Blood–Brain Barrier Permeability Abnormalities in Vascular Cognitive Impairment

Saeid Taheri, PhD; Charles Gasparovic, PhD; Branko N. Huisa, MD; John C. Adair, MD; Elaine Edmonds, MD, PhD; Jillian Prestopnik, PhD; Mark Grossetete, PhD; N. Jon Shah, PhD; John Wills, MD; Clifford Qualls, PhD; Gary A. Rosenberg, MD

Background and Purpose—Disruption of the blood–brain barrier has been proposed to be important in vascular cognitive impairment. Increased cerebrospinal fluid albumin and contrast-enhanced MRI provide supporting evidence, but quantification of the blood–brain barrier permeability in patients with vascular cognitive impairment is lacking. Therefore, we acquired dynamic contrast-enhanced MRI to quantify blood–brain barrier permeability in vascular cognitive impairment.

Method—We studied 60 patients with suspected vascular cognitive impairment. They had neurological and neuropsychological testing, permeability measurements with dynamic contrast-enhanced MRI, and lumbar puncture to measure albumin index. Patients were separated clinically into subcortical ischemic vascular disease (SIVD), multiple and lacunar infarcts, and leukoaraiosis. Twenty volunteers were controls for the dynamic contrast-enhanced MRI studies, and control cerebrospinal fluid was obtained from 20 individuals undergoing spinal anesthesia for nonneurological problems.

Results—Thirty-six patients were classified as SIVD, 8 as multiple and lacunar infarcts, and 9 as leukoaraiosis. The albumin index was significantly increased in the SIVD group compared with 20 control subjects. Permeabilities for the patients with vascular cognitive impairment measured by dynamic contrast-enhanced MRI were significantly increased over control subjects (P<0.05). Patient age did not correlate with either the blood–brain barrier permeability or albumin index. Highest albumin index values were seen in the SIVD group (P<0.05) and were significantly increased over multiple and lacunar infarcts. Kᵢ values were elevated over control subjects in SIVD but were similar to multiple and lacunar infarcts.

Conclusions—There was abnormal permeability in white matter in patients with SIVD as shown by dynamic contrast-enhanced MRI and albumin index. Future studies will be needed to determine the relationship of blood–brain barrier damage and development of white matter hyperintensities. (Stroke. 2011;42:2158-2163.)

Key Words: albumin • blood–brain barrier • cerebrospinal fluid • MRI • vascular cognitive impairment

Vascular cognitive impairment (VCI) is an important cause of intellectual decline in the elderly.¹⁻⁵ Imaging and pathological studies have shown white matter hyperintensities (WMHs) on MRI in patients with VCI that are suggested to be due to silent strokes.⁴⁻⁶ However, an alternate hypothesis is that an inflammatory response initiates disruption of the blood–brain barrier (BBB) with subsequent damage to the white matter.⁷ Serial MRIs in patients with small vessel disease shows progressive growth of WMHs, suggesting a generalized abnormality of the white matter.⁸ Brain tissue from patients with VCI shows serum-derived proteins.⁹ Elevated levels of cerebrospinal fluid (CSF) albumin are frequently found in patients with VCI.¹⁰⁻¹¹ Qualitative contrast-enhanced MRI studies demonstrate leakage of contrast agents.¹²⁻¹³ Recently, dynamic contrast-enhanced MRI (DCEMRI), using gadolinium-diethylentriamine penta-acetic acid (Gd-DTPA), was used to measure BBB permeability in animals with strokes.¹⁴⁻¹⁵ We adapted this method to study BBB permeability in humans and have used it for measurements in patients with VCI.¹⁶ We compared the results of DCEMRI with CSF albumin index (Qₐₐₚ), an independent measure of BBB integrity.

Subjects and Methods

Subjects
Sixty patients with cognitive complaints and abnormal white matter signal on brain MRI were entered into the study. Patients were from

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From the Departments of Neurology (S.T., C.G., B.N.H., J.C.A., E.E., J.P., M.G., G.A.R.), Neurosciences (G.A.R.), Cell Biology and Physiology (G.A.R.), and Anesthesia (J.W.), and the Clinical Translational Science Center (C.Q.), University of New Mexico Health Sciences Center, Albuquerque, NM; the Institute of Neuroscience and Medicine (N.J.S.), Forschungszentrum Juelich GmbH, Juelich, Germany; and the Department of Neurology (N.J.S.), Faculty of Medicine, JARA, RWTH Aachen University, Aachen, Germany.
The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.611731/DC1.
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the University of New Mexico Hospital and the Albuquerque Veterans Administration Hospital. Only those patients capable of giving informed consent for lumbar puncture were enrolled in the study. The study was approved by the University of New Mexico Hospital and Albuquerque Veterans Administration Hospital Human Research Review Committees.

