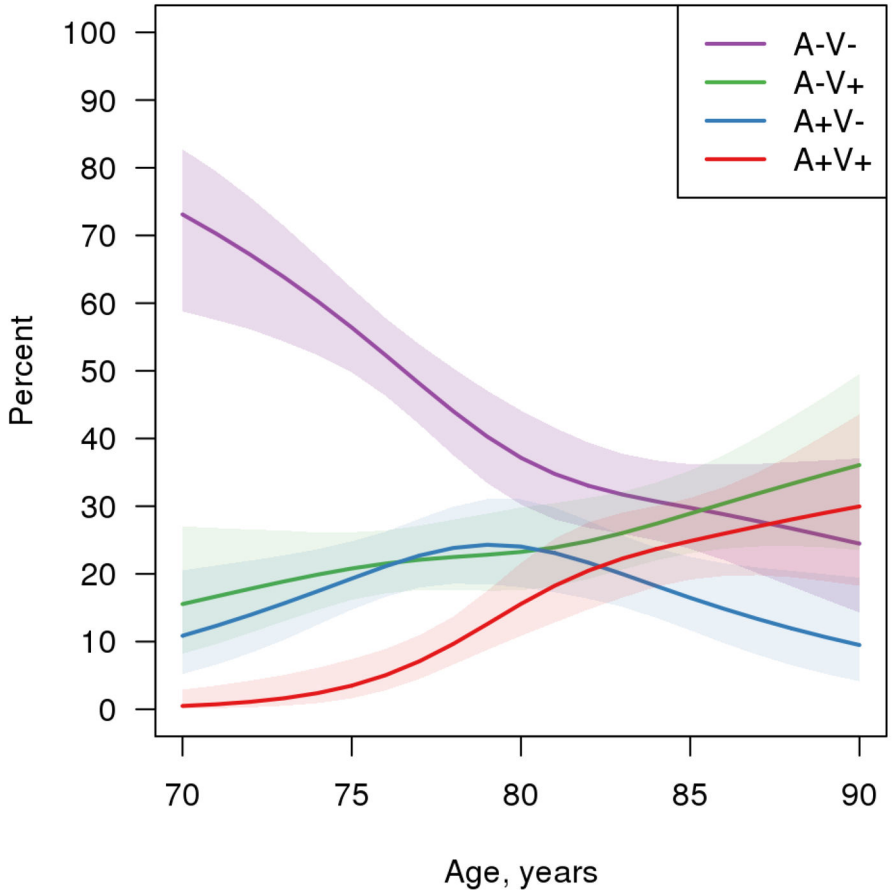

Figure 2.
Prevalence of Amyloid positivity (A+) and Vascular Positivity (V+) in cognitively normal elderly.

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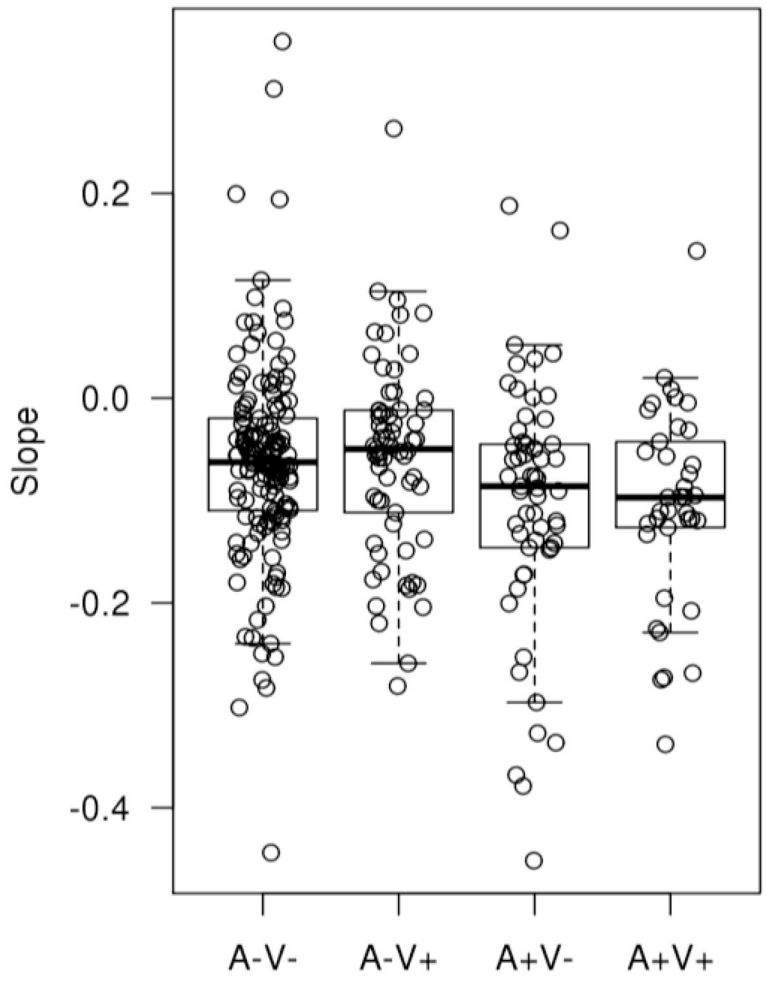

