Multimodal Markers of Inflammation in the Subcortical Ischemic Vascular Disease Type of Vascular Cognitive Impairment

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Vascular cognitive impairment (VCI) is a heterogeneous disease that is caused by a wide variety of vascular factors. Pathological studies have shown that both large- and small-vessel damage occurs in patients with VCI. Large-vessel disease leads to strokes with a stepwise course as a result of multiple infarctions that result in concomitant loss of intellect. Small-vessel disease has several forms: it may either produce lacunes mainly in the basal ganglia without white matter damage or extensive changes in the white matter with or without lacunes (Table I in the online-only Data Supplement). The term subcortical ischemic vascular disease is often used for both lacunar state and white matter disease, but there may be different pathophysiologies involved, particularly when there is cerebral hypoperfusion, which has a major effect on the vulnerable deep white matter.

Binswanger disease (BD) was first described in 1894 in patients with arteriolarosclerotic demyelination. Patients with BD have a symptom complex that includes vascular risk factors, cognitive impairment, small stroke-like events, hyper-reflexia, and imbalance (Table II in the online-only Data Supplement). Neuropsychological testing shows executive dysfunction, whereas difficulties with memory and language occur more commonly in Alzheimer disease (AD); overlap occurs in neuropsychological testing in BD and AD, making patterns of cognitive dysfunction only suggestive of diagnoses. The Montreal Cognitive Assessment, which includes tests of executive function, when compared with minimental status examination is more often abnormal in patients with BD, making it a better screening test.

Clinical features alone may be insufficient to diagnose BD, and a multimodal approach with biomarkers may be helpful. The biomarkers that have been suggested include neuropsychological testing, brain imaging, and cerebrospinal fluid (CSF) studies. Routine MRI shows white matter hyperintensities (WMHs) on fluid-attenuated inversion recovery imaging, which are nonspecific and are often found in normal aging, making the clinical significance of these changes controversial. Earlier, we showed that 30% of normal elderly patients aged >65 years had moderate WMHs with severe WMHs in 7%. WMHs are associated with myelin loss, age, and vascular risk factors. A decline in executive function was associated with WMHs, and memory loss was correlated with decreased hippocampal volume. Hypertension and diabetes mellitus are associated with WMHs, and WMHs are linked to VCI. Of the risk factors, diabetes mellitus remains uncertain as a primary cause of WMHs; in the elderly diabetes mellitus, hypertension and aging are found together. The 3-year follow-up of the Leukoaraiosis and Disability in the Elderly cohort found that in outpatients who seek medical attention for non-disabling complaints, severe changes in white matter independently and strongly predicted rapid global functional decline, and that severe WMHs together with lacunes contributed to decline of psychomotor speed, executive control, and global cognitive function. However, a study of a cohort of normal individuals followed up for 30 years with repeated IQ testing showed that in the octogenarians, WMHs explain only a small part of the age-related decline in intelligence.

Both diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (1H-MRS) when compared with fluid-attenuated inversion recovery are more accurate in identifying abnormal white matter MRI. In addition, dynamic contrast-enhanced MRI (DCEMRI) detects disruption of the blood–brain barrier (BBB), which is seen with neuroinflammation, and is also reflected in CSF by an increase in albumin ratio. In-depth knowledge about ongoing inflammatory and cell/tissue disrupting processes can also be gained by means of biochemical markers in CSF.

Neuroinflammation and Mechanisms of White Matter Damage

Hypertension and diabetes mellitus lead to fibrosis of blood vessels and thickening of the vessel wall, narrowing the
internal diameter, restricting cerebral blood flow, and predis-posing to thrombosis with infarction.\textsuperscript{17–19} Deep white matter regions are the most vulnerable because a reduction in blood flow affects the watershed areas.\textsuperscript{4} Arteriolosclerotic blood vessels fail to respond to increased oxygen need because of limited reserve, leading to intermittent hypoxia when there is a demand for increased blood flow.\textsuperscript{20} Hypoxia triggers a series of events that lead to tissue injury with neuroinflammation, BBB disruption; the axons are damaged, oligodendrocytes die and myelin loss is seen. Changes on MRI fluid-attenuated inversion recovery sequences show the extensive WMHs, which are nonspecific, and could be related to a number of pathological changes; enlarged perivascular spaces, axonal loss, and myelin break down could all be involved.

