A New Visual Rating Scale to Assess Strategic White Matter Hyperintensities Within Cholinergic Pathways in Dementia

Christian Bocti, MD; Richard H. Swartz, MD, PhD; Fu-Qiang Gao, MD; Demetrios J. Sahlas, MD, MSc; Pearl Behl, BSc; Sandra E. Black, MD

Background and Purpose—One possible mechanism of cognitive decline in individuals with subcortical vascular disease is disruption of cholinergic fibers by ischemic lesions, such as strategically located white matter hyperintensities (WMH). The authors applied a new MRI visual rating scale to assess WMH within cholinergic pathways in patients with Alzheimer Disease (AD) and subcortical ischemic microvascular disease.

Methods—Subjects included 60 AD patients with and without WMH, matched for age, as well as 15 control subjects. A visual rating scale was developed based on published immunohistochemical tracings of the cholinergic pathways in humans. On 4 selected axial images, the severity of WMH in the cholinergic pathways was rated on a 3-point scale for ten regions, identified with major anatomical landmarks. A published, consensus-derived, general WMH scale was also applied. All subjects underwent standardized neuropsychological testing.

Results—The Cholinergic Pathways HyperIntensities Scale showed reliability and was validated with volumetry of strategic WMH. After accounting for age and education in a multiple linear regression model, The Cholinergic Pathways HyperIntensities Scale ratings were associated with impaired performance on the Mattis Dementia Rating Scale \( r = 0.40; P = 0.02 \) and accounted for 12% of the variance (corrected \( r^2 \)). A similar model was not significant for general WMH scores.

Conclusions—The new MRI rating scale for WMH in cholinergic pathways is reliable and shows stronger correlations with cognitive performance than a general WMH rating scale in AD with WMH. This new rating scale provides indirect evidence that localization of WMH within neurotransmitter systems may contribute to cognitive decline. (Stroke. 2005; 36:2126-2131.)

Key Words: Alzheimer disease ■ dementia ■ leukoaraiosis ■ magnetic resonance imaging

Cerebral white matter hyperintensities (WMH) are a frequent finding on MRI scans of elderly subjects with or without dementia.\(^1\)–\(^3\) Although the appearance of WMH is not specific for etiology, a substantial body of evidence supports the role of microvascular ischemic disease in their pathogenesis in elderly individuals.\(^4\)–\(^7\) The presence of lacunes or WMH in Alzheimer disease (AD) has been associated with reduced cognitive scores in studies using resource-intensive quantitative MRI.\(^8\) However, studies using simple visual rating scales to assess total WMH burden have yielded less consistent associations between cognition and WMH in AD.\(^9\)–\(^10\) In studies of healthy elderly subjects, associations with executive functions, including information processing speed, have been reported more consistently.\(^11\)–\(^14\)

One mechanism by which WMH may exert their negative impact on cognition is by disruption of corticocortical association fibers or fronto-subcortical neuronal networks.\(^15\)–\(^16\) Another possible mechanism of cognitive decline with WMH is interference with projecting pathways of modulating neurotransmitter systems in the white matter, such as the cholinergic system. The anatomical trajectory of cholinergic fibers has been demarcated in human brains using immunohistochemical procedures.\(^17\) The corticopetal cholinergic pathways project to most cortical areas from the nucleus basalis, are mostly unmyelinated, and are vulnerable to strategically located vascular lesions.\(^17\) The precise role of acetylcholine (ACh) in cognition is still a matter of discussion, although the cholinergic hypothesis of AD has led to the first successful therapeutic strategy for this disease.\(^18\) Electrophysiological studies and animal models with specific corticopetal cholinergic lesions suggest that ACh may be primarily involved in attentional processes with secondary impact on learning and memory functions.\(^19\) The hypothesis that

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cortical cholinergic denervation arises from cerebrovascular disease (CVD) and contributes further to cognitive decline provides a novel approach to the study of the role of WMH in cognitive impairment.20,21 The objective of the present study was to apply a new MRI visual rating scale to better quantify WMH specifically within cholinergic pathways. Our hypothesis was that disruption of cortical cholinergic pathways by WMH would have a more specific impact on cognitive functions than the global cerebral WMH burden, as measured with a general WMH rating scale.22

