Is Breakdown of the Blood-Brain Barrier Responsible for Lacunar Stroke, Leukoaraiosis, and Dementia?

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Background—The pathogenesis of and relationship between small deep (lacunar) infarcts, cerebral white matter disease (leukoaraiosis or white matter hyperintensities), and progressive cognitive impairment or dementia are much debated.

Summary of Comment—We hypothesize that cerebral small-vessel endothelial (ie, blood-brain barrier) dysfunction, with leakage of plasma components into the vessel wall and surrounding brain tissue leading to neuronal damage, may contribute to the development of 3 overlapping and disabling cerebrovascular conditions: lacunar stroke, leukoaraiosis, and dementia. This hypothesis could explain the link between ischemic cerebral small-vessel disease and several apparently clinically distinct dementia syndromes. This hypothesis is supported by pathological, epidemiological, and experimental studies in lacunar stroke and leukoaraiosis and observations on the blood-brain barrier with MRI. We suspect that the potential significance of blood-brain barrier failure as a pathogenetic step linking vascular disease with common, disabling brain diseases of insidious onset has been overlooked. For example, lipohyalinosis, which has a pathological appearance of uncertain origin and is possibly responsible for some discrete lacunar infarcts, may be one end of a clinical spectrum of illness manifested by blood-brain barrier failure.

Conclusions—Proof that blood-brain barrier failure is key to these conditions could provide a target for new treatments to reduce the effects of vascular disease on the brain and prevent cognitive decline and dementia. (Stroke. 2003;34:806-812.)

Key Words: Alzheimer disease ■ cerebrovascular disorders ■ dementia ■ lacunar infarction ■ leukoaraiosis ■ vascular diseases
linic process may narrow the lumen, it must therefore occlude the lumen, inducing infarction. Fewer further pathologic studies have found occluded small vessels, yet the occlusion mechanism has been vigorously debated. Others suggest that lacunar infarction results from the same factors responsible for cortical ischemic stroke, i.e., emboli, atherosclerosis occluding the mouth of the perforating artery, or hypoperfusion. A small embolus could enter and occlude a perforating artery, but the available evidence suggests that cardiac or artery-to-artery embolism from carotid or middle cerebral artery atheroma is unlikely to be a frequent cause of lacunar stroke.

If lipohyalinosis is a cause of lacunar infarction, then what is it, and what starts it? Fibrinoid necrosis can be induced in small cerebral cortical arteries in animal models after severe hypertension-induced vasospasm and therefore might occur after vasospasm of the perforating arteries in patients. However, vasospasm has never been observed in perforating arteries, and severe hypertension is now uncommon. In the 1950s, hypertension was perhaps less well managed than it is today, and therefore possibly Fisher observed more dramatic pathological small-artery changes. While hypertension is still a recognized risk factor for lacunar stroke, few patients have severe hypertension of the degree associated with vasospasm and fibrinoid necrosis in animal models. It is possible that some more insidious process, involving mildly but chronically elevated blood pressure, causes lipohyalinosis and that the luminal narrowing, a by-product of whatever starts the arterial wall disorganization, then causes ischemia/infarction of the adjacent brain.

Alternatively, could lipohyalinosis and perivascular damage occur secondary to altered small-vessel permeability? We recently described a variant, or possibly intermediary stage, of lacunar infarction (type 1b, or “incomplete lacunar infarction”), defined as “selective neuronal necrosis with relative preservation of glial elements around a penetrating artery.” This was essentially the same as the “edema-related gliosis” described by Ma and Olsson. These incomplete infarcts occurred in the same parts of the brain and in the same sorts of patients as completed (type 1a) lacunar infarcts. The striking histological similarities to edema-related lesions induced in experimental animals—parenchymal vacuolation, perivascular lesion distribution, and fibrinogen immunoreactivity—suggest that edema may be at least partly responsible for the brain tissue damage. If edema fluid is not neurotoxic, why is there a blood-brain barrier? Thus, leakage of plasma through the blood-brain barrier could account for the perivascular edema and neuronal damage, but could it also account for the arterial wall disorganization or lipohyalinosis? Possibly yes: experimental injection of plasmin, the active form of an enzyme present in plasma, into the brain parenchyma produced acute fibrinoid necrosis in the perforating artery walls and increased endothelial permeability. Other animal studies have also indicated that leakage of plasma constituents into the perforating artery wall and surrounding brain tissue is the first step in the development of fibrinoid necrosis and perivascular lesions. The blood-brain barrier opening could be intermittent and short-lived (as seen in hypertensive crises) or chronic and insidious. Either could lead to progressive vascular and brain parenchymal damage over a period of time.