Patients underwent neurological and neuropsychological testing, lumbar puncture for collection of CSF, structural MRI, and BBB permeability measurements with DCEMRI. Imaging studies always preceded lumbar puncture.

Neuropsychological tests included the Mini-Mental State Examination and standardized assessments of memory (Hopkins Verbal Learning Test, Rey-Osterrieth Complex Figure Test recall), attention (Digit Span forwards, Trail making test Part A), executive function (Wisconsin Card Sort, Trail making test Part B, Digit Span backwards), and language (Boston Naming, Controlled Oral Word Association). CSF was analyzed for routine studies (cells, protein, glucose, culture) and blood was collected for calculation of a demyelinating profile and albumin index.

Twenty control subjects had an MRI with Gd-DTPA to obtain normal values for DCEMRI, and control CSF was obtained from 20 subjects without neurological diseases during spinal anesthesia.

Diagnoses

Patients had an abnormal MRI and reported cognitive difficulties. Study neurologists (J.C.A., E.E., G.A.R.) separated patients into diagnostic subgroups based on the results of the neurological, neuropsychological, and anatomic MRI findings without knowledge of DCEMRI and CSF results: (1) suspected microvascular disease with extensive white matter involvement (SIVD); (2) large vessel multiple or small vessel lacunar infarcts limited primarily to gray matter (MI/LAC); and (3) leukoaraiosis when WMHs were small and not thought to be related to VCI. Patients with SIVD had cognitive complaints, focal neurological findings, gait disturbances, and WMHs on MRI.17–19 MI/LAC was suspected in patients with stroke-like episodes that were evident on MRI. Patients with subjective complaints and abnormalities in the white matter on MRI but who did not meet the criteria for VCI were classified as leukoaraiosis.4,5 All patients had medical evaluations to exclude other causes of white matter disease and cognitive impairment. None of the patients had a CSF demyelinating profile or clinical course compatible with multiple sclerosis.

MR Data Acquisition Protocol

The method of MRI measurements of BBB permeability has been described.16 Briefly, MRI investigation was performed using a 1.5-Tesla Siemens whole-body clinical scanner with a standard 8-channel array head coil (Siemens AG, Erlangen, Germany). The MRI protocol consisted of anatomic and contrast-enhanced sequences with Gd-DTPA contrast (Bayer Corp). The BBB measurement was based on a time series of 8 T1 maps acquired with a fast T1 mapping sequence with partial inversion recovery.21,22 One T1 map was acquired before Gd-DTPA injection and the rest were sampled post injection resulting in a 2-dimensional time series data set of MR images.

We used a quarter dose of Gd-DTPA, which provided sufficient washout curves. In the vicinity of this dose, there is an approximately linear relationship between T1 intensity and the concentration of Gd-DTPA with a relatively steep slope, conferring high sensitivity of the linear relationship between T1 intensity and the concentration of Gd-DTPA with a relatively steep slope, conferring high sensitivity of that are used in the graphical method of permeability calculation.

We used pooled data from the healthy control subjects to obtain an upper limit and confidence intervals for normal BBB permeability coefficients. Normative permeability data came from successfully completed studies in 17 of the 20 control subjects, ranging in age from 22 to 80 years (mean ± SEM of 44 ± 4 years). The permeability data from this group were combined to generate histograms of the permeability distributions, fitting the data to a distribution function with the statistical program R (R Development Core Team, 2007). The normal value of Ki in white matter was defined as the upper limit of the 95% range of normal value, which was $3 \times 10^{-4}$ mL/g-min.14,16

Statistical Methods

Statistical analyses for between-group differences for neuropsychological tests and clinical history were done using SPSS (SPSS for Windows, 16.0.1). For the BBB and Qm, data, we determined statistical significance with nonparametric analysis of variance with Kruskal-Wallis corrections for multiple comparisons and with Spearman rank nonparametric correlations or linear correlations (Prism 5: GraphPad Software, Inc, La Jolla, CA). The data were analyzed using receiver operator characteristic analysis with the receiver operator characteristic function to determine cut points for Ki. Statistical significance was set at $P<0.05$. The data were represented as mean ± SEM.

