Role of Vascular Disease in Alzheimer-Like Progressive Cognitive Impairment

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The Case
A 75-year-old woman is evaluated for difficulties with memory and daily function. Over the past 2 years, she has had progressively worsening short-term memory and difficulties paying bills accurately or cooking complex meals. Her medical history is positive for hypertension and coronary artery disease with no recent cardiac symptoms and no history of transient ischemic attack or stroke. Her neurological examination is notable for a mini-mental state examination score of 24. Magnetic resonance imaging scan shows mild-to-moderate cortical atrophy, mild-to-moderate white matter hyperintensities, and a chronic lacunar infarct in the left thalamus.

The Question
Is vascular disease a significant contributor to this patient’s cognitive impairment?

Vascular Disease Is a Significant Contributor To This Patient’s Cognitive Impairment
Anand Viswanathan

Is cerebrovascular disease contributing to this woman’s cognitive impairment? The answer is a resounding yes. With all respect to my colleague on the other side of this controversy, it would be a gross clinical misjudgment to assume minimal or no contribution of stroke to this individual’s cognitive state.

If we had been living in the late 19th and early 20th centuries when Dr Alois Alzheimer made his discoveries regarding neurodegeneration, we would not even be having this debate. At that time, it was widely accepted that vascular disease was the most important cause of cognitive impairment and dementia. Neurodegenerative pathology as a cause of dementia was considered the rare exception as Alzheimer’s first case report clearly showed. So what has changed? Cerebrovascular disease is now a common accompanying finding in patients diagnosed with neurodegenerative dementia, contributes to cognitive impairment independently of AD pathology, and accelerates cognitive decline in patients presenting to memory clinics. The current patient’s hypertension and coronary artery disease are strongly associated with more rapid cognitive decline, particularly in the domains of global cognition, naming, and information processing speed. Executive function deficits are evidenced in this patient by difficulties in paying bills and cooking complex meals. The silent lacunar strokes and white matter hyperintensities (or leukoaraiosis) in this patient, though commonly detected, are also clearly associated with cognitive dysfunction and elevated dementia risk.

Cerebrovascular disease is, thus, most certainly contributing to cognitive impairment in this elderly patient, although it is difficult to ascertain the magnitude of the contribution. How much is AD and how much small vessel disease? If this patient indeed has underlying AD pathology, would it have manifested clinically in the absence of the small vessel disease? At this point, we may not have the necessary clinical tools to fully discern this. In vivo amyloid imaging is now a widely used research tool, but infrequently used in clinical practice. And though we are able to visualize and quantify numerous markers of cerebral small vessel disease, we are only beginning to address the independent impact of each lesion on cognition. Furthermore, recent studies have suggested that even relatively small and thus benign appearing lacunar infarctions can significantly disrupt brain networks and are responsible for cortical atrophy, which can then impact cognition.
Further support for the importance of cerebrovascular disease and vascular risk factors in age-related cognitive impairment comes from recent epidemiological data on the prevalence of dementia. These studies show that the prevalence of dementia has declined over a 2-decade period. In the absence of any effective therapy to date for Alzheimer’s pathology, these data imply that better control of vascular risk factors over the last 20 years has at least in part reduced dementia burden in the population. This is of particular importance in envisioning future therapeutic trials to reduce dementia incidence. It is also encouraging to the practicing clinician, who can offer specific vascular-based prevention strategies (such as treating mid-life hypertension, reducing obesity, increasing exercise and physical activity) to a patient like this rather than only being able to offer empathy.

In summary, I suggest that this case critically highlights our need as clinicians to consider cerebral small vessel disease, no matter how seemingly insignificant, when treating elderly patients with cognitive impairment. Although we have made great advances in our ability to visualize these vascular lesions, recent work makes it is clear that we have much to learn about the true implications of what we are seeing and not seeing. A small lacunar infarction with leukoaraiosis that may seem insignificant or even normal in itself may actually be the sole clue to an extensive underlying vascular pathology that we are currently unable to see with clinical tests. To ignore the importance of small vessel disease in this patient would be to remain blind to what is in front of our eyes.

**Vascular Disease Is Not a Significant Contributor To This Patient’s Cognitive Impairment**

Philip Scheltens

The answer to this question in this particular patient must be NO. Let us have a look at the arguments that drive this decision.

The age of the patient is 75. At this age, the a priori chance of having AD is over 20% and even higher when her APOE status would include of 1 or 2 E4 alleles. Then, the course of the disease with a 2 year history of a nonacute, slowly progressive memory loss and executive dysfunction fits with a typical presentation of AD and speaks against a primary vascular origin. The prior history of hypertension does not preclude AD because hypertension has been identified as a factor in many population studies and shown to promote amyloidogenic processing of the amyloid precursor protein. In addition, the patient has experienced no recent transient ischemic attack or other vascular incident.

The mini-mental state examination score of 24 is just at the cut off for dementia, but lower than usually seen in patients with vascular cognitive impairment. Finally, the magnetic resonance imaging shows generalized atrophy (no information on hippocampal atrophy is given), and only mild–moderate atrophy (unfortunately no grading is mentioned), which probably does not qualify for vascular dementia according to the most recent radiological criteria put forward by the International Society of Vascular, Behavioural and Cognitive Disorders (VASCOG) group. The one lacune in the left thalamus by itself may be responsible for cognitive dysfunction and would qualify radiologically, but then the onset is usually acute or subacute, and the course is rarely progressive.