In BD, white matter is gliotic with astrocytosis and loss of oligodendrocytes (Figure 1A). Cerebral arterioles are fibrosed, which when extensive leads to arteriolosclerosis and lipohyalinosis (Figure 1B); thickening of the vessel wall with narrowing of the lumen (Figure 1C). An important feature of the pathophysiology of BD is the accumulation of inflammatory cells around the damaged blood vessels (Figure 1D). These inflammatory cells stain for markers of microglia/macrophages, but other types of white blood cells have not been studied.

Abnormal permeability results in an increase in CSF albumin ratio in patients with vascular dementia.\textsuperscript{21} Autopsy studies of patients with BD show extravasation of serum-derived proteins;\textsuperscript{22} MRI shows enhancement with gadolinium–diethylene-triaminepentacetate.\textsuperscript{23–25} Pathological studies reveal an increase in matrix metalloproteinase (MMP)–containing inflammatory cells around blood vessels.\textsuperscript{26,27} Macrophage/microglia activity around hypertensive, fibrosed vessels could lead to protease secretion with inflammatory (by-stander) demyelination.\textsuperscript{28}

Arteriolosclerosis with fibrosis and lipohyalinosis can be seen in the white matter blood vessels. Although the constitutive MMP-2 is present in high concentration in astrocytic foot processes as reflected in the CSF, the inducible MMPs, MMP-3 and MMP-9, are released as part of the inflammatory response, opening the BBB and attacking myelin.\textsuperscript{29}

Damage to the white matter in VCI progresses for many years. Several factors are necessary for the tissue to be damaged, and these can be visualized as a series of Hits (Figure 2). Initially, the blood vessels are narrowed by hypertension or other vasculopathic processes; this leads to impaired blood delivery to the vulnerable white matter, particularly during times when the reserve is needed (Hit 1). Hypoxia/ischemia caused by reduced blood flow and small strokes activates the hypoxia cascade, mobilizing a wide range of hypoxia genes that are induced by hypoxia inducible factor-1α (Hit #2), which is increased in white matter from patients with vascular dementia.\textsuperscript{30} Hypoxia inducible factor-1α increases under hypoxic con-ditions and induces a large cassette of genes involved in both the inflammatory and the repair processes.\textsuperscript{31} Gliosis, inflammation, and myelin loss represent irreversible changes to the white matter, which can be seen with 1H-MRS and DTI (Hit 3).

White matter injury is often slowly progressive rather than after a vascular distribution with abrupt changes. Regions showing white matter changes are often symmetrical, extending into the subcortical white matter, sparing the cortex and U-fibers beneath the cortex. Such patterns could be explained by progressive inflammation spreading from the edges of the WMHs, similar to the patterns of white matter damage seen in the primary progressive form of multiple