Results

Patient Classification

Clinical diagnoses of the 60 patients with VCI are given in Supplemental Table I (http://stroke.ahajournals.org). Forty-four patients had neurological, neuropsychological, and neuroimaging findings consistent with VCI–no dementia.4,5 Thirty-six patients were classified as SIVD and 8 as MI/LAC. Nine of the patients with lesions in the white matter could not be diagnosed as VCI–no dementia. Because the diagnosis in these patients was uncertain, they were classified with the nonspecific designation of leukoaraiosis.20 We excluded 7 patients due to technical problems related to the MRI.

Ages of the patients in the different groups were similar statistically (Supplemental Table I) and ranged from 31 to 82 years. Average ages were not statistically different between the groups. The incidence of hypertension, diabetes, and hyperreflexia were similar in the 3 groups. Incidence of imbalance was highest in the SIVD group ($P<0.05$), and hyperreflexia was highest in the MI/LAC group (Supplemental Table II).

Neuropsychological test results were significantly different for the various diagnostic categories for language function only with the poorest performance seen in the patients with SIVD and the highest in the leukoaraiosis group (Supplemental Table III).

BBB Permeability in Patients With VCI and Control Subjects

A histogram of pixels from a representative control permeability map shows no pixels with permeability statistically significant above the threshold value of $3 \times 10^{-2}$ mL/g-min (Figure 1A). In contrast, in patients with VCI, there were regions of permeability above the threshold value. A perme-
ability map and corresponding histogram from a representative patient with SIVD showed permeability values that were shifted to the right in the histogram (Figure 1B).

Patients classified as SIVD had large areas of WMHs. Leakage of contrast was restricted to smaller areas that were within the center of the WMHs. However, regions with elevated blood-to-brain transfer rate of Gd-DTPA could not be predicted from the fluid-attenuated inversion recovery MRI as seen in a series of representative fluid-attenuated inversion recovery MRI with corresponding permeability maps taken from the same slices through the brain, where the disparity between the 2 imaging methods is apparent (Figure 2).

**Albumin Index and MRI Permeability Coefficients**

Comparison of patients’ ages with either the albumin index or the mean permeability coefficients failed to show a correlation with either parameter (Figure 3). In the control CSF, a correlation was found for age with $Q_{\text{alb}}$ ($P<0.05$), but DCEMRI controls failed to show a correlation with age (data not shown).

**Permeability Constants and Albumin Index in Diagnostic Groups**

Albumin index was highest in the SIVD group and significantly greater than either the leukoaraiosis or control subjects ($P<0.05$; Figure 4A). Similarly, we found the highest values for the BBB permeability in the SIVD group, which was statistically higher than the controls (Figure 4B). We failed to find a correlation between the levels of $K_i$ and $Q_{\text{alb}}$, possibly because the DCEMRI measures white matter permeability, whereas $Q_{\text{alb}}$ is a composite of white matter, gray matter, and choroid plexus.

Receiver operator characteristic analysis was performed to test the ability of the mean abnormal permeability to discriminate between SIVD and control subjects. The area under the receiver operator characteristic curve was 0.88. The cut point

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**Figure 1.** Density distribution of permeability values for white matter (WM) voxels of a control and a patient with VCI. **A**, The color-coded permeability map shows normal permeability, which is below the threshold of $3 \times 10^{-4}$ mL/g-min, which was established in 17 control subjects. **C**, The histogram of permeability values for the control subject shown in **A**. **B**, The permeability map of a patient with VCI showing the regions of increased permeability in yellow and red. **D**, Permeability histogram shows the shift to the right of permeability values for the patient in **B**. VCI indicates vascular cognitive impairment.
of 0.0018 mL/g-min provided 84% sensitivity and 81% specificity (Figure 5).

Discussion

BBB permeability was abnormal in patients with VCI. This was demonstrated with increased CSF albumin as shown by others and by a novel method to quantify BBB permeability in humans. Albumin index was greatest in the patients with SIVD and differed significantly from those with MI/LAC and control subjects. Although DCEMRI was greater for patients with SIVD compared with control subjects, there was no difference between SIVD and MI/LAC. Our results support the earlier studies that showed an increase in CSF albumin and contrast agent leakage and provide the first quantitative data to support a role for BBB disruption in VCI.

Comparison of MRI fluid-attenuated inversion recovery images of WMHs with regions of increased permeability showed that the areas of increased permeability were within the WMHs. We observed the highest permeability in the center of WMHs and not around the periphery. Our results provide a link between the white matter damage and the alterations in the vasculature that most likely represent vasogenic edema.

Pathological studies show extravasation of serum proteins into the white matter in SIVD. Several prior contrast-enhanced MRI studies showed abnormal BBB permeability qualitatively inBinswanger disease and lacunar strokes. In a recent study comparing MRI with pathological findings in VCI, regions of WMHs on MRI had histological evidence of arteriosclerotic blood vessels, corresponding to regions with demyelination.

