Understanding White Matter Disease
Imaging-Pathological Correlations in Vascular Cognitive Impairment

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Abstract—Most strokes are covert and observed incidentally on brain scans, but their presence increases risk of overt stroke and dementia. Amyloid angiopathy, associated with Alzheimer Disease (AD) causes stroke, and when even small strokes coexist with AD, they lower the threshold for dementia. Diffuse ischemic white matter disease impairs executive functioning, information processing speed, and gait. Neuroimaging techniques, such as tissue segmentation, Diffusion Tensor Imaging, MR Spectroscopy, functional MRI and amyloid PET, probe microstructural integrity, molecular biology, and activation patterns, providing new insights into brain-behavior relationships. MR-pathological studies of periventricular hyperintensity (leukoaraiosis) in aging and dementia reveal arteriolar tortuosity, reduced vessel density, and occlusive venous collagenosis which causes venous insufficiency and vasogenic edema. Activated microglia, oligodendroglial apoptosis, clasmatodendritic astrocytosis, and upregulated hypoxia-markers are seen on immunohistochemistry. Further research is needed to understand and treat this chronic subcortical vascular disease, which is epidemic in our aging population.  (Stroke. 2009;40[part 2]:000-000.)

Key Words: silent stroke ▪ white matter hyperintensities ▪ venous collagenosis ▪ tissue segmentation ▪ neuropathology

After a stroke approximately one third of patients become demented, increasing their dependence and tripling mortality.1 However, clinically overt stroke is the tip of a more ominous cerebrovascular disease (CVD) iceberg. Silent strokes are 10 to 20 times as prevalent as overt strokes.2 In the Rotterdam Study (>1000 normal elderly over age 60 followed over 4 years), subcortical lacunes (≥3 mm) occurred in 25%, conferring twice the dementia risk3 and a 5 times risk of clinical stroke.4 Incidental hyperintensities, called leukoaraiosis,5 are focal or confluent on Proton Density (PD)/T2 or FLAIR MRI. Relatively hypointense on T1 images, they are observed in 96% of community volunteers over age 65.6 However, periventricular hyperintensities (PVH) appear clinically silent except in 20% with extensive PVH, who showed impaired cognition, and gait.6

Cerebrovascular and Alzheimer Disease Relationships

Even small infarcts, when combined with Alzheimer disease (AD), can lower the dementia threshold. In the “nun” autopsy study, 57% of elderly sisters meeting pathological AD criteria were predominately demented, but in 39% with subcortical infarcts, cognitive function was lower, less AD pathology was needed for dementia, and 93% met dementia criteria.7 Similar studies confirm this finding, some reporting additive infarct effects8 and others claiming impact only in milder stage AD.9 Population autopsy series reveal combined pathologies as the rule for dementia.10 In a British study, the frequency of vascular pathologies (78%) exceeded AD (70%),11 and AD+CVD was the commonest dementia substrate in a U.S. community sample.12 For dementia associated with infarcts alone, multiple microinfarcts, not macroscopic infarcts, appear to be culprit.13 These close AD+CVD interrelationships, including shared vascular risk factors,14 suggest ischemia may drive pathophysiology in sporadic AD.15 Amyloid β (Aβ) is toxic to vascular endothelium and neurons;16 Aβ40 deposits in arterioles and most capillaries in AD-vulnerable regions, causing occlusion, vasculitis, hemorrhage, and vessel obliteration.14,17 Vascular myocytes in AD constrict rather than dilate arterioles in response to ischemia.18 Some contend that sporadic AD is a primary vasculopathy,14 but selective vulnerability of particular neuronal networks counts against this. Others propose that synaptic loss with aging is a contributing precondition for emergence of AD dementia.19

Measuring Small Vessel Disease in Vivo: Challenges and Opportunities

To understand the burden of vascular disease in aging and dementia, optimal deployment of in vivo and postmortem neuroimaging is vital. Reliable gray, white, and cerebrospinal fluid (csf) tissue segmentation with separate hyperintense
lesion analysis is desirable. Progress using tissue volumetrics has been slow in dementia because researchers have concentrated on whole brain or focal atrophy, which correlates with global cognitive performance. However this precludes evaluation of selective effects of hyperintensities, and failure to classify the lesion compartment may erroneously allocate PVH to gray matter, inflating its regional volumes (Figure 1). In contrast, others have focused on hyperintensities, neglecting the host brain. Lesion rating scales or lacune counts have been a popular, clinically pragmatic way to estimate small vessel disease burden. Some studies show that hyperintensities in cortical cholinergic projections correlate better with executive function and with response to cholinesterase inhibitors in AD, than do general hyperintensity rating scales. Generally, however, rating scales are less powerful in addressing complex brain-behavior relationships and longitudinal changes.