Materials and Methods

Subjects
Patients were selected from a larger longitudinal study of brain-behavior correlations in dementia, based in a university hospital referral clinic. The main focus of the study was to measure WMH in cholinergic pathways, so subjects included were possible or probable AD with a range of WMH severity based on visual inspection of T2-weighted and proton-density (PD) MRI. Subjects met the National Institute of Neurological Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) research criteria for possible or probable AD (n=60).21 Patients with possible AD attributable to microvascular ischemic CVD were selected to be matched to those without WMH on age (mean=±5 years) and education, and had a higher prevalence of hypertension and past history of stroke (n=5) or transient ischemic attack (n=4). A group of age-matched elderly individuals, recruited from the community and free of any major medical, neurological, or psychiatric history, served as a control group (n=15). Demographic characteristics of subjects are shown in Table 1. All subjects underwent semi-structured medical, neurological, and office cognitive evaluations, including the Folstein test.24 Drugs were coded, and presence of vascular disease and risk factors was assessed. Comorbid conditions were also documented.

Neuropsychological Assessment
Subjects underwent standardized neuropsychological testing to assess cognitive domains of interest (attention, episodic memory, executive functions), and to provide a valid overview of other domains, while limiting time requirements to facilitate subject participation. The following tests were used: the Mattis Dementia Rating Scale (DRS),25 the California Verbal Learning Test,26 and a word generation test with phonemic cues (letters F, A, and S).27

Neuroimaging Acquisition
T2-weighted and PD images (interleaved axial spin echo with echo times of 30 and 80 ms, 3 s revolution time, 0.5 number of excitations, 22×22 cm field of vision, 0.859×0.859 mm in-plane resolution and 3 mm slice thickness) were acquired on a 1.5T Sigma scanner (GE Healthcare Technologies). Digital images of both PD and T2 were reviewed on a personal computer monitor using the MRICro software.28

General WMH Rating Scale
The Age-Related White Matter Changes (ARWMC) rating scale of the European Task Force was used as a general measure of WMH severity.22 In short, this scale uses a four-point severity rating (0-normal; 1-punctate; 2-beginning confluence; 3-diffuse involvement) for each of 4 brain regions: frontal, parieto-occipital, temporal, and infra-tentorial. The region of the basal ganglia is included with a similar rating scheme. Total score ranges from 0 to 30.

Cholinergic Pathways HyperIntensities Scale
This new visual rating scale was developed based on published immunohistochemical tracings of the cholinergic pathways in humans, superimposed on structural MRI scans.17 To improve on a previous scale devised by our group,23 the medial pathway (cingulate gyrus white matter) and lateral pathway (external capsule and claustrum) were separated into 10 regions, using major anatomical landmarks on 4 index slices spanning the third and lateral ventricles in the axial plane (Figure 1 and Table 2). Severity of WMH was visually rated on a 3-point scale for each region (0=normal; 1=mild [≤50% of region involved]; 3=moderate to severe [≥50% of region involved]). Each slice was weighted to account for the decreasing concentration of cholinergic fibers as they project up and fan out in the white matter (maximum weight (4) for slice 1; minimal weight (1) for slice 4). Lesions of the nucleus basalis proper were not observed in this population. The maximum score is 50 per hemisphere when combining each regional score with the appropriate factor, with a total maximum of 100 per scan. All scans were assessed blinded to group assignment and clinical information. The time required for a single subject analysis was approximately five minutes.

