Cerebrovascular Pathologies in Alzheimer Disease

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This commentary addresses current views about the interaction of vascular disorders and Alzheimer disease, including vascular pathologies that may be intrinsic to the Alzheimer process as identified through demonstration of amyloid plaques and neurofibrillary tangles. The common cerebrovascular pathologies accompanying aging, mainly atherosclerosis and arteriosclerosis, will coincide in varying proportions with the Alzheimer pathology, also a concomitant to aging. Because interventions are available to modify both risks and complications of these vasculopathies, an important goal of dementia research is to develop means to characterize the contribution of cerebrovascular disease in Alzheimer and other dementias. Realization of this goal is confounded by the recognition that Alzheimer pathology, usually considered a parenchymal process, involves important vascular changes.

Key words: *Alzheimer disease, dementia, cerebrovascular, pathology, imaging.*

Introduction

Since the earliest inquiries,[1] vascular pathologies have been implicated in dementia as we now define it. This definition specifies a syndrome of progressive and disabling cognitive impairment resulting from cerebral pathologies that intensify while they slowly advance to involve new regions. The most common pathology that correlates with this definition is that described by Alzheimer disease and which is characterized by amyloid plaques and neurofibrillary tangles. The advances of the last quarter century, which continue unabated, not only have elucidated the cellular pathophysiology of the Alzheimer process, but also have identified additional pathophysiologies that may interact with the Alzheimer process. Indeed, it is intuitively plausible that multiple disorders affecting the aging organism occur in concert.

Among the pathologies that underlie the dementia syndrome are those affecting blood vessels primarily, with injury to the brain parenchyma as a consequence. Some vascular disorders cause local anatomic injury only to leave fixed cognitive deficits that may be disabling but do not assume the progressive course of the dementing disorders as defined above. Neurologists refer to disabling cognitive deficits due to fixed cerebral lesions, such as with head injuries and many kinds of stroke, as a form of dementia, but these clearly differ from those referred to above.

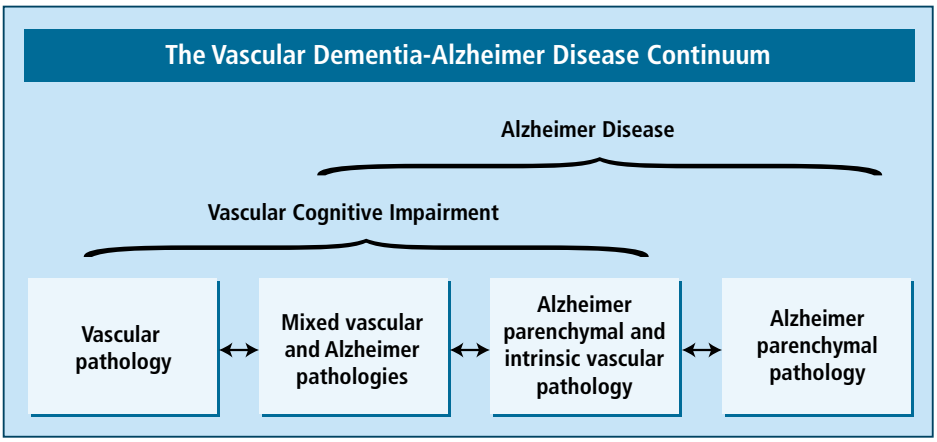
Vascular pathologies that are thought to cause a dementia syndrome involve multiple, usually smaller, vessels that supply different cerebral regions. These are pathologies that will extend to involve additional vessels and regions of supply and will progress in severity. We can expect that cerebral blood vessels, as complex organs in their own right, will be subject to a wide variety of pathologies so that multiple vascular pathophysiologies can be associated with the dementia syndrome. The most common vascular disorder is atherosclerosis which, like Alzheimer disease, increases in incidence with age. Analogous to pathologies thought to affect primarily the cerebral parenchyma in the dementias, atherosclerosis is a cellular degenerative process that is complex and incompletely understood.[2] Unlike Alzheimer disease, several risk factors for atherosclerosis are well defined and can be modified. As well, many secondary effects of the vascular lesions occurring in atherosclerosis, including thrombosis, embolism and hemorrhage, are well understood and treatable with measures that prevent progression and recurrence. Similar considerations pertain to the other common vascular disorder—hypertension. This has encouraged a sense of urgency in the early detection of cerebrovascular disorders, such as atherosclerosis and hypertension, that affect a high proportion of the population at risk for dementia, to prevent progressive brain tissue ("end organ") damage.[3]

Coincidence of Vascular and Alzheimer Pathologies

Specific clinical diagnosis of the disorders causing dementia is an absolute prerequisite to specific therapy. The knowledge gained in the last 15 years has taught us that specific clinical diagnosis of dementing diseases can be very difficult, particularly for those forms in which vascular processes play either a primary or contributing role. Until recently, dementia with primary vascular pathology, considered the second most common form of dementia, has been classified separately from Alzheimer disease. A great deal of recent and converging evidence not only recognizes the coincidence of cerebrovascular and Alzheimer pathologies, but now implicates vascular mechanisms in the pathophysiology of Alzheimer disease *per se*. A plausible case can be made for a primary vascular etiology in Alzheimer disease.[4] The conventional view is that pure Alzheimer disease and pure vascular dementia occupy the poles of a continuum, along which there are variable ratios of these two pathologies and in which the addition of vascular change amplifies the clinical effects of the Alzheimer changes (Figure).[5] With multiple forms of Alzheimer disease, multiple vascular pathologies may be combined (as well as other "neurodegenerative" pathologies in combination with these two, such as

presence of Lewy bodies). Patients with dementia in whom these multiple pathologies co-exist are said to have "mixed dementia", now considered by some to be the most common form of dementia.[6]

Authorities now urge a retrenchment from the earlier, specific terminology that emphasized dementia of purely vascular origin, such as "multi-infarct dementia" and "vascular dementia", to a usage that subsumes all forms of cognitive impairment accompanied by brain injury consequent to vascular disease under the term "vascular cognitive impairment"[7] (Figure). This term recognizes that manifold vascular disorders lead to cognitive impairment and dementia, and that vascular disorders causing little or no cognitive change could be treated at an early stage before irreversible and disabling cognitive impairment has occurred.



