Atherosclerosis and Neurodegeneration
Unexpected Conspirators in Alzheimer’s Dementia

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N eurodegeneration, a process of neuronal dysfunction and death independent of vascular factors, has long been considered the main pathogenic process underlying Alzheimer’s disease (AD), the most common form of dementia in the elderly. At the other end of the spectrum, “vascular dementia” was attributed exclusively to vascular alterations resulting in cerebral blood flow (CBF) reductions. In this issue of *Arteriosclerosis, Thrombosis and Vascular Biology*, Roher et al provide new and provocative data indicating that cerebrovascular alterations are a prominent feature of AD neuropathology. These authors examined consecutive autopsy cases in which a diagnosis of AD was made according to well established neuropathological criteria. By comparing AD brains to a group of carefully matched controls, they found that the incidence of vascular narrowing due to atherosclerosis of the circle of Willis is greater in AD than in nondemented controls. Not only was the number of stenoses greater, but also the vascular narrowing was more severe in AD than in controls. The data provide quantitative evidence that atherosclerotic lesions of cerebral blood vessels constitute a major feature of AD neuropathology, perhaps, as prominent as amyloid plaques or neurofibrillary tangles, the traditional pathological hallmarks of the disease.

It has long been suggested that cerebrovascular factors contribute to AD. Alterations in the morphology of cerebral capillaries, smooth muscle cells, blood-brain barrier, and CBF have been reported in AD for several decades (see Kalaria and de la Torre for a review). Furthermore, white matter lesions resembling ischemic lesions have been well known to pathologists since the first description of the disease by Alois Alzheimer in 1906 (see Brun et al for a review). However, it could not be established whether these cerebrovascular alterations were a cause or a consequence of the neurodegenerative process. Therefore, leading theories on the pathophysiology of AD have not emphasized the contribution of vascular factors. Rather, the presence of cerebrovascular disease is considered an exclusion criterion for AD diagnosis. Recent clinical studies, however, have begun to challenge the assumption that AD is the result of a pure neurodegenerative process independent of vascular insufficiency. First, risk factors for vascular disease, such as diabetes, hypercholesterolemia, hypertension, hyperhomocysteinemia, and aging are also risk factors for AD (see Breteler for a review). Therefore, factors that predispose to cerebrovascular diseases also increase the risk for AD. Second, the presence of ischemic brain lesions worsens the cognitive deficits in AD, suggesting a pathogenic interaction between vascular insufficiency and neurodegeneration. Third, asymptomatic patients at risk for AD exhibit marked alterations in CBF and in cerebrovascular regulation, as assessed by positron emission tomography or magnetic resonance imaging. Because these CBF alterations precede the onset of cognitive decline, they cannot be attributed to the brain dysfunction produced by the disease. In accord with these epidemiological, clinical, and cerebral hemodynamic data, the finding that atherosclerotic narrowing is more prominent in large cerebral arteries of AD patients provides further evidence that cerebrovascular alterations are a critical feature of AD. Furthermore, the data suggest an explanation for why risk factors for atherosclerosis and vascular diseases are also present in AD.

A growing body of data on the vascular biology of the amyloid-β peptide (Aβ), the main constituent of the amyloid plaques, strengthens the argument that vascular factors play a pathogenic role in AD. The Aβ peptide produces constriction of systemic and cerebral arteries, attenuates endothelium-dependent cerebrovascular dilatation, and impairs the increase in CBF produced by neural activity. Furthermore, transgenic mice overexpressing mutated forms of the amyloid precursor protein (APP) have a reduction in resting CBF and an impairment in the CBF increases evoked by endothelium-dependent vasodilators or brain activation. In addition, cerebrovascular autoregulation, a property of cerebral blood vessels through which CBF is maintained stable in the face of changes in systemic arterial pressure, is profoundly altered in APP mice. These findings suggest that Aβ, a peptide thought to be critical in the pathobiology of AD, also has notable cerebrovascular effects that may contribute to the brain dysfunction produced by Aβ.

The discovery by Roher et al that atherosclerosis produces significant stenosis in large cerebral artery of AD patients, in concert with the experimental findings of Aβ-induced vasoconstriction, provides strong evidence suggesting that cerebrovascular insufficiency is a pathogenic factor in AD. Furthermore, the fact that Aβ alters critical homeostatic mechanisms of the cerebral circulation, such as functional hyperemia and autoregulation, indicates that the oligemia might be worse under conditions of brain activation and hypotension. Although the pathogenic significance of such static and dynamic vascular insufficiency cannot be deter-

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Atherosclerosis of large cerebral vessels leads to vascular narrowing and reduction in CBF (Oligemia). At the same time, processing of the APP by secretases leads to formation and accumulation of Aβ. While oligemia influences the proteolytic processing of APP and increases Aβ formation, Aβ aggravates the oligemia by producing vasoconstriction of cerebral blood vessel and by attenuating vasodilatory responses. In addition, Aβ is neurotoxic and could worsen brain function also through this mechanism. The neurotoxic effects of Aβ, in combination with oligemia, alter brain function and produce dementia.

While Aβ constricts cerebral blood vessels and reduces CBF, the CBF reduction, in turn, facilitates the process of cerebral amyloidogenesis (Figure). For example, cerebral ischemia upregulates local APP expression and promotes the cleavage of Aβ from APP, presumably by modulating the activity of the APP-processing enzymes secretases. Therefore, the oligemic state is likely to occur in parallel with neuronal dysfunction induced by Aβ and, as such, it might worsen it by increasing the susceptibility of the brain to injury. Therefore, vascular insufficiency enhances Aβ-mediated neurotoxicity thereby amplifying its deleterious effects (Figure). This view is supported by the observation that APP mice are more susceptible to cerebral ischemic injury.

A more direct link between Aβ and atherosclerosis has recently been suggested by De Meyer and colleagues in a study of human carotid plaques. These investigators found that macrophages, which phagocytize platelets after intraplaque microhemorrhages, can process platelet-derived APP into Aβ. This peptide, in turn, activates macrophages and leads to expression of proinflammatory genes that play a role in atherogenesis. Considering that APP levels in platelets are similar to those in the brain, these findings provide a plausible biological basis for the abundance atherosclerotic lesions observed in AD patients. In this regard, a detailed study of extracerebral atherosclerotic lesions in other vascular districts of AD patients would be of interest.

However, Roher et al also point out that in some cases of AD, there is no evidence of atherosclerotic lesions in the circle of Willis. This suggests that cerebrovascular atherosclerosis, and perhaps vascular insufficiency, are not an absolute requirement for the development of AD. Thus, we may be dealing with a spectrum of diseases in which vascular factors and neurodegeneration coexist with varying degrees of overlap. Nevertheless, the prominence of the vascular lesions reported by Roher et al suggests that atherosclerosis and neurodegeneration are unexpected “partners in crime” in many cases of sporadic AD. While the findings call for a revision of the diagnostic criteria for vascular and neurodegenerative dementia, they open the way to new strategies for the diagnosis and treatment of these devastating neurological diseases.

References


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