Increased levels of albumin in the CSF are seen in VCI, suggesting that this indicator of BBB damage can be used as a biomarker in VCI (see for review Farrall and Wardlaw). In surveys of patients with Alzheimer disease and vascular causes of dementia, patients with vascular disease have higher CSF albumin levels than seen in Alzheimer disease. When the patients were divided into diagnostic categories by clinical criteria, we found that those with SIVD had the highest values for both the mean permeability and Qalb. No relationship was observed between age and either Qalb or K\textsubscript{r} for the patient groups. However, the control subjects showed a significant increase with age for the Qalb, which has been reported by others, but this was not seen in the patients. The K\textsubscript{r} failed to show an increase with age in the controls (data not shown).

Quantitative measurements of BBB permeability in humans have been done with MRI and CT. Routine contrast-enhanced MRI with Gd-DTPA, which is performed with circulation of the contrast agent for several minutes, fails to show enhancement in VCI. We used a lower dose of Gd-DTPA and a longer circulation time to detect the subtle changes in BBB permeability. The measurements of permeability were obtained from an average of all sites with leakage. Using receiver operator characteristic plots, we found a cut point for K\textsubscript{r} values determined by DCEMRI of 0.0018 mL/min-g, which resulted in a high sensitivity and specificity for detection of SIVD compared with control subjects.

Various theories have been proposed to explain the selective damage to the central white matter in patients with the small vessel form of VCI. The vasculature supplying the deep white matter is a border zone between several vascular territories, and the arteries have a long course that could be...
further compromised by arteriolosclerosis. Veins in the deep white matter have increased collagen deposition, which could interfere with removal of interstitial fluid and proteins and drainage of blood. A recent pathological study in patients with VCI showed an increase in hypoxia inducible factor-1α, suggesting a chronic hypoxic state.

The diagnoses are provisional and may be modified with long-term follow-up or at autopsy. Many of the patients have been followed for ≥2 years with only 2 that have died and undergone autopsy. As a group, they had mild cognitive changes. We found that the majority of patients had the SIVD form with small vessel disease, which is consistent with other studies based on autopsies. Many had hypertension, whereas fewer had diabetes. A smaller number had large vessel strokes or a single strategic stroke. Separation of SIVD from those with both Alzheimer disease and VCI is difficult clinically, and some of those with extensive white matter disease in the SIVD group may have mixed disease.

In conclusion, we showed disruption of the BBB in VCI using 2 independent measures. Both the DCEMRI method and elevated albumin in the CSF showed the greatest disruption in the patients with SIVD, suggesting a link between the extensive changes in the white matter and opening of the BBB. However, further studies will be needed to define the relationship of BBB dysfunction to the development of white matter lesions. If these results are confirmed in larger studies with long-term follow-up, DCEMRI, which is less invasive than lumbar puncture, may both aid VCI patient selection and serve as a biomarker for treatment trials.

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Support provided by the National Institutes of Health to G.A.R. and the University of New Mexico General Clinical Research Center Grant (M01-RR00997 National Center for Research Resources/ National Institutes of Health) and from the Bayer Pharmaceutical Corp.

Disclosures

None.

References


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Supplemental Tables for Taheri et. al. “BBB in VCI”

Supplemental Table 1: Numbers of vascular cognitive impairment (VCI) patients and controls studied separated into preliminary diagnostic categories. Subcortical ischemic vascular disease (SIVD) had extensive white matter hyperintensities, focal neurological findings, and imbalance. The group included those with suspected mixed Alzheimer’s disease and VCI. Large vessel or lacunar strokes (MI/LAC) had multiple large or lacunar strokes or a single strategic stroke. Patients with white matter hyperintensities with minimal symptoms were classified as leukoaraiosis (LA). Several patients could not be classified into one of these groups or were technical failures.

