Comments, Opinions, and Reviews

Pathogenesis of Leukoaraiosis

A Review

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Background Changes in the cerebral hemispheric white matter, detectable with increasing frequency by modern neuroimaging methods, are associated with aging and conceivably may contribute to the development of specific cognitive deficits. The pathogenesis of these cerebral white matter abnormalities (sometimes described as leukoaraiosis) is unknown. This review evaluates the available evidence in support of the hypothesis that the etiology of leukoaraiosis is related to a specific type of cerebral ischemia and highlights mechanisms by which ischemic injury to the brain may induce selected structural alterations limited to the cerebral white matter.

Summary of Review The review is based on the critical analysis of over 100 publications (most appearing in the last decade) dealing with the anatomy and physiology of the arterial circulation to the cerebral white matter and with the pathogenesis of leukoaraiosis.

Conclusions A significant number of clues support the hypothesis that some types of leukoaraiosis may be the result of ischemic injury to the brain. Structural changes affecting the small intraparenchymal cerebral arteries and arterioles that are associated with aging and with stroke risk factors, altered cerebral blood flow autoregulation, and the conditions created by the unique arterial blood supply of the hemispheric white matter each seem to contribute to the development of leukoaraiosis. To the best of our ability to interpret current information, the type of ischemic injury that is most likely responsible for these white matter changes involves transient repeated events characterized by moderate drops in regional cerebral blood flow that induce an incomplete form of infarction. This hypothesis could be tested in appropriate experimental models. (***Stroke.*** **1997;28:652-659.**)

Key Words • cerebral ischemia • small-vessel disease • leukoaraiosis • leukoencephalopathy • white matter

Abnormalities involving the cerebral WM, in particular the centrum ovale, are a subject of great current interest. Partly this is because modern neuroimaging methods detect subcortical WM changes with increasing frequency in persons older than 60 years[1] and also because these abnormalities may be associated with specific neurobehavioral deficits, including dementing syndromes.[1-5] The descriptive term "leukoaraiosis,"[6] frequently applied to these neuroimaging abnormalities of the WM, refers to bilateral and either patchy or diffuse areas of hypodensity on CT or hyperintensity on T2-weighted MRI. However, the lesions detected by these two techniques are not completely superimposable as to number, site, and extension. The pathogenesis of WM abnormalities detectable by each of these methods is different, especially because MR detects tiny WM alterations that are of doubtful significance. Because it is impractical to delve separately into the pathogenesis of each set of abnormalities, in this review we discuss CT- and MR-detectable changes jointly, and we emphasize only the more severe types of LA. The terminology used by various authors, the probable clinical significance, and some pathological correlates of these WM changes were recently reviewed.[7] Here we analyze selected publications dealing with the presumed pathogenesis of LA. In particular, we reassess evidence suggesting an ischemic origin for LA. We also analyze an alternative but not mutually exclusive hypothesis that explains cerebral WM abnormalities on the basis of disturbances in the circulation of the CSF and changes in the permeability of the BBB to macromolecules. Understanding the pathogenesis of LA is essential before preventive measures and therapeutic interventions can be attempted.

Pathogenesis of Leukoaraiosis: Possible Role of Ischemia

Clues suggesting an ischemic pathogenesis for LA derive from analysis of anatomic, physiopathologic, and clinicopathologic data. Recent observations on experimental models of ischemic injury lend support to this hypothesis.

Selective injury to the hemispheric WM has been noted in a limited number of human conditions characterized by hypoxia/ischemia to the brain.[8,9] These leukoencephalopathies are associated with prolonged depression of oxygenation and impaired circulation, and in some instances the brain injury becomes clinically manifest after a latent period of several days.[9] Carbon monoxide poisoning is a representative form of anoxic leukoencephalopathy (Grinker's myelinopathy), although in this condition, direct carbon monoxide toxicity could contribute to the brain lesion.[10] The histological

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Received September 3, 1996; final revision received November 7, 1996; accepted November 27, 1996.