\begin{figure}
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\caption{Autopsy from a patient with Binswanger disease that began at age of 47 years with death 7 years later. A, White matter gliosis was extensive as shown by GFAP staining. B, Arteriolosclerotic changes in an arteriole in the white matter (H&E stain). C, Blood vessel is shown with thickening (PAS stain). D, Macrophages/microglia (CD68 immunostain) are seen around the arteriole in the white matter (iba1 immunostain).}
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\begin{figure}
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\caption{Schematic diagram of mechanism of white matter damage in spontaneously hypertensive stroke-prone (SHR-SP) rats. Hypoxia is postulated to be a key factor that triggers a series of molecular events. In general, there is hypertension, diabetes mellitus, or other vasculopathic processes that restrict perfusion of the vulnerable deep white matter. Pyrrolidinohistamine (PHD) is induced, leading to persistence of the hypoxia inducible factor (HIF)-1α. Multiple genes are activated, particularly matrix metalloproteinase (MMP)-2, which breaks down myelin and disrupts the blood–brain barrier (BBB). Vasogenic edema and oligodendrocyte death are the consequence of the hypoxia. Another pathway that includes the activation of inflammatory components induces MMP-3, MMP-9, and cyclooxygenase-2 (COX-2), contributing to the tissue damage. The entire process occurs slowly through the stages characterized as 3 hits: (1) hypertension damages blood vessels, limiting blood flow to deep white matter; (2) hypoxia initiates the molecular injury cascade and the repair mechanisms, such as angiogenesis and erythropoiesis; and (3) an inflammatory response completes the injury process. AP-1 indicates activator protein-1; EPO, erythropoietin; NF-κB, nuclear factor kappa B; SDF, stromal cell-derived factor, TNF, tumor necrosis factor; and VEGF, vascular endothelial growth factor.}
\end{figure}
sclerosis. Astrocytosis is extensive in the regions of injury and inflammation is generally absent once the astroglia scar has formed. In the cassette of hypoxia inducible factor-1α genes activated by the hypoxia are genes involved in recovery, including vascular endothelial growth factor and transforming growth factor-β.

Another common small-vessel disease is cerebral amyloid angiopathy (CAA) situated in meningeal and intracortical arteries; microbleeds frequently are seen with CAA. It is a characteristic feature of AD but may also occur without AD pathology. Moreover, at autopsy, patients with AD often display subcortical arteriolosclerotic vessel wall lesions and white matter damage in addition to CAA. However, patients with pure BD usually lack signs of CAA. The combination of arteriolosclerosis, white matter damage, and CAA may underlie what is called mixed-type dementia (mixed AD/VCI). Microbleeds and enlarged perivascular spaces in the basal ganglia may be seen in severe hypertensive disease.

Need for Biomarkers to Aid Early Diagnosis of BD
The goal of biomarker development is to identify patients at an early stage when treatment may be effective in blocking the permanent damage to the white matter. Because autopsy data are difficult to obtain, long-term follow-up to determine the diagnosis is used. Rarely is one type of pathology present at autopsy because by the time of death there is evidence of β-amyloid, phosphorylated τ, α-synuclein, and hypoxia/ischemic injury. Combination treatments may be needed in many patients, and it will be important to determine the pathology present at onset of the illness.

White Matter Lesion Volume
White matter lesion volume was used as an early surrogate marker of VCI. Lesions grew over time in those elderly individuals with hypertension; and lesion growth was reduced in those with lower blood pressures as measured by continuous 24-hour ambulatory monitors. Accrual of periventricular WMHs in a normal elderly population was associated with decline in mobility, impaired cognition, and depressive symptoms with those with higher blood pressures showing the greatest changes. Large surveys link these changes in the white matter with cognition. White matter changes are nonspecific and are present in patients with different forms of VCI (Figure 3). Volume measurements are needed for studies of progression, and the types of changes seen on MRI have been recently defined.

Diffusion Tensor Imaging
DTI is a method to show integrity of the white matter tracts by the use of proton diffusion in 3 dimensions. Unidirectional diffusion and bulk flow occurs along white matter tracts, demyelination reduces the fractional anisotropy and increases the mean diffusivity.

Hyperintensity on fluid-attenuated inversion recovery can be because of either normal aging with increased water or myelin damage, whereas a reduction in fractional anisotropy is indicative of damaged white matter, making it a better biomarker to aid in selection of patients with vascular demyelination. DTI shows stronger correlations with cognition than with WMH volume. In addition, in the Leukoaraisis and Disability in the Elderly study, ultrastructural abnormalities of normal appearing tissue were found to have a strong and independent effect on cognitive functions.

Proton Magnetic Resonance Spectroscopy
Protons on water constitute the major magnetic resonance signal; protons on other molecules can be detected by the use of pulse sequences that suppress water protons. When water is suppressed, a large proton signal from N-acetylaspartate (NAA) is observed in the proton spectra; other molecules that can be measured include creatine (Cr) and choline (Cho). Although the exact role of NAA in brain metabolism remains obscure, when the axons are damaged by ischemia, as in BD, the NAA signal is reduced, which is a nonspecific finding in a variety of injuries to the white matter. Executive function correlates with NAA and Cr, but fails to correlate with volume of WMHs (Figure 4).

