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The 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 TIA or stroke. Her neurologic examination is notable for a Mini-Mental State Examination (MMSE) score of 24. MRI 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?

Dr. Viswanathan: YES

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 was much more common and extensive in the 19th and early 20th centuries before the advent of anti-hypertensive therapy and other medical interventions. Better treatment of cardiovascular disease and blood pressure that has reduced

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stroke¹ has likely also reduced the overall burden of cerebral small vessel disease. Furthermore, life expectancy in the 20th century has increased, consequently increasing the risk of Alzheimer's disease (AD) pathology, which is strongly age-associated. But this certainly does not mean that vascular disease is no longer an important cause of cognitive impairment in the elderly.

Extensive data from epidemiologic and pathologic studies demonstrate that cerebrovascular disease is a common accompanying finding in patients diagnosed with neurodegenerative dementia, contributes to cognitive impairment independently of AD pathology,² and accelerates cognitive decline in patients presenting to memory clinics.³ 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.⁴ 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 leukoaraiaosis) in this patient, though commonly detected, are also clearly associated with cognitive dysfunction and elevated dementia risk.⁵

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.⁶ 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.⁷

Further support for the importance of cerebrovascular disease and vascular risk factors in age-related cognitive impairment comes from recent epidemiologic data on the prevalence of dementia. These studies show that the prevalence of dementia has declined over a two decade period.⁸ 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 twenty 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)⁹ 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 work⁷ makes it clear that we have much to learn about the true implications of what we are seeing and not seeing. A small lacunar infarction with leukoaraiaosis 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.¹⁰ To ignore the importance of small vessel disease in this patient would be to remain blind to what is in front of our eyes.

Dr. Scheltens: NO

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 one or two E4 alleles. Then, the course of the disease with a 2 year history of a non-acute, slowly progressive memory loss and executive dysfunction, fits with a typical presentation of AD and speaks against a primary vascular origin.¹¹ The prior history of hypertension does not preclude AD, since hypertension has been identified as a factor in many population studies and shown to promote amyloidogenic processing of the amyloid precursor protein.¹² In addition, the patient has experienced no recent TIA or other vascular incident.

The MMSE score of 24 is just at the cut off for dementia, but lower than usually seen in patients with vascular cognitive impairment.¹³ Finally, the MRI shows generalized atrophy (no information on hippocampal atrophy is given), and only mild- moderate atrophy (unfortunately no grading is mentioned), which probably does not quite qualify for vascular dementia according to the most recent radiological criteria put forward by the VASCOG group.¹⁴ 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 subacute¹⁵ and the course is rarely progressive.

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.¹⁶ This scenario can only be verified by adding an amyloid biomarker to the diagnostic workup, either CSF 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, of 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.¹⁷

Dr. Viswanathan: 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 TIA or stroke.¹⁸ Furthermore, while 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. While generalized atrophy is common at later stages of

AD, it appears less common than regional medial temporal atrophy earlier in the disease. By contrast, generalized atrophy is a common feature of vascular cognitive impairment. While 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: 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.

Dr. Greenberg: Comments

With Ciceronean 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).^{16, 19} 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.²⁰ Teasing apart these contributions during Jones’ and Smith’s lifetimes remains quite 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.²¹ Even the promising approach of amyloid imaging is not specific for AD dementia, as it is positive in a substantial proportion of cognitively normal elderly²² and non-demented individuals with advanced cerebral amyloid angiopathy.²³ An emerging alternative is molecular imaging of tau deposits,²⁴ 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,²¹ 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 exceptions²⁵) largely invisible to noninvasive imaging.¹⁰ An alternative approach for estimating the vascular contribution is to use widespread, larger scale markers such as white matter hyperintensities of presumed vascular origin^{17, 21} or diffusion-tensor based structural network integrity,²⁶ 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 cannot 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,²⁷ but recent reports of improved cognitive performance in a randomized trial of at-risk cognitively normal individuals²⁸ and falling age-specific dementia prevalence in population-based observational studies⁸ suggest small (and surprisingly uncelebrated) victories in the ongoing battle against age-related dementia. I join my co-authors in encouraging readers to think critically and act decisively in evaluating and treating the vascular contribution to their patients' cognition.

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