Periventricular Lesions on MRI
Facts and Theories
Marc I. Chimowitz, MD, Issam A. Awad, MD, and Anthony J. Furlan, MD

Patchy subcortical lesions are frequently identified on magnetic resonance imaging (MRI) of the brain in the elderly.1-4 On computed tomography (CT) these lesions appear as periventricular zones of lucency and have been termed “leuko-araiosis” by Hachinski and colleagues.5 Despite limited knowledge of the pathological correlates of the lesions, there has been speculation about their nature, pathophysiology, and clinical significance.

**Epidemiology**
Subcortical MRI lesions are most commonly seen in the elderly, occurring in 30–92% of patients older than 60 years of age1,2 and also in 22% of persons under the age of 40.2 The lesions are found scattered throughout the deep cerebral white matter, notably in the frontal and parieto-occipital periventricular regions, and basal ganglia, especially the globus pallidus and putamen. On T2-weighted MRI, the lesions are hyperintense and may appear as thick rims surrounding the lateral ventricles, as caps around the poles of the lateral ventricles, as uniform patches, or as multifocal subcortical patches that at times are confluent (Figure I).6

Risk factors associated with these lesions include old age, a history of ischemic cerebrovascular disease, and hypertension.2-7-9 With one exception,10 studies have shown no significant association between these lesions and diabetes, cardiac disease, and carotid disease. However, these studies lack statistical power. There is a high incidence of subcortical MRI lesions in patients with clinically suspected Alzheimer’s disease (AD) and senile dementia of the Alzheimer type (SDAT) regardless of their vascular risk factors.1,5-11

**Clinical Significance**
The data on the clinical significance of these radiological lesions are conflicting. Awad et al12 found no relation between subcortical lesions on MRI and dementia or any particular entity with the exception of prior stroke. However, the data base in this study did not include a large cohort of demented patients, and detailed neuropsychological testing was not performed. Inzitari et al7 found a strong association between hypodense periventricular lesions on CT and stroke as well as dementia. Further analysis indicated that the association between hypodense lesions and dementia was explained mainly by the history of stroke. Other studies in patients with periventricular lesions on CT or MRI suggest a high incidence of dementia, pseudobulbar palsy, and long tract signs, especially among patients with lesions restricted to the inferior frontal lobes.12,13 Autopsy findings in several of these cases included diffuse areas of periventricular demyelination, numerous white matter and basal ganglia infarctions with cavitation, dilated ventricles, and marked atherosclerotic changes in the penetrating medullary arteries that irrigate the deep white matter. These pathological findings are characteristic of Binswanger’s subcortical arteriosclerotic encephalopathy, a disease with a variable clinical picture but usually including the following features: history of hypertension, slowly progressive dementia with occasional temporary plateaus in the course of the illness, and prominent motor signs.14 The dementia exhibits no clinical characteristics that reliably distinguish it from AD, SDAT, or multi-infarct dementia (MID).

The conflicting data from these studies have led to widely different interpretations. Roman15 argues that these radiological lesions are indicative of Binswanger’s disease, the clinical spectrum of which ranges from asymptomatic radiological lesions to dementia with focal deficits, frontal signs, pseudobulbar palsy, gait difficulties, and urinary incontinence. The opposing argument is that Binswanger’s disease is rarely seen in large unselected autopsy studies and, therefore, cannot be the etiology of subcortical MRI lesions in a large proportion of patients. Proponents of the latter argument suggest that several incompletely understood entities may produce these radiological findings without causing symptoms and that dementia in many of these patients is related not to the subcortical lesions but rather to coexistent AD, MID, or both.16

**Neuropathological Correlates**
Areas of hyperintensity (increased signal) on T2-weighted MRI indicate increased tissue proton den-
sity. This finding is compatible with a number of pathophysiological processes, including inflammation, cytotoxic or vasogenic edema, or vacuolation of brain parenchyma with development of microscopic or macroscopic fluid-filled spaces. Brain infarction is associated with increased $T_2$ signal because of interstitial and intracellular edema in the acute stage, persistent edema and inflammation in the subacute stage, and replacement of necrotic brain by a fluid-filled space chronically. Glialosis results in MRI hyperintensity because the replacement of myelinated axons by astrocytic processes is associated with an increase in water content per unit volume of tissue. It is doubtful that myelin loss per se (without associated edema, inflammation, or glialosis) causes significant MRI abnormality since myelin contributes little to the MRI signal at 1.5 Tesla.

Several pathological studies on selected patients with motor and cognitive deficits and marked subcortical lesions on CT or MRI have been reported. The pathological findings in these patients include sharply delineated areas of necrosis, diffuse demyelination of the deep white matter, gliosis, small infarcts in the basal ganglia and thalamus, arteriolar sclerosis, and dilation of the ventricular system. Three recent reports have addressed the pathological correlates of subcortical MRI lesions in patients not specifically selected for the presence of motor and cognitive deficits. These studies revealed that a broad spectrum of pathological processes underlie the radiological lesions. Awad et al performed postmortem MRI on the brains of seven consecutive elderly patients dying of nonneurological causes. Subcortical MRI lesions were identified and examined pathologically. In addition, pathological correlations were obtained from an eighth patient who underwent MRI 11 days before death. Four of the eight patients were neurologically asymptomatic, one was demented, and three had a history of transient ischemic attacks prior to death. An association between subcortical lesions on MRI and dilated perivascular spaces, arteriosclerosis, and vascular ectasia was found. These pathological changes are characteristic of *état criblé*, which was first described by Durand-Fardel in 1843. In addition, gliosis and small areas of infarction occasionally coexisted with *état criblé* in Awad's study (Figure 2).