Reliability and Validity of the New Scale
Inter- and intrarater reliability studies were performed before the present study on a separate cohort of subjects. Two experienced raters (C.B., F.Q.G.) assessed a set of 10 training scans, then participated in a consensus conference. Raters thereafter independently assessed a separate validation sample (n=20), blinded to clinical information, and intraclass correlation coefficients were derived. Volumetric analysis of WMH was performed using a locally developed semi-automated protocol that combines an individualized 3D template on T1 with an automatic lesion analyzer (T2-PD) that requires minimal manual editing.29,30

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Characteristics of Subjects</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age, y±SD, 77.4±3.2</td>
</tr>
<tr>
<td>Male sex, n(%)</td>
</tr>
<tr>
<td>Education, y±SD, 14.9±3.4</td>
</tr>
<tr>
<td>MMSE, score ±SD, 28.3±1.0*</td>
</tr>
<tr>
<td>Disease duration, y±SD, . . .</td>
</tr>
<tr>
<td>Treatment with Cl, n(%)</td>
</tr>
</tbody>
</table>

Tertiles of CHIPS score: first=0 to 4; second=5 to 15; third=17 to 72. CI indicates acetylcholinesterase inhibitors. P<0.001 controls vs AD; all P values nonsignificant for comparisons between tertiles.
adjusted to account for multiple comparisons (CHIPS and ARWMC scores, and the cutoff for significance was if it significantly altered the model. Separate models were built for them into the first block, then the WMH score was entered step-wise to study the association between DRS total score and WMH scores.

The effects of age and education were accounted for by entering demographics using an analysis of variance (ANOVA, with severity differed among groups. The tertiles were compared based on CHIPS data. Subjects were divided into three equal groups, the tertiles of the total CHIPS score, to investigate whether factors other than CHIPS differences. Two-block multiple linear regression models were built between the rating scales, and between Cholinergic Pathways HyperIntensities Scale (CHIPS) score and strategic WMH volumetric data. Subjects were divided into three equal groups, the tertiles of the total CHIPS score, to investigate whether factors other than CHIPS severity differed among groups. The tertiles were compared based on demographics using an analysis of variance (ANOVA, with $\alpha=0.05$). Neuropsychological scores were analyzed in a similar way and also dichotomized at the upper tertile of severity to confirm differences. Two-block multiple linear regression models were built to study the association between DRS total score and WMH scores. The effects of age and education were accounted for by entering them into the first block, then the WMH score was entered step-wise if it significantly altered the model. Separate models were built for CHIPS and ARWMC scores, and the cutoff for significance was adjusted for account for multiple comparisons ($\alpha=0.025$). All analyses were performed using SPSS 11.0 for Mac (SPSS Inc).

**Statistical Analysis**

Spearman correlation coefficients were used to compute association between the rating scales, and between Cholinergic Pathways HyperIntensities Scale (CHIPS) score and strategic WMH volumetric data. Subjects were divided into three equal groups, the tertiles of the total CHIPS score, to investigate whether factors other than CHIPS severity differed among groups. The tertiles were compared based on demographics using an analysis of variance (ANOVA, with $\alpha=0.05$). Neuropsychological scores were analyzed in a similar way and also dichotomized at the upper tertile of severity to confirm differences. Two-block multiple linear regression models were built to study the association between DRS total score and WMH scores. The effects of age and education were accounted for by entering them into the first block, then the WMH score was entered step-wise if it significantly altered the model. Separate models were built for CHIPS and ARWMC scores, and the cutoff for significance was adjusted for account for multiple comparisons ($\alpha=0.025$). All analyses were performed using SPSS 11.0 for Mac (SPSS Inc).