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Selected Abbreviations and Acronyms

AD = Alzheimer's disease
BBB = blood-brain barrier
CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBF = cerebral blood flow
CSF = cerebrospinal fluid
LA = leukoaraiosis
WM = white matter

changes of the WM in cases of hypoxic/ischemic injury range from coagulative necrosis and cavitation[9] to nonspecific tissue changes such as sponginess, patchy demyelination, and astrocytic proliferation.[10] Such changes are comparable with the lesions observed in patients with LA.[11] We hypothesize that the nature and the extent of damage to the WM depends on the severity, expressed in terms of regional CBF values, and duration of ischemia. According to this hypothesis, the degree of ischemic injury in patients with LA would be sufficient to injure only selected WM constituents, such as oligodendrocytes and axons. The reasons why some ischemic injuries selectively affect the WM are unknown, but the unique pattern of blood supply to the WM could be both a predisposing and a localizing factor.

Blood Supply of the Cerebral White Matter

The cerebral hemispheric WM receives most of its blood supply through long penetrating arteries originating from the pial network located on the surface of the brain. These penetrating arteries arise at right angles from the subarachnoid vessels, run through the cortical layers perpendicular to the brain surface, and enter the WM along the course of myelinated fibers.[12] Each of these vessels measures from 20 to 50 mm in length depending on their tortuosity.[13] At their origin, the average diameter of these carrying vessels or rami medullares is 100 to 200 μm; such caliber remains unchanged until each vessel ends at some distance from the walls of the lateral ventricles. Carrying vessels do not arborize but give off perpendicularly oriented short branches (distributing vessels) that irrigate the WM; each of the distributing vessels from a single penetrating artery provides the blood supply to a cylindrically shaped metabolic unit.[14]

A region of the WM immediately adjacent to the walls of the lateral ventricles receives its blood supply from ventriculofugal vessels arising from subependymal arteries; these branches originate either from the choroidal arteries or from terminal branches of the rami striati.[14] These ventriculofugal vessels supplying portions of the basal ganglia, the internal capsule, and part of the thalamus arise from arteries situated at the base of the brain.[15] The ventriculofugal vessels, measuring about 15 mm in length, run toward the penetrating centripetal vessels coming from the pial surface (carrying vessels or rami medullares). Anastomoses between the vessels originating at the surface and those branching off the subependymal system are either scarce[16] or absent.[17]

This pattern of vascularization suggested to de Reuck[17] that the periventricular WM harbors an arterial border zone (or watershed) that is particularly susceptible to being injured as a result of systemic or focal decreases in CBF. Arteriolosclerosis might be the substrate for the decreases in blood flow observed in the WM of aged and hypertensive patients. An additional factor that may impair the WM irrigation among the elderly is the tortuosity and elongation of these vessels that accompany aging.[18,19] The existence of a periventricular arterial border zone has been challenged by those who hold the view that the ventriculofugal vessels described by van den Bergh[15] and de Reuck[17] are veins rather than arteries.[13,20,21] If such an interpretation is correct, the periventricular WM might be considered a "distal irrigation field" or an area prone to become seriously ischemic under conditions of moderate blood flow deficit; this is attributed to the scarcity of anastomoses that interconnect branches of the long medullary penetrating carrying vessels or rami medullares.[12,16] Moreover, the arrangement of each metabolic unit is such that, although anastomoses do exist at the precapillary level, one distributing vessel irrigates only one metabolic unit.[14]

A strip of cerebral WM (3 to 4 mm in width) located immediately beneath the cerebral cortex (the so-called U-fibers) is irrigated not only by the long penetrating vessels but also by shorter vessels that straddle both the WM and the adjacent cortex.[13,14] This distinctive arterial supply might account for the fact that the U-fibers are consistently spared in cases of subcortical leukoencephalopathy of presumed ischemic origin.

Clinical and Pathological Features of Leukoaraiosis

The strong epidemiological association that exists between LA and several cerebrovascular diseases suggests that ischemia may be a contributing factor. Notwithstanding the fact that some studies failed to demonstrate an association between WM abnormalities and cerebrovascular risk factors,[7] LA is usually seen more frequently in patients with history of strokes and in individuals with cognitive deterioration of presumed vascular origin.[22-27] Also, persons with severe LA are at increased risk to develop stroke and myocardial infarction.[28] The most common risk factor for LA is aging[7,27]; arterial hypertension, diabetes mellitus, and cardiac diseases are additional risk factors frequently associated with LA.[29-31] Aging, chronic hypertension, and diabetes share a common substrate in the type of alterations that these conditions induce on the small penetrating arteries and arterioles of the WM. Such changes include replacement of the smooth muscle cells by fibro-hyaline material with thickening of the wall and narrowing of the vascular lumen (arteriolosclerosis).[32-34] Arteriolosclerosis, almost always detected within areas of LA,[35-37] may be one of the reasons the blood supply to the WM is altered, and this vascular alteration may lead to either localized ischemic areas of necrosis and cavitation (ie, lacunes) or diffuse rarefaction (ie, LA).