Marshall et al performed postmortem MRI on the brains of 14 patients older than 60 who had no history of disease of the central nervous system except cerebrovascular disease. Multiple hyperintense white matter lesions were identified in three of the 14 brains, and lacunar infarcts were seen in the basal ganglia of two of the brains. Histopathology of the periventricular white matter lesions showed necrosis in the center of these lesions, axonal loss, and demyelination indicative of infarction. In addition, reactive astrocytes oriented along the degenerated axons were noted up to several centimeters from the central infarct. Several specimens showed thickened, fibrohyalinized arterioles.

Braffman et al performed postmortem MRI on 36 brains of patients between 30 and 94 years of age. Included were neurologically asymptomatic and symptomatic patients although no clinical details were provided. Subcortical hyperintense lesions were found in 13 brains. The pathological features included basal ganglia lacunar infarctions, *état criblé*, white matter infarctions, plaques of demyelination, gliosis, a brain cyst, and a congenital diverticulum of the lateral ventricle. The authors suggested that MRI allowed the distinction between lesions with fluid-containing spaces (cystic infarction, brain cyst, and ventricular diverticulum) and those without (noncystic infarction, gliosis, or demyelination) but did not allow further differentiation among specific lesions in a particular group. Additionally, the authors claimed it was possible to distinguish between lacunar infarcts and *état criblé* in vivo by varying the pulse sequences on MRI.

Other pathological studies without MRI-CT correlation shed important light on the issue of subcor-

---

**Figure 1.** Magnetic resonance images of the brain of a 79-year-old woman showing hyperintense punctate lesions in the cerebellum and periventricular rims, caps, and patches (arrows). (Reprinted from Awad et al with permission.)
Chimowitz et al  Periventricular Lesions on MRI  965

FIGURE 2. Panel A: Histology of a periventricular section which appeared as a cap on MRI showing gliosis (a), dilated perivascular space (b), and sclerotic vessels (c). Panel B: Histology of a periventricular section devoid of MRI lesions of the same brain showing normal parenchyma and vessels. (Reprinted from Awad et al with permission. 19)

tical lesions in the elderly. The classic pathological studies of Tomlinson et al24,25 on brains of demented and nondemented old people provide a wealth of information on the neuropathology of aging. Observations relevant to this discussion included the following: 1) Multiple, small, widely scattered subcortical softenings were seen in both demented and nondemented groups; 2) the pathology in brains of demented old people showed mixed degenerative and vascular lesions in at least 40% of patients; and 3) in the six patients with pure arteriosclerotic dementia, significant softening of white matter was always seen in association with cortical infarction. In a recent autopsy study Brun and Englund26 found white matter changes in 11 of 20 patients with AD, 19 of 28 with SDAT, 23 of 23 with MID, and two of 26 nondemented normotensive patients. The white matter pathology was characterized by partial loss of myelin, axons, and oligodendroglial cells with mild reactive astrocytic gliosis and macrophage infiltration, as well as fibrohyalinized arterioles. The authors felt that these findings were indicative of incomplete infarction confined to white matter. Remarkably, none of the patients with AD or SDAT had long-standing hypertension, but hypotensive episodes were frequent in this group. Kirkpatrick and Hayman27 studied 15 clinically healthy subjects who died of nonneurological causes between ages 52 and 72 years. Small white matter lesions were found in 12 brains. Eight of these showed perivascular demyelination with unusually tortuous sclerotic vessels within these areas. Other lesions occurring alone or in combination with perivascular demyelination included small vascular malformations in the centrum ovale in four patients, diverticula of the lateral ventricle extending into the white matter in three, and an isolated central white matter infarction in one. The findings in these postmortem studies provide further evidence that a number of pathological processes underlie the patchy subcortical lesions seen on MRI in the elderly.

Pathophysiology of MRI Subcortical Lesions

After excluding congenital MRI lesions (vascular malformations, brain cysts, and diverticula) and those related to well-understood acquired causes (e.g., multiple sclerosis and lacunar infarctions), there remains a large subgroup of radiological lesions with unexplained etiology. These lesions are characterized by a spectrum of pathological changes ranging from \textit{état criblé} to perivascular demyelination to necrosis. Could this residual subgroup be linked by a common pathophysiological mechanism? Any unifying theory about the pathophysiology of these lesions needs to explain the following epidemiological, clinical, and pathological observations: 1) the high incidence of these lesions in elderly, hypertensive patients with a previous history of ischemic cerebrovascular disease,2,7,8 2) the seemingly paradoxical cases which are character-
ized not by hypertension but rather by a history of hypotensive episodes, 26 3) the wide spectrum of pathological changes associated with these lesions, 19-22, 27 4) the high incidence of these lesions in Alzheimer's disease, 1, 9, 11 and 5) the frequent lack of correlation between MRI lesions and the clinical findings. 2, 7