Dynamic Contrast-Enhanced MRI
MRI is a unique method to both quantify and locate sites of subtle changes in BBB permeability. An MRI method that
uses multiple rapid T1 measurements >20 minutes can detect leakage of gadolinium–diethylenetriaminepentacetate across the BBB, and the quantified T1 values can be used to calculate transport constants for gadolinium movement across the BBB; Patlak graphical method, which was developed in animals using autoradiography, was adapted for an MRI initially in rats and subsequently in humans. Several studies, using qualitative methods, have shown BBB abnormality in patients with diabetes mellitus, lacunar infarction, and BD.

DCEMRI has the unique ability to both quantify BBB permeability and to form a permeability map, showing the specific sites of vascular inflammation. The pattern of BBB disruption seen at 3 T with DCEMRI shows that the increased permeability tends to be around regions with WMHs (Figure 5). Elevated BBB permeability is a sensitive, but not specific, biomarker for BD. In addition, demonstration of continued leakage for months to years provides strong support to the concept that the opening of the BBB is related to a persistent inflammatory process.

**CSF Biomarkers**

Elevated levels of MMP-9 in CSF have been shown in patients with VCI and mixed AD/VCI but not in AD. Furthermore, tissue inhibitor of metalloproteinase-1, a regulator of the MMP system, has also been found to be elevated in CSF; the tissue inhibitor of metalloproteinase-1 CSF concentration has been shown to be correlated to the albumin ratio, possibly reflecting an overall regulation of different MMPs that might be involved in the BBB opening. Because a disrupted BBB may allow blood-derived proteins to enter the brain, a more informative way to evaluate CSF proteins, which can distinguish endogenous from exogenous proteins, is to measure the MMPs in both CSF and blood compartments, forming an index with the albumin in both the CSF and the plasma that is similar to the IgG index used to diagnose multiple sclerosis. Using this approach, we showed that although MMP-9 was elevated in CSF, the MMP-9 index was not elevated. However, MMP-2 index was reduced, suggesting possible endogenous consumption. These results are complicated by changes occurring in both MMPs and albumin, and further studies will be needed to clarify the role of blood and CSF levels of the MMPs in the CSF.

An assay for the active form of MMP-3 showed elevated CSF levels in some patients when compared with control CSF samples obtained from patients undergoing spinal anesthesia. Pathological studies indicate that MMP-2 is primarily in

![Figure 4. A. Square root white matter hyperintensity (WMH) volume vs executive function T score (results are not significant with P=0.765), (B) N-acetylaspartate (NAA) and (C) creatine (Cr) vs executive function T score. Significance is P=0.056 for NAA and P<0.001 for Cr. Reprinted from Gasparovic et al. Copyright ©2013, The Authors (see: http://creativecommons.org/licenses/by-nc/3.0/).](http://stroke.ahajournals.org/)

![Figure 5. Permeability maps from 3 representative patients with Binswanger disease and 2 control patients. Vascular cognitive impairment (VCI) 1: A patient with large white matter hyperintensities (WMHs) on fluid-attenuated inversion recovery (FLAIR; shown as the green areas). Arrows show increased permeability in subcortical and perilesional regions. Note the absence of permeability within the WMHs. VCI 2 and VCI 3 show additional patients. Controls show a small increase in permeability (red regions) in a nonspecific pattern. The regions of FLAIR increased signal were outlined with the semiautomated program (JIM) and colored green. The areas of increased permeability are seen as red and yellow (higher). There is little increased permeability within the WMHs, but the increases occur around the lesions (courtesy of Arvind Caprihan, MIND Research Network, Albuquerque, NM).](http://stroke.ahajournals.org/)
the astrocytes with MMP-3 seen in the macrophage/microglia.27 Other CSF biomarkers for VCI are myelin basis protein and neurofilament light, suggesting that these could be useful in diagnosis of BD; heart fatty acid–binding protein is elevated in CSF from patients with VCI and AD, making it a nonspecific biomarker.57,59