Blood Pressure Dysregulation

Evidence of elevated blood pressure does not exist in all symptomatic patients with LA.[38-41] Yet, complex alterations in blood pressure regulation might contribute to the pathogenesis of LA. Compared with matched control subjects, persons with LA have both higher blood pressure values and a different circadian rhythm that is characterized by either a lack of the nocturnal physiological drops in blood pressure[42,43] or wide daily fluctuations.[44,45] Moreover, the observation that a sub-

group of symptomatic patients with LA suffer frequent hypotensive crises[45,46] is consistent with the demonstration of impaired cerebral autoregulation in hypertensive patients who have severe periventricular LA.[47,48]

Within a well-defined range of blood pressure values (mean arterial pressure of 60 to 150 mm Hg), CBF is maintained constant (average of 55 and 20 mL · 100 $g^{-1} \cdot min^{-1}$ in the gray matter and WM, respectively) despite changes in systemic arterial blood pressure. Different from other organs,[49] the cervical segment of the carotid arteries and the large intracranial arteries also play a role in the regulation of vascular resistance in the cerebral circulation.[50] Notwithstanding the contribution of the large-caliber vessels, the physiological responses of the small cerebral vessels are essential for autoregulation, and their response to blood pressure changes is caliber dependent. In the cat, vascular responses to variations in mean arterial blood pressure between 110 and 160 mm Hg affect mainly pial vessels >200 μm. Arterioles with an average caliber of <100 μm dilate only at blood pressures <90 mm Hg; at <70 mm Hg, the degree of dilation in these small arterioles exceeds that of the larger vessels.[51]

If human intraparenchymal vessels are controlled by similar mechanisms, then in hypertensive patients with arteriolosclerotic vessels a drop in blood pressure of the type that occurs during cardiac dysrhythmias or as a result of impaired autoregulation could lead to a decrease in blood flow attributable to the inability of sclerotic vessels to dilate.[52] Autoregulatory limits are shifted upward in hypertensive patients[53]; thus, a rapid reduction of blood pressure, within physiological limits, might markedly reduce CBF in the WM of patients with chronic hypertension. Consequently, the cerebral WM of hypertensive patients could become ischemic at blood pressure levels considered normal for normotensive subjects.[54] Moreover, autoregulatory responses in the WM vessels of experimental animals are less effective than they are in the vessels of the gray matter; therefore, at low blood pressure values, the decreases in blood flow are more pronounced in the WM than in the gray matter.[55,56]

Cerebral Blood Flow Studies in Leukoaraiosis

Support for the hypothetical ischemic origin of LA could be derived from studies based on estimates of the CBF. Several authors report whole brain or gray matter alterations in the CBF of patients with LA,[57-65] but few studies have compared regional CBF values in brain areas with and without LA. In one study, CBF values were depressed in areas of LA when compared with normal white matter areas.[66] Similar results were obtained using single-photon emission CT[67] or xenon CT,[68,69] although the latter technique does not allow a sharp separation between gray matter and WM.[70]

Decreased regional CBF together with an increased oxygen extraction fraction has yet to be shown in areas with LA; this leaves unresolved the question of whether the decreased blood flow is the cause of LA or the consequence of the reduced metabolism in WM that became atrophic by other causes.[66,70-72] Decreased blood flow in the frontal and parietal but not in the occipital WM was demonstrated in nondemented subjects with LA, suggesting that the pathogenesis of LA varies depending on its topographic location in the brain.[72] Other studies have failed to demonstrate CBF alterations in patients who have patchy WM abnormalities[73]; this might be because the pathogenesis of small WM lesions is different from that responsible for the more diffuse WM changes.