Is lipohyalinosis still the main pathological lesion in lacunar infarction? There have been few detailed neuropathologic studies in patients dying after lacunar infarction since the 1960s. Patients rarely die soon after lacunar stroke, and far more detailed dissection is required to examine the suspect perforating artery than is usually performed in routine autopsies. The few studies that have been done, which involved only a small number of patients, have suggested that lipohyalinosis (whatever that is), although the subject of considerable debate, is still a major vascular pathological finding.

What other evidence points to a leaking process in lacunar infarction? Progressing neurological symptoms are much more common after lacunar than after nonlacunar infarcts (65% versus 24%, respectively; P<0.001). Progression of stroke in lacunar infarction is difficult to attribute to hemorrhagic transformation or mass effect. Although progression has been attributed to stepwise occlusion of small perforating arteries, there is no obvious reason why this should occur in small perforating arteries more than in larger arteries unless possibly the surrounding infarct edema can compress a perforator more than a large cortical artery. Progressing lacunar stroke would also be consistent with ongoing damage to surrounding neurons and glia from ongoing vascular leakage. Microbleeds (hemorrhagic leaks from small vessels) are increasingly recognized in the brains of older patients on MRI. In one study these occurred in 68% of 68 patients with clinical lacunar strokes but only 5% of healthy elderly individuals.

Epidemiological Observations in Clinically Diffuse Disease: Leukoaraiosis and Dementia

Patients with lacunar stroke often have other “silent” lesions elsewhere in the white matter and basal ganglia. Diffuse white matter disease, or leukoaraiosis, originated from the observation on CT scans of hypodensity in the hemispheric white matter, subsequently shown as hyperintensities on MRI. Numerous studies have established a correlation between the presence and extent of these lesions and cognitive impairment, from mild slowness of thinking to full-blown dementia. White matter hyperintensities and vascular dementia are associated with typical vascular risk factors, such as arterial hypertension, cigarette smoking, history of vascular disease, diabetes mellitus, and carotid atheroma, although not all patients have these risk factors. White matter hyperintensities also occur in other common dementias such as Alzheimer disease and entities like cerebral amyloid angiopathy. It is difficult to distinguish cause and effect among common processes that become more prevalent with age. Mixed vascular and Alzheimer disease pathologies are common, and vascular risk factors increase the risk of Alzheimer disease. In 209 elderly patients (of whom 100 were demented), a third of the nondemented subjects had densities of Alzheimer disease neuropathology equivalent to those of the demented subjects. There were no clear thresholds of neuropathological status that predicted the clinical features. Thus, the development of dementia in
patients with Alzheimer disease pathology is not entirely explained by the neuropathological features traditionally regarded as indicative of Alzheimer disease, suggesting some additional contributing factors. Genes may be important but thus far have not fully explained more than a small number of either cerebrovascular or Alzheimer disease cases.

What other epidemiological evidence might link damaged cerebral small vessels and dementia? Some drugs that affect the vascular endothelium reduce the risk of dementia. Statins and antihypertensive drugs both appear to reduce the risk of dementia. Improved blood pressure control may reduce the development of white matter hyperintensities. Patients with Alzheimer disease have neurovascular instability on tilt table testing.

One major problem in the study of dementias has been the lack of specificity of clinical diagnostic criteria. Erkinjuntti et al applied 6 widely used dementia diagnostic criteria to 1879 subjects and found that the prevalence of dementia varied 10-fold, from 3.1% to 29.1%, depending on the classification method used. Only 20 of 1879 subjects (1%) were diagnosed as demented on all 6 systems. Pohjasvaara et al found similar variation in scales to classify vascular dementia. The clinical differentiation between vascular dementia and Alzheimer disease is similarly problematic. It seems that many risk factors are shared by both vascular and Alzheimer dementias, and therefore perhaps investigators should continue to focus on the relationships between risk factors, pathology, and the degree of cognitive impairment rather than attaching too specific a dementia diagnostic label.