Reduced amyloid-β_{1-42} (Aβ42) and elevated levels of both total and phosphorylated τ (T-τ and P-τ, respectively) are found in patients with AD. However, the variability of levels of AD proteins in the CSF, particularly in the presence of WMHs and advanced age, has limited their use in the diagnosis of patients with both VCI and AD.57 Although low levels of Aβ42 may be seen in BD and AD, normal levels of Aβ42 are more characteristic of BD. Increased levels of total τ and phosphor-τ are rarely observed in VCI, suggesting that both normal levels of Aβ42 and phosphor-τ could be considered biomarkers supportive of a diagnosis of BD. Important negative findings in the CSF of patients with VCI include the absence of white blood cells and negative tests for multiple sclerosis, which are important to rule out other causes of white matter damage.

CSF albumin ratio has been most extensively studied and provides the strongest evidence of a disruption of the BBB in BD.60 Changes in MMPs are consistent with neuroinflammation, and myelin basic protein and neurofilament light suggest myelin damage. Taken together these CSF biomarkers provide evidence of inflammatory BBB disruption with demyelination, which is supportive of a diagnosis of BD. However, at the present time, few patients have been reported with measurement of the CSF biomarkers for them to be used clinically.

Combining Biomarkers into a BD Scale Score
Although biomarkers are present in patients with BD, none of the ones discussed are sufficient by themselves to make an early diagnosis. This is because of the overlapping symptom complexes in the early stages of different forms of dementia and the high prevalence of WMHs in the normal elderly population. Because individual biomarkers show different types of pathophysiology, combining several biomarkers into a BD Scale (BDS) has the potential to improve diagnostic accuracy. Potential biomarkers include 3 axes: clinical and neuropsychological findings, multimodal MRI, and CSF/blood studies. Components from each axis can be combined into the BDS; patients with the highest scores most likely to have BD (Table).

The main components comprising the clinical axis are the vascular risk factors, including hypertension, which is the major factor, diabetes mellitus, and hyperlipidemia, which are similar to those found in vascular disease of the heart and peripheral vessels. Other factors that can lead to WMHs, which are not included in the present BDS because they are rare, include the hypercoaguable states (antiphospholipid antibodies), the hereditary forms, such as cerebral autosomal dominate arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL) and leukodystrophies, and B_{12} vitamin deficiency. Executive dysfunction on neuropsychological testing is present with disease on the white matter, whereas memory is generally less involved, making poor function on executive function tests another potential marker.61,62 Clinical signs found with neurological examination are focal findings, such as hemiparesis, hyperreflexia, and imbalance. Motor weakness is variably present. Gait is a prominent abnormality, particularly when frontal white matter is affected, and may be found in cognitively normal elderly, whereas WMHs are associated with a higher incidence of falls.63 Hyperreflexia is important because it shows that the findings in the white matter are pathological, particularly in those without cortical or basal ganglia infarcts and with large white matter lesions. When there are signs of weakness and increased reflexes in these patients, this is a strong indicator of injury to the white matter.

Routine MRI is used in the initial identification of WMHs, which are then quantified with specialized programs; other MRI methods are more reliable in detecting pathological damage to the white matter, such as DTI measurements of fractional anisotropy and 1H-MRS measurements of NAA and Cr.51,64,65 DCEMRI shows increased BBB permeability in VCI.25 Transfer constants for gadolinium from blood to brain provide 2 types of data: (1) calculation of the mean of _K_ values over all voxels in white matter and (2) number of voxels above a threshold permeability. The area of the increased permeability can be displayed as a map of regional changes in the white matter. For purposes of a scale, the quantification of permeability with DCEMRI, which provides a number for white matter permeability, is superior to the semiquantification methods.25,66

Towards a Scale of Binswanger Type of VCI
Combining clinical, laboratory, and imaging findings in patients with VCI provide a comprehensive feature set that can be correlated with patient diagnoses after long-term follow-up. Lacking autopsy verification in the majority of patients, clinical course is by necessity the only way to move toward a diagnosis, which could eventually be made by autopsy. Because of the absence of a definitive diagnostic test or clinical finding to
diagnose BD, we constructed a BDS to reflect a spectrum of changes in all 3 axes with low scores, indicating white matter changes of uncertain pathogenesis, which have been called leukoaraiosis, and higher scores suggestive of BD. Although some components of the BDS are either present or absent, several are based on a cut point determined from a control series or a spectrum of the illness.