Hereditary Leukoencephalopathy of Probable Vascular Origin

CADASIL is a condition characterized by multiple subcortical infarcts, leukoencephalopathy, and an autosomal dominant pattern of inheritance.[74] Among patients with CADASIL, small arteries (in the brain, skin, and peripheral nerve) show granular osmiophilic deposits in the tunica media; the lumen in these vessels is narrowed secondary to the deposits of this electron-dense material,[75] and the normal autoregulatory responses may be impaired because of the structural changes in smooth muscle cells. These changes can result in WM damage.

Experimental Studies of Brain Ischemia

Histopathological studies of either rat or gerbil brains exposed to various types of ischemic injury suggest that both oligodendrocytes and myelinated axons are highly vulnerable to ischemia[76] and that chronic cerebral hypoperfusion produces progressive "rarefaction"[77-79] and glial activation[80] in the WM. Permanent middle cerebral artery occlusion of up to 24 hours in duration in Wistar rats caused oligodendrocytes in the subcortical cerebral WM to significantly swell as early as 30 minutes after the occlusion of the artery.[76] In this model, 3 hours after the arterial occlusion, oligodendrocytes display histological changes characteristic of irreversible injury, such as pyknosis and plasma membrane rupture. The contemporaneous vacuolization of the WM that develops in these animals corresponds to (1) spaces formed by the separation of the inner myelin layer sheaths from the axolemma, (2) enlarged extracellular spaces, and (3) swelling of the astrocyte processes.[76] All of these changes in the WM precede the appearance of irreversible neuronal injury (ie, eosinophilia), thus suggesting that the early WM damage is independent of injury to the neuronal perikaryon. Studies based on either bilateral narrowing of the carotid artery in gerbils[77-78] or bilateral carotid occlusion in rats[79-80] consistently demonstrate two types of changes in the WM: reactive astrogliosis and nonspecific rarefaction of the WM. Significantly, increased extracellular fluid accumulation and astrogliosis are two of the main pathological features noted in areas where CT and MRI show LA in humans.[7]

Pathogenesis of Leukoaraiosis: Alternative Hypotheses

Hypotheses alternative to ischemia have been proposed to explain the origin of LA. We suggest that these mechanisms may be interrelated to the ischemic origin of LA.

Leukoaraiosis and Disturbances in Cerebrospinal Fluid Circulation

Patients with normal pressure hydrocephalus have a high prevalence of alterations in the WM that are detectable by either CT or MRI.[81] Experimental hydro-

cephalus in dogs causes changes in the WM that can be reversed by shunting.[82] On the basis of these observations, the authors hypothesized that disturbances in CSF circulation may play a role in the pathogenesis of LA, particularly the extensive periventricular lesions. The question of whether normal pressure hydrocephalus causes LA or vice versa is unresolved; this is because subjects with extensive LA often have enlarged lateral ventricles,[29] an abnormality that may be the result of ex-vacuo dilatation. Román[83] suggested two mechanisms for the development of LA in patients with normal pressure hydrocephalus. (1) The increased accumulation of CSF in the ventricles raises interstitial pressure in the periventricular parenchyma and causes ischemia to the WM. In fact, while the mean CSF pressure may be normal, the pulse pressure can be markedly increased in normal pressure hydrocephalus.[84] The hypothesis that increased ventricular pressure causes ischemic changes in the WM is supported by observations showing that among patients with normal pressure hydrocephalus, blood flow in the WM returns to normal values after shunting procedures that lower the intraventricular pressure; this is accompanied by parallel clinical improvement and reduction in the severity of LA.[85] (2) The second mechanism could involve alterations in the ependymal lining. Leakage of CSF into the adjacent brain parenchyma may be the result of structural alterations in the ependymal cells. Age-related changes affecting the penetrating vessels and altering the BBB could hinder the reabsorption of this excessive interstitial fluid.[86,87] Abnormalities in the BBB, in the form of increased concentration of CSF proteins, have been described in a group of patients with LA.[88]

The chronic effects of arterial hypertension, a condition that is more prevalent in normal pressure hydrocephalus patients than in control subjects, are a third factor that may cause rarefaction of WM in patients with normal pressure hydrocephalus.[89,90] The arteriopathic changes of hypertension may contribute to the occurrence of multiple microinfarcts (lacunes) in the periventricular WM, leading to loss of tissue and consequent expansion of the lateral ventricles.[89]

