Bicaudate Ratio as a Magnetic Resonance Imaging Marker of Brain Atrophy in Multiple Sclerosis

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Context: Brain atrophy has emerged as a useful surrogate marker of disease involvement in multiple sclerosis (MS). The relationship between whole-brain or regional atrophy and cognitive dysfunction is poorly understood.

Objectives: To determine whether the bicaudate ratio (BCR)—the minimum intercaudate distance divided by brain width along the same line—is increased in MS and to compare the ability of the BCR, whole-brain atrophy, and other magnetic resonance imaging markers to predict cognitive dysfunction.

Design: Case-control study.

Setting: University-affiliated clinic.

Participants: Sixty patients with MS and 50 age- and sex-matched control subjects.

Main Outcome Measures: Bicaudate ratio, whole-brain atrophy, T2 lesion load, T1 (“black hole”) lesion load, and caudate volume were measured quantitatively using fluid-attenuated inversion recovery, T1-weighted, and gradient-echo magnetic resonance imaging scans. Symbol Digit Modalities Test was used to assess cognitive function.

Results: The BCR (mean [SD]) was higher in patients with MS (0.11 [0.03]) than in controls (0.09 [0.02]) (P<.001), suggesting subcortical atrophy in MS. The BCR was related to total T2 (r=0.56, P<.001) and T1 (r=0.40, P<.002) lesion volumes, but not caudate volume in patients with MS. Regression modeling selected BCR (P<.05), but not whole-brain atrophy, T1 or T2 lesion volume, or caudate volume as predictive of Symbol Digit Modalities Test score in patients with MS.

Conclusions: The BCR is increased in MS and is more closely associated with cognitive dysfunction than are other magnetic resonance imaging surrogate markers including whole-brain atrophy. Increased BCR is best explained by frontal horn ventricular enlargement due to atrophy of deep frontal subcortical white matter. This highlights the close relationship between subcortical atrophy and cognitive impairment in patients with MS.

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Total hyperintense T2 lesion load is an established magnetic resonance imaging (MRI) measure used to assess the disease progression of multiple sclerosis (MS). Hyperintense lesions on T2-weighted images, however, are nonspecific in defining underlying pathologic abnormalities that includes a range of tissue changes and has poor sensitivity for detection of important microscopic disease.1 Hyperintense T2 lesions correlate poorly with physical disability and long-term disease course in patients with MS.2 Because the principal clinical challenge in treating MS is to monitor and suspend chronic disease progression, current research has investigated other methods to assess the global MS disease process. Advancing brain atrophy has been identified as a possible surrogate marker of this long-term progression.3 It has been suggested that atrophy in MS represents destructive and irreversible pathologic processes, making it a more reliable indicator of disease progression than the non-specific T2 lesion load assessment.4

Using computer algorithms of volume reconstruction, whole-brain atrophy has been identified in patients with relapsing-remitting and secondary progressive MS.3,5,6 Several research groups showed that whole-brain atrophy correlated with physical disability and predicted disease progression in patients with MS.3,5,6 These studies also demonstrated that whole-brain atrophy begins early in the disease process of MS.

Atrophy appears to be widespread, affecting the cerebral cortex, corpus callo-
SUBJECTS AND METHODS

SUBJECTS

A consecutive series of 60 patients with MS and 50 controls were scanned using the same MRI unit following the same MRI protocol at a tertiary care university hospital. All patients with MS were clinically confirmed and were treated at a university-affiliated MS clinic. None of the patients with MS had any other major medical illnesses, were younger than 20 years or older than 60 years, had a history of substance abuse, had acute exacerbations, or had used a corticosteroid within the previous 4 weeks before clinical and MRI testing. Using established definitions of clinical course, 42 patients had relapsing-remitting MS and 18 had secondary progressive MS. Physical disability was assessed within 1 week of undergoing MRI by a single experienced neurologist (R.B.), who was blind to the MRI findings. Using the Expanded Disability Status Scale (EDSS), physical disability ranged from 0 (best) to 8.0 (worse) (mean [SD], 3.7 [1.9]). The patients’ disease duration of MS ranged from 0.5 to 38 years (mean [SD] disease duration, 10.6 [9.4] years). Controls included healthy volunteers recruited from hospital staff (n=8) and consecutive patients referred to the MRI center (Imaging Services, Kaleida Health, Buffalo, NY) for dizziness, headaches, and new-onset reactive or idiopathic seizures (not chronic epilepsy) who had normal neurologic test results and no abnormalities on MRIs and in whom MS was excluded clinically. An experienced observer (R.B.) reviewed the MRI scans of the controls to ensure that there were no abnormalities. Patients with MS (41 women [68%]) and controls (35 women [70%]) were sex-matched. Patients with MS (mean [SD] age, 42 [9] years) and controls (mean age [SD], 42 [10] years) were also age-matched. Lifetime corticosteroid use in the MS group was moderate overall, as detailed separately. Different aspects of these patients and controls have been presented recently as part of a separate study.