More recent studies, which quantify all tissue compartments simultaneously, including total intracranial volume to correct for head size, reveal that brain parenchymal fraction (bpf) best predicts global cognitive measures, with PVH contributing little variance. Rather, PVH correlates with executive dysfunction, irrespective of location, possibly reflecting compromised association tracts anywhere along their anterior-posterior trajectories. In a factor-analytic study of tissue volumetrics in a clinic sample, brain atrophy best predicted overall cognition, but small vessel disease burden independently predicted memory, language and some executive functions.

The relative contributions to behavior of PVH and deep white hyperintensities, which are highly correlated, remain unclear. Location, volume, acuity, and severity of pathology likely influence impact. There may be a threshold effect (approximately 10cc), but cognitive correlates in aging and dementia have varied. The most consistent finding is reduced speed of information processing and the so-called dysexecutive syndrome, implicating dorsolateral prefrontal cortex, with impaired conceptualization, initiation, planning, sequencing, and set-shifting. Some question this specificity, however; executive and memory performance did not distinguish subcortical Vascular Dementia from AD in a recent clinico-pathological study. Gait difficulty, urinary incontinence, dysarthria, and mood disorder are also common. New MR techniques go beyond signal intensity counts and volumetric measures to inferences about brain microstructure, vascular pathology, blood flow, and neuronal health. Lobar microbleeds on gradient echo MRI signal amyloid angiopathy. Diffusion Tensor Imaging (DTI) probes microstructural integrity, and MR Spectroscopy reveals metabolite profiles. Functional MRI reveals activity patterns of brain networks, and amyloid PET ligands directly demonstrates AD pathology in vivo.

**Clinical-Pathological Correlates of Small Vessel Disease**

The pathological correlates of subcortical hyperintensities in white matter and deep nuclei can be dichotomized into: (1) necrotic, black cystic lesions, isointense to csf on T1 MRI and (2) diffuse, demyelinating lesions, hyperintense to gray matter on T1 and T2 MRIs. Some lesions may be T1 hypointense and T2 hyperintense. The pathological correlates of subcortical hyperintensities in white matter and deep nuclei can be dichotomized into: (1) necrotic, black cystic lesions, isointense to csf on T1 MRI and (2) diffuse, demyelinating lesions, hyperintense to gray matter on T1 and T2 MRIs. Some lesions may be T1 hypointense and T2 hyperintense. The relative contributions to behavior of PVH and deep white hyperintensities, which are highly correlated, remain unclear. Location, volume, acuity, and severity of pathology likely influence impact. There may be a threshold effect (approximately 10cc), but cognitive correlates in aging and dementia have varied. The most consistent finding is reduced speed of information processing and the so-called dysexecutive syndrome, implicating dorsolateral prefrontal cortex, with impaired conceptualization, initiation, planning, sequencing, and set-shifting. Some question this specificity, however; executive and memory performance did not distinguish subcortical Vascular Dementia from AD in a recent clinico-pathological study. Gait difficulty, urinary incontinence, dysarthria, and mood disorder are also common. New MR techniques go beyond signal intensity counts and volumetric measures to inferences about brain microstructure, vascular pathology, blood flow, and neuronal health. Lobar microbleeds on gradient echo MRI signal amyloid angiopathy. Diffusion Tensor Imaging (DTI) probes microstructural integrity, and MR Spectroscopy reveals metabolite profiles. Functional MRI reveals activity patterns of brain networks, and amyloid PET ligands directly demonstrates AD pathology in vivo.
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Blood brain barrier disruption.51 Another compelling expla-
nation invokes perivascular pathways in PVH, revealing capillary endothelial activation, activated microglia, clasmadendritic astrocytosis, axonal myelin loss, and reactivating oligodendroglia.44,50,56 as well as upregulated hypoxia markers.57 In a single case study, cells positive for an apoptosis marker (TUNEL) was 2.5X more frequent in PVH compared to nearby normal white matter, suggesting that oligodendroglial apoptosis could be a pathophysiological mechanism.

(csf density on CT), and (2) nonnecrotic, so-called “incident-
tal” lesions, hyperintense to gray matter on T2 (hypodense on
CT, if seen at all).

Necrotic lesions most often result from arteriopathies, in-
cluding intimal hyperplasia, atherosclerosis, dissection, ar-
teriosclerosis, lipohyalinosis, amyloidosis, aneurysms, vascu-
laritis, and CADASIL.40 Supplied by arterioles (diameter
<200 μm) penetrating from pial surface arteries 20 to 50 mm
depth into white matter with little collateral supply, periven-
tricular white matter is vulnerable to ischemia.40 Furthermore,
arteriolar tortuosity, appearing around 50 years, accelerated
by atherosclerosis and aging, necessitates higher perfusion
pressure to irrigate white matter, increasing vascular resist-
tance and facilitating chronic ischemia. Decreased pulsations
from tortuous vessels may also impede interstitial fluid (IF)
flow and clearance of Aβ along perivascular spaces.41,42