White Matter Changes and Cerebral Edema

WM changes similar to those of LA (pallor of the WM sparing the U-fibers, accompanied by reactive astrogliosis and small-vessel thickening) have been described in conditions in which brain edema might have preceded the appearance of LA.[91] This suggests that transient cerebral edema might be an added cause of WM changes. The increased interstitial fluid concentration in the WM of patients with LA, which gives rise to CT hypodensities, may be a consequence of arterial hypertension and the subsequent alterations in the BBB. The BBB may be leaky, and the capillary permeability to proteins may be increased in patients with systemic hypertension.[92,93] In addition to the effects of sustained hypertension, hypertensive bouts of short duration could cause fluid transudation and protein leakage.

Impaired venous return in the deep WM compartment is another possible cause of interstitial WM edema.[94] This idea has received increasing attention after the demonstration of structural alterations in the periventricular venules of patients with LA.[95] Changes in these veins, characterized by deposition of collagen fibers in the vessel wall, may be responsible for narrowing the venular lumen. This may disrupt the BBB at the venular level and may increase the perfusion pressure on the arterial side of the capillary bed.

Leukoaraiosis in Alzheimer's Disease

A considerable proportion of patients with AD have radiologically and structurally detectable WM changes, although they are usually less severe than in patients with cerebrovascular disease.[96] The hypothesis that LA in patients with AD might simply reflect wallerian changes secondary to cortical loss of neurons[97,98] seems unlikely. The histological markers of wallerian changes, such as abundant lipid-laden macrophages, are missing in most areas of LA, and the discrepancy between the severity of changes in adjacent cortical and WM areas also militates against this hypothesis.[96] That wallerian changes may be undetectable at autopsy appears unlikely, since this process is a long-lasting phenomenon.[99] Moreover, it is difficult to understand why many AD patients with severe cortical atrophy and "loss" of neurons lack demonstrable WM changes at autopsy.[96] Data derived from MR spectroscopy confirm that decreases in myelin phospholipids exist in areas of LA, in the absence of changes in the concentration of *N*-acetylaspartate, a marker for neuronal perikarya.[100] This reinforces the hypothesis that the changes in the WM can occur independently of the alterations involving the gray matter.

LA among patients with AD may have an ischemic origin secondary to structural changes in the small blood vessels, as suggested by the observation that amyloid angiopathy (a small blood vessel disease) is present in almost 90% of AD patients.[101] The hypothesis that amyloid angiopathy in AD patients may be causally linked to LA is supported by the observation that subcortical leukoencephalopathy was demonstrated in patients with cerebral amyloid angiopathy who lacked changes characteristic of AD.[102-104] Leukoencephalopathy also exists in presymptomatic carriers of the amyloid precursor protein gene codon 693 mutation, which is responsible for hereditary cerebral hemorrhage with amyloidosis (Dutch type).[105] Furthermore, the extent and frequency of changes affecting the tunica media and tunica adventitia of the WM vessels is higher among AD patients than in age-matched control subjects[32,96,106]; these vascular changes might be a heretofore overlooked cause of LA in AD patients.

Extensive damage to the WM among AD patients could be a consequence of changes in the permeability of the BBB to proteins and the accumulation of fluid in the extracellular space. This leakiness might be the result of structural alterations, such as thickening of the basal lamina and pericapillary gliosis affecting the precapillary arterioles.[107,108]

Conclusion

The causes of LA are incompletely understood. In part this is because the neurological and histological abnormalities associated with LA are nonspecific.[7,109] Both hypodensity on CT and hyperintensity on MRI reflect an increase of brain water content that can be accounted for by several conditions[110]; therefore, more than one mechanism could be responsible for LA. Notwithstanding the heterogeneity of radiological-