COGNITIVE TESTING

The Symbol Digit Modalities Test (SDMT) is a commonly used neuropsychological test of information processing speed. Subjects are asked to write the digits that substitute for geometric symbols shown in a key at the top of the page. The score is the number of correct responses recorded in 90 seconds. Subjects responded by writing their answers; none of the patients had significant dominant upper extremity weakness that would compromise their ability to write. Twenty-three randomly chosen patients with MS (15 patients with relapsing-remitting MS and 8 patients with secondary progressive MS) took the SDMT within 1 week of MRI scanning. Patients who took the SDMT were demographically similar to those who did not take the SDMT for age (P=0.58), sex (P=0.67), and clinical course (P=0.49). Mean (SD) EDSS score in the group that took the SDMT (3.2 [1.6] points) was slightly, but significantly, lower than in the group that did not take the SDMT (4.1 [1.8] points) (P=0.04). The remaining controls or patients with MS did not take the SDMT. A modified version of the brain parenchymal fraction was measured on the MRIs of these same 23 patients as described in the “MRI and Variables” subsection, to correct for whole-brain atrophy in the patients who took the SDMT.

MRI AND VARIABLES

T1-weighted (repetition time, 385 milliseconds; echo time, 20 milliseconds; and number of signal averages, 1) and fast spin-echo fluid-attenuated inversion recovery (FLAIR) images (repetition time, 8000 milliseconds; echo time, 120 milliseconds; number of signal averages, 2; and inversion time, 2200 milliseconds) were obtained in the axial plane using 5-mm contiguous, interleaved slices at 1.5 T, with an in-plane resolution of approximately 1 mm. Fast FLAIR included an echo train length (number of echoes) 20; echo spacing, 12 milliseconds; field of view, 24 cm; acquisition matrix, 189 x 256 pixels; and bandwidth, 217.3 Hz/pixel. A presaturation band was placed caudal to the image volume. Detailed imaging parameters of our FLAIR protocol were published previously. A subset of the patients with MS (n=24; 16 patients with relapsing-remitting MS and 8 patients with secondary progressive MS) underwent an additional protocol that was tailored to the detailed depiction of anatomical structures. This was a 3-dimensional (nongapped) gradient-echo volume study performed in the coronal plane, with a repetition time of 24 milliseconds, echo time of 7 milliseconds, slice thickness of 1.8 mm, acquisition matrix size of 256 x 256 pixels, and an in-plane resolution of 0.977 mm. Images were transferred by computer network to Unix-based workstations on which images were analyzed quantitatively (EasyVision, Release 2.1.2; Philips Medical Systems, Best, the Netherlands; Sun Ultra 10; Sun Microsystems, Mountainview, Calif). A trained observer (R.A.B.) who was blinded to clinical information performed the