Figure 3.

Slopes of Hippocampal volume on serial MR scans seen in cognitively normal individuals classified by amyloid and vascular positivity and negativity at baseline. Note that the mean values are all negative indicating some loss in all 4 groups. Subjects with A+V− and A+V+ had significantly greater decline in hippocampal volume in comparison to both the A−V− and AV+ groups.

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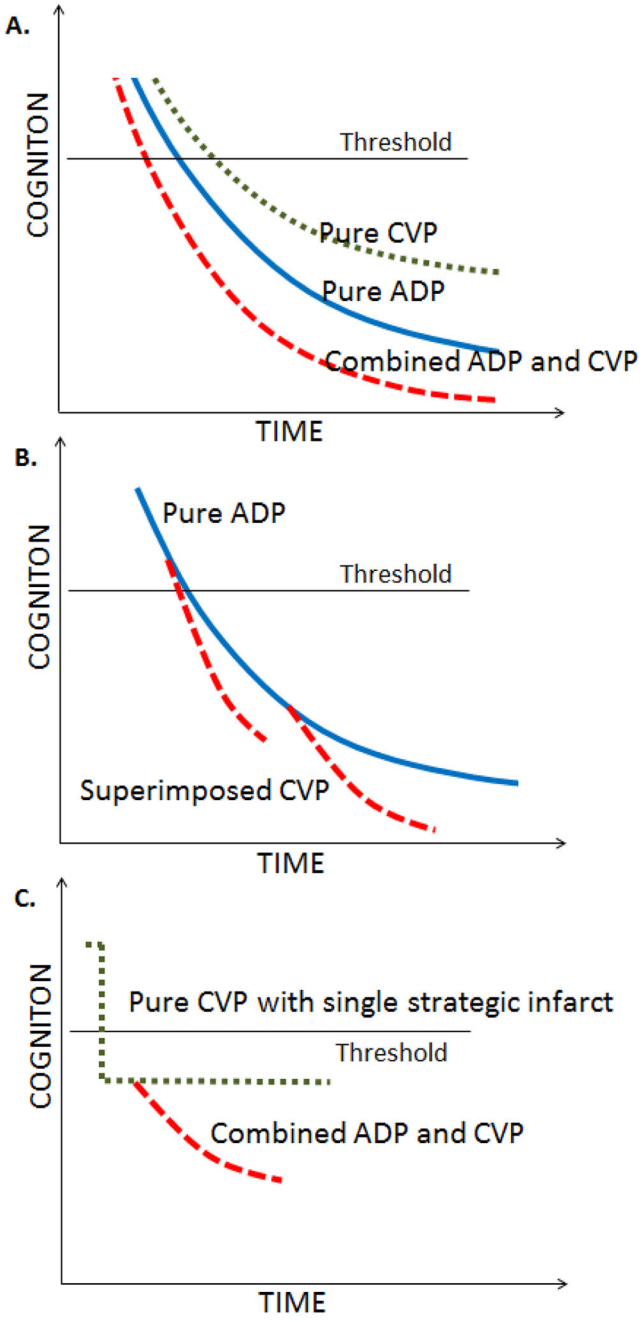

Figure 4.

Typical cognitive decline trajectories that may be expected in pure vs. multi-etiology dementias as a function of time. Panel A illustrates trajectories when the evolution of CVP and ADP are nearly at the same time. Panel B illustrates trajectories when CVP starts at a later time after the onset of ADP. Panel C illustrates trajectory where the event of a single strategic infarct (pure CVP) is followed shortly by the onset of ADP. The threshold shown in the figure indicates the cognitive threshold for dementia detection.