Clues Pointing to an Ischemic Origin of Leukoaraiosis

	Reference
Clinical	
Association with cerebrovascular diseases	7, 22-27
Association with risk factors for cerebrovascular diseases	7, 29-31
Increased risk of cardiovascular events (stroke and myocardial infarction) at follow-up	28
Pathological	
Histological similarity with human leukoencephalopathy of hypoxic/ischemic origin	8-10
Association with structural alterations of small vessels	35-37, 76, 96
(arteriolosclerosis, amyloid angiopathy) supplying the cerebral WM	102-104
Association with alteration of venules (periventricular venous collagenosis)	95
Topographic distribution of the lesions (watershed areas, sparing of U-fibers)	14, 17
Similarity with lesions visible at the margins of complete infarcts	96
Pathophysiological	
Dysregulation of circadian blood pressure changes	42-45
Disturbed autoregulation	47, 48
Disturbances of the BBB permeability related to ischemia	85, 89, 90
Experimental	
High vulnerability of oligodendrocytes and myelinated axons to ischemia in the rat	76
Microscopic similarity between LA and lesions induced in WM by chronic cerebral hypoperfusion in rats and gerbils	77-80

pathological correlates, the most consistent histological substrate of LA is a diffuse pallor of the WM attributed to rarefaction of the myelin sheaths.[11,36,111,112] The studies reviewed herein suggest that in a large group of patients, this type of myelin alteration may be related to ischemic injury (Table). Appraisal of alternative hypotheses such as those involving alterations in the CSF circulation and disturbances in the BBB also suggests a possible connection with ischemia. A unifying theory to explain diffuse WM changes of the type seen in LA has been proposed.[113] Aging, arterial hypertension, and diabetes mellitus each produce structural alterations in the wall of small blood vessels, and the consequent narrowing or occlusion of the arteriolar lumen may cause small infarcts in the WM. This event may be accompanied by a breakdown of the BBB, with consequent leakage of macromolecules and ensuing activation of astrocytes. Activated and swollen astrocytes, typically seen in areas of LA, may contribute to the alterations commonly detected by CT and MRI.[110,111]

The myelin rarefaction typical of LA has been interpreted as the expression of incomplete infarct or the result of an ischemic event not severe enough to cause pannecrosis.[96] According to this suggestion, under yet-to-be-described conditions, ischemic injury may affect selected components of the WM while sparing many others. This hypothesis is supported by the observation that lesions similar to those of LA are detectable in the marginal zones of brain infarcts where the degree of ischemia is less severe than in the center.[96] However, direct demonstration for the ischemic origin of LA is lacking. Ipsilateral WM changes in patients undergoing therapeutic occlusion of the internal carotid artery became demonstrable by MRI shortly after arterial occlusion.[114] These patients had been pretreated with anticoagulants, and the postoperative angiograms had shown patent large arteries; thus, secondary thromboembolic occlusion of the large collateral vessels seemed an unlikely cause of the WM changes. Instead, the authors hypothesized that in these patients a failure in the regulatory function of the intraparenchymal small blood vessels could have been responsible for the WM changes.[114]

These and similar observations strongly suggest that microvascular disturbances may have a central role in the pathogenesis of LA. The structural changes of arteriolosclerosis, those seen in CADASIL patients, and perhaps those of cerebral amyloid angiopathy may lead to deficits in the mechanisms regulating the blood flow to the WM.

In patients with small-vessel alterations, the cerebral WM may suffer brief and repeated episodes of hypoperfusion that eventually result in rarefaction, reactive gliosis, and edema; injury to the BBB permeability may contribute to the escape of macromolecules and the development of changes typical of LA.

Future Developments

Defining the structural changes of WM in an experimental model of moderate brain ischemia would be extremely valuable to clarify some of the unresolved issues regarding leukoencephalopathy and ischemia. In a study based on short-term occlusion (<3 hours) of the middle cerebral artery in Wistar rats, oligodendrocytes and axons were extremely sensitive to the effects of this type of ischemia, and pallor (rarefaction) of the subcortical WM was recognized in the involved territory before neuronal necrosis appeared.[76] Modifying the severity of the ischemic injury in this or similar models may provide the means with which specific hypotheses can be tested: eg, can selective injury to the WM, in the absence of injury to neuronal perikarya, be induced by moderate ischemia?

Acknowledgments

Partial financial support for this study was provided by US Public Health Service grant NS 31631. We thank Nancy Vesey and Maureen Malek (Detroit) for excellent secretarial support.

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