This is only an initial attempt at defining a set of features that are characteristic of the progressive form of VCI that is postulated to have an inflammatory component. Although clinical diagnosis of BD is problematic at an early stage, over time as the course is ascertained, the diagnosis can be made with greater certainty, using published criteria given above. Another confounding factor to the use of autopsy is that by the time of autopsy, the elderly brain has a plethora of changes, making it difficult to select the dominant one unless the course is known. In lieu of pathology, long-term follow-up increases the diagnostic certainty. Adding biomarkers to the accepted clinical features should aid in identifying a subgroup of patients that could be entered into clinical trials.

A major concern with this biomarker approach is that the subcortical white matter disease, which is the hallmark of BD, in reality, represents a spectrum of pathophysiologies related to arterial, venous, and inflammatory factors. At one end of the spectrum are patients with white matter changes of aging that have few if any clinical symptoms and are best described by the term leukoaraiosis; longitudinal MRI studies indicate that normal changes of aging occur mainly in the periventricular regions. At the opposite end of the spectrum are patients with pure BD that have extensive gliosis of the white matter with arteriolosclerosis in the absence of changes in the gray matter; these patients are generally hypertensive, suggesting tissue hypoperfusion with hypoxia. Another potential vascular pathology involves venous collagenosis, which could interfere with drainage of CSF, and lead to enlarged perivascular spaces in the gray and white matter. In between lie a large number of patients with features of AD and BD that has been called mixed dementia. In addition, this type of classification fails to include those with multiple strokes or multi-infarct dementia and those with only lacunes in the basal ganglia. Some of these patients overlap with the BD group. In spite of the diagnostic problems encountered in using any one term, it can be argued that using the term BD to represent those with symptoms because of white matter hypoxia/ischemia that have inflammatory markers in the CSF and disruption of the BBB can operationally define a subgroup of the patients with VCI who can be the initial target for clinical trials. Although the approach described requires a high level of technical expertise for the MRI studies and biochemical expertise for the CSF studies, because larger series of patients are studied in select centers, the optimal biomarkers can be narrowed, possibly reducing the biomarkers to those more generally accessible.

Conclusions

There is converging evidence that the small vessel form of VCI, mainly because of hypertension, diabetes mellitus, and other vascular risk factors, is the major form of a heterogeneous group of vascular causes of dementia. Deep white matter is a watershed area of cerebral blood flow, making it vulnerable to multiple insults that lead to hypoxia/ischemia, which initiates an inflammatory response with induction of proteases and free radicals, BBB opening, and ultimately myelin breakdown. This process is multifactorial and involves a series of hits: (1) damage to the vessels that compromises blood flow to white matter; (2) hypoxia induces hypoxia inducible factor-1α and initiates molecular cascades involved in both injury and repair; and (3) inflammation disrupts the BBB and leads to damage to the myelinated fibers and death of the oligodendrocytes. BD is used to describe a subgroup of patients with VCI who have small-vessel disease with a progressive inflammatory process that leads to large WMHs. A BDS is proposed, which is based on a multimodal approach including clinical, laboratory, and imaging axes to select patients early in the course that are at risk for progressive inflammatory damage. Using such an approach, biomarkers can be selected, including BBB permeability and CSF inflammatory proteins, which may be useful to monitor treatment for shorter time periods. This is a description of an approach that will require validation in a large series of patients with follow-up for several years, and which will require multiple centers using the same criteria for diagnosis and confirmation of diagnoses. If verified, the BDS approach could be used to select the patients at risk of progression for inclusion in clinical trials. This would improve the chance of success because the patients included would represent a homogeneous subpopulation of the larger group of patients with VCI.

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References


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