**TABLE 2. The Cholinergic Pathways HyperIntensities Scale**

<table>
<thead>
<tr>
<th>Slices</th>
<th>Regions</th>
<th>Score*</th>
<th>Factor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low External Capsule</td>
<td>EC anterior 0–1–2</td>
<td>4</td>
<td>0–4–8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC posterior</td>
<td>0–1–2</td>
<td>4</td>
<td>0–4–8</td>
</tr>
<tr>
<td>2. High External Capsule</td>
<td>Cingulate 0–1–2</td>
<td>4</td>
<td>0–4–8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC anterior</td>
<td>0–1–2</td>
<td>3</td>
<td>0–3–6</td>
</tr>
<tr>
<td></td>
<td>EC posterior</td>
<td>0–1–2</td>
<td>3</td>
<td>0–3–6</td>
</tr>
<tr>
<td>3. Corona Radiata</td>
<td>Anterior 0–1–2</td>
<td>2</td>
<td>0–2–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior 0–1–2</td>
<td>2</td>
<td>0–2–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cingulate 0–1–2</td>
<td>1</td>
<td>0–1–2</td>
<td></td>
</tr>
<tr>
<td>4. Centrum Semiovale</td>
<td>Anterior 0–1–2</td>
<td>1</td>
<td>0–1–2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior 0–1–2</td>
<td>1</td>
<td>0–1–2</td>
<td></td>
</tr>
</tbody>
</table>

EC indicates external capsule.

*0=none; 1=mild (<50% of area); 2=moderate-severe (≥50%).

**Results**

**Reliability**

The new rating scale was reliable, with an intraclass correlation coefficient showing very good agreement for both interrater (ICC=0.97) and intrarater (ICC=0.94) reliability. The correlation between total CHIPS score and total ARWMC rating scale score was high (Spearman $\rho=0.82$, $P<0.001$).

**Validation of the Rating Scale**

**Quantification of WMH in Cholinergic Pathways**

The CHIPS total score showed good correlation with volumetric analysis of WMH within standardized region-of-interest encompassing the cholinergic pathways (Spearman $\rho=0.87$, $P<0.0001$; Figure 2).

**Association Between CHIPS and Cognitive Functions**

There was a significant association between CHIPS score and performance on the DRS. CHIPS accounted for 12% of the variance after accounting for the effects of age and education ($F=3.46; \text{df}=2,57; P=0.02$; total $r^2=0.16$; CHIPS $r^2=0.12$). Figure 3 shows the scatterplot graph of DRS scores for each CHIPS score. The three tertiles did not significantly differ on any demographic measure (age, education, duration of disease). In addition, the groups were not different in general severity (Mini Mental State Examination scores equal across groups, $P>0.05$). There was a significant difference in DRS across the three groups (ANOVA $F=3.2, \text{df}=2, 55; P=0.04$).

**Figure 1.** CHIPS scoring illustrated on T2-weighted MRI; total score for this subject is 20. (A), Low External Capsule: Anterior (Right=0, Left=0, Factor$=\times4$, Total=0); Posterior (Right=0, Left=0). (B), High External Capsule: EC anterior (Right=1, Left=0, Factor$=\times3$, Total=6); EC posterior (Right=0, Left=1); Cingulate (Right=0, Left=0). (C), Corona Radiata: CR anterior (Right=1, Left=0, Factor$=\times2$, Total=6); CR posterior (Right=0, Left=2); Cingulate (Right=0, Left=0). (D), Centrum Semiovale: CS anterior (Right=2, Left=2, Factor$=\times1$, Total=8); CS posterior (Right=2, Left=2). (E), Coronal view of the immunohistochemical tracings of the cholinergic pathways from Selden et al17 with levels for selected slices (A-D) in axial plane.

**Figure 2.** Scatterplot showing CHIPS total score and semi-automatic volumetric analysis of WMH within cholinergic pathways ($r=0.87; P<0.001$).

**Figure 3.** Scatterplot depicting total DRS scores and CHIPS total score, with linear regression line ($r^2=0.16$; adjusted $r^2=0.12$; $P=0.02$).
and this was possibly driven by attention and memory subscores, because there was a trend in that direction (P=0.08 and 0.05). When CHIPS severity scores were dichotomized at the upper tertile, significant differences became evident (ANOVA F=4.7; df=1, 56; P<0.03). Demographic and neuropsychological scores are shown in Tables 1 and 3.

**Association Between ARWMC and Cognitive Functions**

When a similar model was built for the general WMH scale, the ARWMC score did not enter the model using the forward stepwise method, after accounting for the effects of age and education (r=0.24; P=0.07).