The high incidence of cerebrovascular risk factors in these patients and the coexistence of état crible and perivascular demyelination with areas of infarction and hyalinized, sclerotic, and ectatic subcortical vessels suggest that these MRI lesions have a vascular etiology. Long-standing, pulsatile trauma from hypertension causes vessels to become sclerotic, elongated, and tortuous and may cause atrophy of the surrounding parenchyma, which is replaced by extracellular water. These dilated, fluid-filled perivascular spaces around ectatic vessels (état crible) integrate into an extensive network of tunnels, which appear as increased signal on MRI. This process accounts for some of the residual group of subcortical MRI lesions. It has been proposed that the remaining lesions are the result of ischemia due to subcortical occlusive small vessel disease, 15 low cerebral blood flow (CBF), 26 or both. The evidence that occlusive small vessel disease plays an etiological role is based on the association between leukomalacia and subcortical arteriolar hyalinosis, 20, 26 atherosclerosis, 12, 13, 28 and amyloid angiopathy. 29 However, these studies do not report in detail the extent of involvement of the subcortical vessels or the topographical relationship of the parenchymal lesions to the vascular changes.

The suggestion that low CBF may be important in the genesis of subcortical MRI lesions is based on a few reports of pathologically confirmed white matter injury associated with hypoxemia and hypotension, 26, 30 and the topography of the lesions on MRI. 6 De Reuck 31 demonstrated a watershed area in the periventricular white matter between the end arteries of the perforating vessels at the base of the brain and descending medullary branches of the main cerebral arteries on the surface of the brain. This periventricular border zone would be highly susceptible to the effects of decreased blood flow in association with hypotension and low cardiac output states (e.g., arrhythmia, heart failure), especially in the presence of subcortical occlusive small vessel disease. Hypertensive patients may be at particular risk of ischemia during even moderate hypotensive episodes, not only because of coexistent small vessel disease, but also because the lower limit of mean arterial blood pressure at which CBF autoregulation is abolished is higher compared with normotensives. Some authors postulate that intermittent or chronic low CBF leads to either incomplete or complete infarction of the periventricular border zone area. 26, 27 It is proposed that incomplete infarction is characterized pathologically by partial loss of myelin, axonal degeneration, gliosis, and macrophage infiltration. In contrast, complete infarction is characterized by more extensive demyelination and axonal loss with sharply delineated areas of necrosis, sometimes with cavitation. This theory could explain the variety of pathological findings associated with the radiological lesions.

CBF studies have provided only partial support for the low periventricular perfusion theory. Although a few studies have shown decreased CBF with normal aging and in patients with chronic, severe hypertension, 32-34 positron emission tomography studies have not demonstrated a significant increase in oxygen extraction fraction in either the gray or white matter in elderly persons, 35 suggesting that the diminished perfusion is a response to decreased brain metabolism. 36 Perhaps the most convincing CBF study supporting the low periventricular perfusion theory was provided recently by Fazekas et al. 10 Using intravenous xenon133 and an external scintillation detector system, they studied age-matched groups of asymptomatic patients with and without white matter signal abnormalities on MRI and showed slightly lower gray matter blood flow and significantly lower white matter blood flow in the group with MRI lesions.

The study by Gray et al 20 on leukoencephalopathy associated with amyloid angiopathy may explain the high incidence of subcortical MRI lesions in patients with AD. In 12 brains selected because of diffuse and severe cerebral amyloid angiopathy, they showed état crible, severe demyelination with partial axonal degeneration, gliosis, and macrophage infiltration in eight. Senile plaques and neurofibrillary tangles were numerous in four of these brains. Three of the eight cases had a cranial CT scan premortem, and all showed marked bilateral hypodensity of the hemispheric white matter. AD is commonly associated with amyloid angiopathy which, in turn, is associated with the pathological findings characteristic of these MRI lesions.

The vascular theory is consistent with the frequent lack of association between the radiological and clinical findings. Currently, MRI cannot reliably distinguish between the various pathological processes underlying these lesions. Infarction in strategic subcortical areas is likely to have a different clinical effect from état crible or perivascular demyelination in identical areas. Recently, gadolinium-enhanced MRI has been used to distinguish new from old lacunar infarcts and symptomatic from asymptomatic multiple sclerosis plaques by enhancing those lesions with associated breakdown of the blood–brain barrier. 37, 38 Perhaps this technique or variations in the MR pulse sequences as suggested by Braffman et al 21 will allow reliable differentiation of the various pathological entities that underlie subcortical MRI lesions and permit accurate clinicopathological correlations. Until then, caution should be the rule when invoking these lesions as the cause of dementia or other neurological syndromes.
References


Key Words • lacunar infarction • magnetic resonance imaging
Periventricular lesions on MRI. Facts and theories.
M I Chimowitz, I A Awad and A J Furlan

Stroke. 1989;20:963-967
doi: 10.1161/01.STR.20.7.963

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/7/963.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/