<table>
<thead>
<tr>
<th>Diagnostic Groups</th>
<th>Numbers of Subjects</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcortical ischemic vascular disease (SIVD)</td>
<td>36</td>
<td>65.64 (2.37)</td>
</tr>
<tr>
<td>Multiple strokes or single strategic stroke (MI/LAC)</td>
<td>8</td>
<td>55.88 (5.77)</td>
</tr>
<tr>
<td>Leukoaraiosis (LA)</td>
<td>9</td>
<td>60.00 (6.56)</td>
</tr>
<tr>
<td>Other Diagnosis and technical failures</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>F (2, 50) = 1.53, ns</td>
</tr>
</tbody>
</table>
Supplemental Table 2: Clinical Information on the patients in the groups identified by diagnoses

<table>
<thead>
<tr>
<th></th>
<th>SIVD*</th>
<th>MI</th>
<th>LA</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Sex (%)</td>
<td>22 (61%)</td>
<td>6 (75%)</td>
<td>4 (44%)</td>
<td>$\chi^2(2) = 1.68$, n.s.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (53%)</td>
<td>6 (75%)</td>
<td>2 (25%)</td>
<td>$\chi^2(2) = 4.04$, n.s.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (25%)</td>
<td>3 (38%)</td>
<td>0 (0%)</td>
<td>$\chi^2(2) = 3.41$, n.s.</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>24 (67%)</td>
<td>80 (100%)</td>
<td>4 (50%)</td>
<td>$\chi^2(2) = 5.07$, $p = .08$</td>
</tr>
<tr>
<td>Imbalance</td>
<td>28 (78%)</td>
<td>5 (63%)</td>
<td>2 (25%)</td>
<td>$\chi^2(2) = 8.39$, $p = .02$</td>
</tr>
<tr>
<td>Stroke History</td>
<td>13 (36%)</td>
<td>7 (88%)</td>
<td>1 (11%)</td>
<td>$\chi^2(2) = 10.91$, $p &lt; .01$</td>
</tr>
</tbody>
</table>

*Numbers(%)
Supplemental Table 3: Neuropsychological test results for patients in the groups identified by diagnoses

<table>
<thead>
<tr>
<th></th>
<th>SIVD</th>
<th>MI</th>
<th>LA</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>26.59 (3.33)</td>
<td>28.12 (2.64)</td>
<td>28.00 (2.18)</td>
<td>F(2,48) = 1.30, n.s.</td>
</tr>
<tr>
<td>Attention†</td>
<td>42.12 (7.07)</td>
<td>44.75 (6.27)</td>
<td>44.12 (4.82)</td>
<td>F(2,47) = 0.68, n.s.</td>
</tr>
<tr>
<td>Memory†</td>
<td>41.18 (12.46)</td>
<td>43.75 (7.19)</td>
<td>46.25 (5.55)</td>
<td>F(2,47) = 0.76, n.s.</td>
</tr>
<tr>
<td>Language†</td>
<td>42.18 (8.90)</td>
<td>45.88 (9.12)</td>
<td>52.25 (10.46)</td>
<td>F(2,47) = 4.03, p &lt;.05</td>
</tr>
<tr>
<td>Executive function†</td>
<td>42.15 (7.19)</td>
<td>45.12 (9.28)</td>
<td>47.12 (7.12)</td>
<td>F(2,47) = 1.66, n.s.</td>
</tr>
</tbody>
</table>

*Mean (SD); † Standardized T-Scores
血管性認知障害における血液脳関門の透過性異常
Blood–Brain Barrier Permeability Abnormalities in Vascular Cognitive Impairment

Saeid Taheri, PhD; Charles Gasparovic, PhD; Branko N. Huisa, MD; John C. Adair, MD; Elaine Edmonds, MD, PhD; Jillian Prestopnik, PhD; Mark Grossetete, PhD; N. Jon Shah, PhD; Saeid Taheri, PhD; Charles Gasparovic, PhD; Branko N. Huisa, MD; John C. Adair, MD; Elaine Edmonds, MD, PhD; Jillian Prestopnik, PhD; Mark Grossetete, PhD; N. Jon Shah, PhD.

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脳血管病変の背景および目的: 血管性認知障害では、脳血管病変が重要である。脳血管障害の脳環境中のアルブミン上昇やMRI所見は、その後の認知機能を悪化させることが知られている。この背景に、我々は、脳血管障害における透過性異常を検討した。脳血管病変の脳環境中のアルブミンの濃度を定量化し、脳血管病変における脳血管透過性を測定した。

方法: 脳血管病変障害が疑われる患者60例を対象とした。脳血管病変のMRIおよび神経心理学的検査を行い、ダイナミックMRIにより脳血管透過性を測定した。脳血管病変のMRI所見のアルブミン濃度を測定した。対照群の脳血管障害群の患者20例に対して、MRIと神経心理学的検査を行い、脳血管病変群のMRI所見のアルブミン濃度を測定した。脳血管病変群のアルブミン濃度は、対照群に比べて有意に高かった。

結論: 脳血管病変のMRI所見およびアルブミン濃度が示すように、SIVD患者は、脳血管病変を特徴とすることが重要である。脳血管病変は、脳血管病変群の脳環境中のアルブミン濃度が高くなる。