The etiology of the nonnecrotic hyperintensities, which
appear as focal, patchy, or confluent PVH, is less clear. Arterial
ischemia has been considered the prime driver,40 but
the underlying neuropathology, myelin pallor, reduced oligo-
dendroglia, astrocytosis with clasmatodendrosis,41 and spon-
giosis, suggests other mechanisms.44 Candidates include focal
loss of ependymal lining (“ependymitis granularis”) with
axonal thinning, demyelination, and gliosis at the dorsolateral
angles of the frontal horn, allowing leakage of ventricular
csf.45,46 Some propose that IF moves through the pervias-
cular spaces.47 Decreased pumping from tortuous arterioles, vaso-
genic edema, and perivascular amyloid could impair this
circulation. IF may also be transported into the venules or
absorbed by the venules and returned to the circulation.88,49

Postmortem MRI using brain slices, allowing direct path-
ological examination of hyperintense areas, has provided
insights into pathological substrates of PVH.50 One of the first
such studies attributed the typical findings to edema related to
blood brain barrier disruption.51 Another compelling explana-
tion invokes perivascular intraparenchymal venular dis-
ease. Postmortem MRI and histopathologic methods, used to
distinguish arterioles and capillaries (alkaline phosphatase)
from venules (Trichrome staining), reveals a noninflamma-
tory, perivascular venulopathy with concentric collagen
deposition causing intramural thickening, stenosis and ulti-
mately luminal occlusion.49 This increases markedly with age
(65% of those >age 65), correlates with PVH severity, and
occurs preferentially around anterior and posterior horns of
the ventricles, where confluent PVH usually begins.49,52

Etiopathogenesis is not known, but genetic vulnerability and
vascular risk factors are implicated. Venous collagenosis
induces ischemia not only by increasing vascular resistance,
but by leaking fluid (vasogenic edema), compromising IF
circulation and, if perivascular pathways are important for Aβ
clearance of in AD, it could enhance amyloid deposition.49,52

Until recently, venulopathy as a substrate of PVH lacked in
vivo corroboration. In a 1.5T MRI study of incidental
hyperintensities in AD and controls followed over 1 year,
Gao et al used PD/T2, coregistered to 3D T1 images, with
contrast adjusted to visualize intraparenchymal venules. They
demonstrated that focal and PVH often relate to venules and
can increase or decrease over time (Figure 2). They propose
that venous collagenosis dilates the veins, making them
macroscopic and causing venous insufficiency with conse-
quently vessel leakage, ie, vasogenic edema. This could parsi-
moniously explain many nonnecrotic hyperintensities, includ-
ing dynamic temporal changes with both volumetric increases
and decreases3 (Figure 3).

Occlusive venous and arterial disease could be mutual
aggravating factors in PVH. Afferent arterial/capillary den-
sity appears to be significantly reduced not only in PVH, but
also in normal appearing white matter, implying a more
general disorder in vascular supply in patients with PVH
disease.54 The final common pathway for all these putative
substrates of PVH, alone or in mutually exacerbating com-
bination, be it circulatory (arterial, capillary or venous), blood
brain barrier leakage, edema, or disruption of IF dynamics, is
chronic hypoperfusion injury to periventricular white matter,
a brain region anatomically vulnerable to ischemia.55

An elegant series of studies applying molecular pathology
and postmortem MRI to PVH has further characterized
cellular reactions in PVH, revealing capillary endothelial
activation, activated microglia, clasmadendritic astrocyto-
sis, axonal myelin loss, and reactivating oligodendro-
glia,44,50,56 as well as upregulated hypoxia markers.57 In a
single case study, cells positive for an apoptosis marker
(TUNEL) was 2.5X more frequent in PVH compared to
nearby normal white matter, suggesting that oligodendro-
glial apoptosis could be a pathophysiological mechanism.
Severe noninflammatory venous collagenosis was seen in the same area.58

Conclusion
In summary, in both aging and dementia, especially with comorbid vascular risk factors including amyloid deposition accelerated by AD, a complex end-game plays out in the cerebral white matter, implicating not only ischemia from arterial and capillary pathology, but also venous insufficiency from periventricular venular collagenosis. Leakage through the ependyma, impaired IF circulation, amyloid congesting perivascular escape routes, as well as vasogenic perivenular edema, may all play a role and exacerbate the resulting chronic hypoperfusion ischemic syndrome. Further research on microcirculatory structure and dynamics are urgently needed in animal models and in vivo and postmortem imaging studies in humans, especially at higher fields, with newer techniques such as Susceptibility Weighted Imaging59 to study venous disease, optimally using quantification methods. Understanding these complex vascular factors, which surreptitiously attack white matter integrity in aging and dementia, could open new targets for prevention and intervention, in a previously under-rated chronic disease, which threatens to undermine autonomy and quality of life of our greying population.

Disclosures
None.

References


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