Do Pathological Studies of Diffuse White Matter Disease Tell Us Anything About the Cause? The archetypal form of leukoaraiotic cerebral small-vessel disease (hypertensive) is associated with demyelination, commonly considered to be ischemic demyelination, due to insidious stenosis or occlusion of small perforating arteries, but the actual mechanism has not been determined. Lipohyalinosis may be present in perforating arteries, but frank stenosis and occlusion are unusual. MR diffusion tensor imaging shows features consistent with disrupted white matter tracts. MR spectroscopic studies show decreased neuronal markers (N-acetyl aspartate) and increased choline, and positron emission tomography studies suggest hypometabolism in affected regions. Positron emission tomography and contrast perfusion MR studies suggest decreased cerebral blood flow (CBF) and increased cerebral blood volume in affected regions. All of the above simply indicate the presence of damage, not how it occurred. Hypometabolism is to be expected in areas with reduced cellularity; decreased CBF could be the result of cell loss (ie, less demand) rather than the cause. Although lipohyalinosis may narrow the lumen and ischemia may therefore be a by-product, we are concerned with what initiates the process of arterial wall disorganization. Hypertensive and diabetic microangiopathy with leakage from small vessels occurs in the kidneys and retina, so might this not also occur in the brain?

Is There Any Direct Evidence of a Leak in Lacunar Stroke, Leukoaraiosis, or Dementia? Several sources suggest that the blood-brain barrier fails with advancing age, in dementia, and in white matter disease. For example, an intravenously injected MR contrast agent, gadolinium-DTPA, leaked into the brain, particularly in the territory of the perforating arteries, more in maturity-onset diabetics and those with white matter hyperintensities than in controls. Although another study of 10 patients with dementia failed to find evidence of leakage into the brain with gadolinium-enhanced MRI, a much less detailed imaging technique was used. A study in 18 aging dogs, imaged after gadolinium-DTPA injection, found leakage in 1 dog with white matter hyperintensities on imaging and Alzheimer disease pathology. Kwa et al found indirect evidence of small-vessel endothelial failure in hypertensive patients in whom the degree of white matter hyperintensities correlated with the severity of retinal arterial changes. Wong et al found that retinal microvascular abnormalities were predictive of stroke after adjusting for other stroke risk factors (any retinopathy: odds ratio, 3.11; 95% CI, 1.71 to 5.65). Studies of experimental hypertension in primates showed cerebral microvascular changes, leaks in the blood-brain barrier, and activation of microglial and astroglial cells in association with cognitive decline. Hypertensive rats have perforating arterial wall thickening and extravasation of endogenous serum proteins into the brain parenchyma, with the arterial wall thickening predating the protein extravasation. Similar appearances are known to occur in the absence of hypertension, and they should be regarded as a nonspecific response of cellular components of vessel walls to injury. However, this does provide evidence of a link between perforating artery wall disorganization (lipohyalinosis) and perivascular edema.

The possibility of blood-brain barrier abnormalities occurring with advancing age, diabetes, and dementia was suspected more than 10 years ago, although results were conflicting between animal species. Leakage of albumin into the cerebrospinal fluid (CSF) was found in patients with established Alzheimer disease and vascular dementia, although the leak was considered to be the result rather than a cause of the dementing process. Recently, however, a small prospective study showed that elderly patients who developed Alzheimer or vascular dementia during 3 years of follow-up had a higher CSF/plasma albumin ratio before the development of dementia than those who remained nondemented at the end of follow-up. Plasma proteins have been found in the tissue around perforating arteries in patients with subcortical dementia and white matter disease, supporting the idea that the proteins reach the CSF via leakage from small perforating arteries.

How Might the Blood-Brain Barrier Fail? We speculate that several mechanisms could contribute to the development of vascular leakage (Figure). Hypertension and diabetes mellitus, both major risk factors for white matter hyperintensities and lacunar stroke, cause macroangiopathy outside the brain (retina, kidneys, heart, and feet). Hypertension and diabetes may facilitate some endothelial damage process, perhaps through the renin-angiotensin system, which might even predate the development of frank hypertension. Alternatively, by the time white matter hyperintensities have developed in late life, the hypertension that was present in earlier life may have normalized. There is no blood pressure
threshold for stroke, and therefore there is no reason to expect a blood pressure threshold for insidious damage to the vascular endothelium. Diabetes was independently related to lacunar infarction in a recent large study.\textsuperscript{61} Abnormalities in the nitric oxide synthase gene\textsuperscript{62} or other genetic factors (for example, the Notch 3 gene mutation responsible for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL])\textsuperscript{63} could increase susceptibility to vascular endothelial damage. Although there is no direct evidence of blood-brain barrier leakage in CADASIL, CADASIL itself provides evidence of at least 1 disease characterized by lacunar stroke, white matter hyperintensities, and dementia. As to what plasma component might actually cause the perivascular damage, there are numerous candidates: plasmin or other proteases, environmental toxins carried in the blood, infectious agents, or simply exposure of the neurons to altered electrolyte levels in the interstitial spaces.