**Discussion**

The present study suggests that localization of WMH within a specific neurotransmitter system may have a measurable negative impact on cognition in a selected population of AD patients with WMH. CHIPS score was associated with cognitive performance on the DRS, and accounted for 12% of the observed variance. Although the magnitude of this effect appears modest, it compares favorably with similar associations using general WMH. General WMH burden as measured by the ARWMC scale was correlated with CHIPS score, but was not significantly related to cognitive performance. This suggests that CHIPS is not simply a marker for greater WMH burden, but rather is reflecting a pathogenesis that may be more specific to cognition.

Previous work from our group has suggested that strategic WMH within cholinergic pathways is associated with executive and visual attentional dysfunction in a heterogeneous cohort of patients with cognitive impairment, both of vascular and degenerative etiologies. The present study improves on the visual assessment used in Swartz et al, providing a more quantitative assessment of cholinergic pathway WMH.

Dysfunction of the cholinergic system has been associated with cognitive dysfunction in the elderly for almost 30 years, and has provided the major theoretical framework for the development of therapy for AD. A few clinical and pathological observations of vascular dementia (VaD) have also suggested cholinergic system involvement, presumably attributable to interference with subcortical cholinergic pathways. It should be noted, however, that cerebrospinal fluid samples were not available for analysis of cholinergic markers levels; thus, a cholinergic deficit could not be explicitly demonstrated. This might be a useful line of inquiry in the future.

Another limit of the MRI analysis method presented here lies in the lack of anatomical landmarks to define the location of the cholinergic pathways above the sylvian fissure. The higher weighting of the two most caudal slices, comprising the external capsule, as opposed to more rostral slices, is likely to minimize this limitation.

A detailed neuropathological case study of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) by Mesulam et al demonstrated that cortical ACh projections from the nucleus basalis could be affected by purely subcortical ischemic lesions. The magnitude of parenchymal disruption in WMH falls short of that seen in subcortical infarcts in the CADASIL case report. Nevertheless, it is reasonable to postulate that damage to the axons that course through WMH is sufficient to interfere to some degree with normal neuronal function. Pathological studies of WMH have demonstrated apoptosis of oligodendrocytes and damage to axonal projections coursing through white matter lesions. A pathological study of AD with and without WMH within the cholinergic pathways would be necessary to establish that cholinergic denervation does occur.

It also may be that WMH within the regions of interest of our scale reflect some other mechanism of cognitive decline. Detailed anatomical tracings for other neuronal networks or neurotransmitter systems that may course through the external capsule have not been defined in humans, to the authors’ knowledge. In the rhesus monkey, the insular cortex and claustrum are common targets for prefrontal and posterior parietal projections, parts of a large neuronal network. Damage to the underlying white matter could affect these association fibers and corresponding cognitive processes, including working memory and attention.
The relative contribution of neurodegenerative and ischemic lesions in dementia is a subject of intense interest. Relatively specific criteria have been developed for both extremes of the AD-VaD spectrum, but in fact most are modeled on AD as the prototypical dementia. There are few rational schemes to classify the mixed AD-CVD dementias. Given that mixed disease may represent the most common form of dementia in Western societies, a better understanding of the role of WMH is needed. Although the cholinergic deficit, of neurodegenerative or vascular etiology, is unlikely to be the only determinant of cognitive decline in AD and VaD, it certainly contributes to it.

The impact of strategic WMH on treatment response to cholinesterase inhibitors remains to be determined. To our knowledge, only one previous study assessed the impact of white matter disease on treatment response in dementia: a high level of leukoaraiosis on CT scans of subjects with AD was associated with poor tolerance to tacrine, but not with clinical response. This is an area of important clinical interest, and CHIPS provides a tool with which to assess the effect of WMH within cholinergic pathways on treatment response.

In summary, this article presents a novel, reliable, semiquantitative visual rating scale of WMH within a specific neurotransmitter system, the cholinergic system. This approach appears to allow more specific correlations between WMH and cognitive functions in AD with WMH, which is particularly prevalent in the elderly.

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