Diagnosis and Construct Validity

Recent reports emphasize the difficulties in defining clinically the role of vascular pathologies in dementia and Alzheimer disease.[8-10] These also emphasize the difficulties in establishing "construct validity" in the characterization of the dementia syndromes and diseases. The concept of construct validity[11] embraces the need for coherence among the various sets of data derived over the course of subjects' disease by the manifold disciplines concerned with dementia. Nowhere is this more apparent than in dementia with vascular involvement. Difficulties in establishing this construct validity are discussed here.

The clinical disciplines of neuropsychology and neurology determine an anatomic localization of cognitive and neurologic deficits in their assessments performed at different points in the course of the illness. Although characteristic syndromes may be identified, such as the cognitive changes in Alzheimer disease and the cognitive and neurologic changes in vascular cognitive impairment,[12] distinct clinical variants of Alzheimer disease[13] and a wide variety of syndromes associated with cerebrovascular disease exist. It is also apparent that the same clinical syndrome is commonly seen with either Alzheimer or vascular pathologies. It is assumed that the different pathologies have affected brain structures in a similar pattern.

Thus, establishment of clinical-pathologic coherence has been difficult in the dementias. Also, multiple clinical presentations correlate with the same vascular pathophysiology, such as in atherosclerosis whereby the brain can be damaged in different ways and patterns. The wide spectrum of vascular pathologies ranges from the common forms of athero- and arteriolosclerosis to an increasing census of less common genetic and inflammatory vasculopathies, each with the potential for expression in a variety of dementia syndromes (e.g., CADASIL, Fabry, hereditary amyloid angiopathy, familial British dementia, antiphospholipid antibody syndrome, pseudoxanthoma elasticum, fibromuscular dysplasia and vasculitis). Characterization of the cerebrovascular pathology and its effects on the brain parenchyma faces important operational hurdles. Neuropathologic assessment of cerebrovascular and parenchymal pathology has become increasingly onerous. Previous prospective studies may not be comparable because different aspects of the pathology were examined; for example, the search for microscopic infarctions may have been incomplete. Correlations of vascular lesions with parenchymal damage may be incomplete. Focal infarctions can affect cognitive functions both locally at the site of tissue damage and at a distance through connections that might be affected.

Structural and functional imaging represent an important set of criteria that require validation and reconciliation with clinical and pathologic criteria in order to bridge the two in diagnosis.[14] Imaging might be expected to identify a vascular component in a clinical dementia through detection of infarctions and hemorrhages. However, small, clinically significant lesions can be missed. The significance of white matter change on CT and MR imaging so commonly attributed to "microvascular disease", presumably arterial, remains poorly defined. Attempts to establish coherence between cognitive and neurological function and white matter changes have produced mixed findings. Other neuropathological lesions can be associated with white matter changes, including Wallerian degeneration of central tracts and possibly benign vascular lesions, such as venous sclerosis[15] and other cellular changes like clasmatodendrosis.[16]

Vasculopathy Intrinsic to Alzheimer Disease

The concept of a vascular/neurodegenerative dichotomy is now seriously confounded in the case of Alzheimer disease, by evidence of vascular pathology intrinsic to the Alzheimer process.[9] Deposition of Aβ amyloid, which is thought to be cytotoxic, in blood vessels is a long-standing observation and

occurs to some degree in virtually all cases. Vascular smooth muscle synthesizes and releases the amyloid precursors, which also may be derived from other cellular sources.[17] Cerebral amyloid angiopathy injures the vessel wall, resulting not only in hemorrhage but also occlusion and infarction and accompanying white matter change on imaging; its importance in Alzheimer disease appears to be quite variable. In addition, a large variety of morphological lesions in the microvasculature of capillaries, arterioles and veins have been described, but it is not clear how these coincide with the development of Alzheimer pathology in the parenchyma. One interpretation holds that the microvascular changes impair both tissue perfusion and the blood brain barrier with consequent disturbance of metabolism in the neuropil. Those postulating a primary vascular cause in Alzheimer disease argue that tissue hypoperfusion consequent to different vascular disorders induces tissue injury, which then induces Alzheimer changes in the parenchyma. This idea is supported by epidemiologic studies showing that many risk factors for vascular disease also increase risk for Alzheimer disease.[18]

Clinical Implications

The clinical implication of these considerations is that diagnosis of dementia should now include a formal assessment of the contribution of vascular disease. In every patient, we should ask: "Could vascular pathology contribute to this patient's cognitive impairment?" If the answer is "yes", we should then attempt to assess its nature and extent. This can be accomplished in the following format:

1. Have the uncommon cerebrovascular disorders been excluded?
2. What vascular risk factors are present and what are the systemic burdens of atherosclerosis and hypertension?
3. What clinical evidence is there for extension of these disorders to the cerebrovascular tree?
4. Are the imaging findings consistent with this evidence?

Continuing interdisciplinary studies are necessary to refine validity of the various dementia constructs, but particularly to develop imaging techniques that better characterize aspects of cerebrovascular disease, including brain injury, cerebrovascular burden of atherosclerosis and arteriosclerosis, amyloid angiopathy and tissue perfusion. ◆

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