What Observations Might Seem Incompatible With a Leak Hypothesis?
Several studies of CBF would seem to favor an occlusion theory.\textsuperscript{45,47} However, these require closer examination. Reduced CBF would occur secondary to reduced brain tissue to supply. Alterations in autoregulation could result from stiff fibrinoid vessels, occlusion, or leak. Autoregulation requires intact vascular endothelium. Impaired autoregulation simply indicates vascular endothelial damage. The interpretation of a reduced absolute CBF depends on the method used to measure CBF. An intravascular tracer might not remain intravascular if the endothelium was leaky. This would lead to an apparently slow wash in or washout phase, which might be interpreted as reduced CBF,\textsuperscript{41} and an apparent increase in cerebral blood volume but would be compatible with vascular leakage. Indeed, physics models suggest that a change in the vessel density, spacing, or distribution (as in atrophy or white matter hyperintensities) could result in an appearance of reduced CBF without there necessarily being any change in flow to the region.\textsuperscript{64}

Might the Leak Simply Be the Result of Progressive Brain Damage Rather Than the Cause?
Demonstration of a leak in the presence of existing disease does not prove that the leak was the initiating event. Much of the aforementioned evidence simply documents leakage in the presence of established neurological disease. However, the presence of high CSF/plasma albumin ratio before the development of dementia,\textsuperscript{57} the observation of a sequence of abnormalities in animal models starting with vessel wall thickening and progressing to leakage into the parenchyma,\textsuperscript{51,52} the clear association between numerous vascular risk factors and the development of dementia, and the fact that statins and antihypertensive agents appear to reduce the risk of dementia\textsuperscript{35–37} all point to completion of Virchow’s triad for the leak hypothesis, small-vessel disease, and dementia.

Finally, if lipohyalinosis is due to blood-brain barrier failure and is the major cause of lacunar stroke, could leakage really be the cause of lacunar infarction? A recent case report described a diabetic patient in whom a small area of enhancement was observed in the thalamus on contrast MRI 24 hours before the development of a lacunar infarct (where the enhancement had been observed).\textsuperscript{65} This suggests that breakdown of the blood-brain barrier was the initiating event leading to the lacunar infarct. However, scanning patients shortly before they develop their stroke is so fortuitous (even more so than finding a blocked perforating artery postmortem) that such observations are likely to remain extremely unusual.

If we may return to Fisher’s original observations, he actually described, in considerable detail, features compatible with a leaky endothelium in his lacunar stroke patients:\textsuperscript{66} “arterial disorganization . . . with local enlargement of the vessel and evidence of focal hemorrhagic extravasation through the wall.” He continues, “Segmental arterial disorganisation includes a variety of focal vascular changes,
mostly old, that had as a common feature a striking loss of the arterial architecture. Whorls, tangles or wisps of more or less fine connective tissue entirely replaced the vessel and obliterated the normal vascular coats. ... In less destructive lesions the general outline of the vessel was preserved and the disintegrating wall consisted of a loose meshwork of collagenous strands separated by empty interstitial clefts. ... There was evidence of extravasation of blood sometimes extensive through the damaged arterial wall.”

What hope is there of furthering these observations when the autopsy rate is declining, lacunar stroke is rarely fatal, and death from dementia may not occur until years after the first symptoms develop or years after the initiating event? Imaging offers some hope. It is now possible to observe thrombosed perforating arteries in recent lacunar infarcts, with features consistent with extravasation of red cells and plasma through the vessel wall.67 Numerous imaging methods are available consistent with extravasation of blood sometimes extensive through the damaged arterial wall.