**Dr Viswanathan’s Rebuttal**

I thank my right honorable colleague for his eloquent and persuasive remarks as to why vascular disease does not contribute to this patient’s cognitive impairment. Unfortunately, the facts are much less convincing and persuasive. Although the risk of AD in a 75-year-old patient is indeed over 20%, studies have shown the likelihood of having a mixed dementia (both neurodegenerative and cerebrovascular pathology) at this age is nearly 50%, the majority never experiencing transient ischemic attack or stroke. Furthermore, although it is true that a 2-year history of progressive memory loss and executive dysfunction is typical of AD, memory impairment also occurs in patients with vascular pathology and can be clinically indistinguishable from pure AD. Although generalized atrophy is common at later stages of AD, it seems less common than regional medial temporal atrophy earlier in the disease. By contrast, generalized atrophy is a common feature of vascular cognitive impairment. Although my colleague rightly states that lacunar infarctions can cause acute cognitive change in some cases, population-based studies show the large majority to be clinically silent, though still strongly linked to progressive cognitive impairment and dementia. Despite these minor differences, we are in strong agreement that it is our job as clinicians to aggressively monitor and treat all vascular risk factors in our patients with cognitive complaints.

**Dr Scheltens’s Rebuttal**

My learned colleague has of course a different opinion on this matter, but looking at the arguments, we are not far apart. The issue at hand was whether vascular disease plays a significant role in the cognitive impairment of this patient. His arguments are all about vascular disease in general and the contribution to dementia, with which I completely agree. Based on all the evidence, one cannot conclude that vascular disease does not play any role, which would be fooling ourselves and withholding this patient proper treatment. But the question of which is the major driver of cognitive impairment in this patient, neurodegeneration or vascular disease, must be answered as the former based mainly on evidence from patients with stroke or extensive white matter disease. Underlying AD is still the most significant driver of cognitive defects in all these studies, but remains incurable. Hence, treatment of contributing and perhaps even eliciting vascular factors may be more sensible for this patient and in fact all elderly patients with cognitive decline.

A compromise between YES and NO could be found in the assumption that this patient already had amyloid deposition in the brain, but insufficient to cause dementia, and the lacunar infarct pushed this patient over the clinical threshold of dementia, as is commonly seen in the elderly. This scenario can only be verified by adding an amyloid biomarker to the diagnostic
workup, either cerebrospinal fluid analysis of β-amyloid or amyloid PET. In the absence of those additional markers, I would maintain that cerebrovascular disease may contribute, but would not be the cause, to this patient’s cognitive impairment. However, this would not dismiss the clinician from the task to carefully treat and monitor the patient’s vascular risk factors.

**Comments by Dr Greenberg**

With Ciceronian rhetoric, Drs Viswanathan and Scheltens have skillfully laid out the vasculo-centric and vasculo-skeptic arguments for age-related cognitive impairment. It is the common elements in their discussions, however, that reveal areas of broad consensus emerging in the dementia field.

One such point is that multifactorial or mixed dementia is likely more common than pure dementia of any type (AD, vascular, or other neurodegenerative). Attributing cognitive impairment to multiple processes runs against our preference for diagnostic parsimony, but common pathologies will tend to overlap as patients age, and parsimony may need to defer to reality.

In this messy world of multiple concurrent pathologies, the term mixed dementia quickly becomes inadequately vague. What we would most like is to describe Mr Jones’ dementia as 90% attributable to AD and 10% to cerebrovascular disease, contrasting with Ms Smith’s dementia that is 70% vascular and 30% AD. Teasing apart these contributions during Jones’ and Smith’s lifetimes remains challenging, however. There are as yet no accurate noninvasive biomarkers of AD severity. Brain atrophy, for example, can occur in vascular disease, as well as AD. Even the promising approach of amyloid imaging is not specific for AD dementia because it is positive in a substantial proportion of cognitively normal elderly and non-demented individuals with advanced cerebral amyloid angiopathy. An emerging alternative is molecular imaging of tau deposits, the other pathological hallmark of AD and potentially a more specific marker of AD- or tauopathy-related dementia.

Noninvasive detection of vascular brain injury suffers from almost the reverse limitation: too many markers, none clearly established as the major cause of dementia. Focal brain lesions, such as lacunes of presumed vascular origin, cerebral microbleeds, and visible perivascular spaces, are commonly detected in association with cerebral small vessel disease, but typically in fairly small numbers that seem unlikely to cause substantial brain dysfunction on their own. Cerebral microinfarcts, conversely, are pathologically numerous in the brain, but (with notable exceptions) largely invisible to noninvasive imaging. An alternative approach for estimating the vascular contribution is to use widespread, larger scale markers, such as white matter hyperintensities of presumed vascular origin or diffusion-tensor–based structural network integrity, which may subsume various smaller lesion types into an overall measure of vascular burden.

A final point of clear consensus is that from a practical standpoint; clinicians should treat each contributor to cognitive impairment to the best of our medical capabilities. Until disease-modifying AD treatments are identified (a day that possibly come too soon), this translates to treatment of vascular risk factors. Whether this approach can slow cognitive decline in patients with symptomatic dementia remains unclear, but recent reports of improved cognitive performance in a randomized trial of at-risk cognitively normal individuals and falling age-specific dementia prevalence in population-based observational studies suggest small (and surprisingly uncelebrated) victories in the ongoing battle against age-related dementia. I join my coauthors in encouraging readers to think critically and act decisively in evaluating and treating the vascular contribution to their patients’ cognition.

**Disclosures**

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**References**


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