Conclusion

We suggest that brain damage arising from small-vessel endothelial leakage is a potential cause of common brain diseases. Perhaps too much attention has focused on permeating artery occlusion as the mechanism of lacunar stroke and white matter disease and on specific pathological features in the brain parenchyma in dementia, despite the failure to find occluded perforating arteries or to link closely the burden of Alzheimer disease pathology with clinical disease. Further studies are required to prove that blood-brain barrier failure and perforating artery endothelial leakage might be a common pathogenetic mechanism for lacunar stroke, white matter hyperintensities, and dementia. If so, new treatments could be targeted toward this new mechanism to prevent the development of or to reduce blood-brain barrier leakage. Detailed gadolinium-enhanced MRI could provide the means of evaluating new treatments before larger trials are performed to determine the effect of treatment on clinical outcome.

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References


Editorial Comment

Does Chronic Brain Edema Explain the Consequences of Cerebral Small-Vessel Disease?

In their article, Wardlaw et al suggest that chronic blood-brain barrier (BBB) leakage leads to neuronal damage, which may contribute to the development of lacunar stroke, leukoaraiosis, and dementia. This is an interesting and provocative concept and it is worth thorough contemplation. However, there are still several aspects that do not appear to fit this theory and should be explained before the concept can be accepted.
The authors present 2 alternatives for lacunar infarction: (1) The traditional view is that the penetrating small arteries are occluded, eg, by lipohyalinosis, small emboli, focal atherosclerosis, or hypoperfusion, which causes ischemic infarction. (2) According to the authors’ hypothesis, the BBB permeability is altered and tissue lesions are caused by the toxic effects of the edema fluid.

The authors present a question: “If edema fluid is not neurotoxic, why is there a blood-brain barrier?” It is an appropriate question, but BBB is not a sine qua non structure. It certainly does have an extremely important function in protecting the brain, but on the other hand, there are many clinical situations in which the BBB is temporarily opened without major destructive consequences. For example, during epileptic seizures and extreme athletic performances, the rise in systolic blood pressure temporarily opens the BBB. It may be that the leakage then is of such a short duration that neuronal damage does not have time to develop (normally the extravasated proteins are cleared relatively rapidly via the cerebrospinal fluid or locally through the vessel wall). On the other hand, the extravasated plasma most likely does not normally contain sufficiently and/or acutely toxic substances, even though toxic effects of plasma constituents have been undisputedly demonstrated. Actually, such toxic effect is therapeutically used, when the BBB is opened with hypertonic solutions to gain entrance, for example, to cancer drugs. Osmotic opening of the BBB has been shown to result in 10-fold increase in the permeability for intravascular small molecules.

However, the toxic effect of chronic edema as the cause of lacunar infarcts presents a problem: the toxic substances should cause only a focal, often well-demarcated lesion, although the plasma exists in all blood vessels and the BBB lesion more likely is also relatively widespread. It is easier to accept that leukoaraiosis and the white matter lesions seen neuropathologically are caused by edema-related toxic substances, because they are diffuse, widespread changes.

The authors’ question of whether “leakage of plasma through the [BBB] . . . [could] also account for the arterial wall disorganization or lipohyalinosis” is supported by convincing animal studies, which have indicated that the leakage of plasma constituents into the perforating artery wall is the first step in the development of fibrinoid necrosis. But it could be possible that the deleterious effects of the chronic BBB leakage are limited to the walls of the arteries and that the consequences thereafter are related to reduced circulation though the fibrotic and narrowed vessels. There is not proof that the penetrating small arteries still leak when they are damaged and thick-walled. Actually, in the archetype of small-vessel disease CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), the leaking vessels are relatively thin-walled vessels in the cortex, where the microbleeds in CADASIL are also found. Thus, one should perhaps also consider the possibility that after the chronic BBB leakage has damaged the vessel walls, the permeability of the BBB is rather reduced. In that case, the return of certain metabolic waste products to circulation would be impeded, another source of toxic substances.

Finally, the authors suggest that the much more common progressing neurological symptoms after lacunar than nonlacunar infarctions could be due to ongoing vascular leakage. That is a possible alternative, but stepwise or gradual occlusion of small perforating arteries may relate to lesser flow reserves in small vessels than in larger vessels. In CADASIL, we have found by positron-emission tomography that the blood flow in the white matter is reduced already in the early asymptomatic stage (S. Tuominen, MD, et al, unpublished data, 2003). Nevertheless, in subcortical arteriosclerotic leukoencephalopathy, the damage which starts the arterial wall disorganization may well be chronic BBB leakage, which, as the authors suggest, does provide a target for new treatments.

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