RESULTS

The BCR was positively correlated with age in patients with MS (Pearson r=0.48, P<.001) and controls (Pearson r=0.33, P=.02); therefore, all correlations involving BCR were age adjusted. To verify that no effects were created as an artifact of age adjustment and to quantify their relative strengths, all correlations are also reported without age adjustment, using the Spearman rank or Pearson product moment correlation test. However, statistical age adjustment did not greatly affect the...
quantitative MRI analysis. The BCR was the minimum intercaudate distance divided by brain width along the same line (Figure 1). The BCR was measured in the FLAIR axial slice where the heads of the caudate nuclei were most visible and closest to one another (Figure 1). Total hyperintense T2 parenchymal plaque lesion load was determined by manual tracing of lesions on FLAIR images. Total parenchymal lesion volume (lesion load) was the sum of the volume (area multiplied by slice thickness) of each lesion seen on each interleaved axial slice; artifacts and other normal hyperintensities seen in the normal population on FLAIR images were avoided. Since hypointense T1 lesions are difficult to delineate manually, the analysis of T1 lesion volume was performed using a semiautomated edge finding and local thresholding technique (Java Image, Version 1.0; Xinapse Systems, Leicester, England; also available at: http://www.xinapse.com). The operator clicks on the edge of the hypointense area and the program examines a region 5 × 5 pixels around the mouse click and computes the maximum intensity gradient within that region. The pixel with the highest intensity gradient is then used as the starting point for contour following, thus outlining the region where the intensity is locally lower than at the starting pixel. A black hole lesion was defined as a lesion appearing visibly hypointense to the surrounding white matter on T1 images, detectable by the edge finding software, and having a corresponding hyperintensity on FLAIR images.

To correct for whole-brain atrophy, the ratio of brain parenchymal volume to the total volume within the surface contour was measured on FLAIR images, modified from a previously described method. The brain parenchymal volume was defined as the intracranial central nervous system tissue with signal intensity of brain parenchyma after the cerebrospinal fluid (subarachnoid space and ventricles) was extracted. Whole-brain atrophy measurement was semiautomated, using computer edge finding to isolate brain tissue from the skull, and intensity thresholding to measure the volume of cerebrospinal fluid space including the sulci and ventricular system (Java Image, 1.0). Caudate volume was measured on coronal gradient-echo images by manually tracing the caudate nuclei bilaterally in each slice where they were visible using an image analysis program (Java Image, 1.0). The posterior boundaries of the caudate nuclei were defined as the point in the tail of the caudate nuclei at which they became too small (or positioned in long axis) and could not be seen. Caudate volume was calculated by summing the number of voxels occupied by the caudate nuclei in each slice, multiplied by slice thickness.

RELIABILITY OF MRI MEASUREMENTS

The same individual (R.A.B.) reanalyzed the MRI scans of 10 randomly chosen patients with MS at least 2 weeks after the initial analysis. Mean intraobserver coefficients of variation were 2.3% for the BCR, 1.2% for total hyperintense T2 parenchymal plaque lesion load, 1.7% for T1 black hole volume, 0.32% for whole-brain atrophy, and 1.64% for caudate volume. A second individual (S.R.P.) measured the BCR in 10 randomly chosen patients with MS, showing a mean interobserver coefficient of variation of 4.2% for the BCR. Two healthy volunteers underwent the MRI protocol twice (1 week apart) to determine the effect of head position and slice selection on the BCR and to assess test-retest reliability. A single observer (R.A.B.) analyzed these serial data from the 2 healthy volunteers, showing a mean interstudy coefficient of variation of 4.36% for the BCR.

STATISTICAL METHODS

We used descriptive statistics and plots to determine whether the variables were normally distributed. All variables were normally distributed, except for total hyperintense T2 parenchymal lesion load, which was skewed to the right, and was converted to the logarithm prior to statistical analysis. Differences between groups and correlations before adjusting for age were assessed using the independent sample t test and the Pearson product moment correlation test or Spearman rank correlation test. Age-adjusted correlations and other multivariate comparisons were made using logistic or linear regression modeling. Each variable was assessed using a separate model that also contained the covariates of interest. The validity of all statistical models was assessed by analysis of variance; any model at P < .05 was discarded. After model validity was established, only assessed variables with P < .05 were considered statistically significant in that model. To correct for the effect of aging on BCR, age was forced into all regression models. To correct caudate volume for head size, total brain volume was forced into the regression model with caudate volume as the other independent variable, based on a previously described method. Statistical analysis was performed using the SPSS software package (Version 10.0; SPSS Inc, Chicago, Ill).
predictive of the SDMT score (age adjustment indicated that the BCR was significantly higher in patients with MS (11.88 mm [3.94 mm]) was significantly higher than in the controls (0.09 [0.02]) (P<.001) and with T1 black hole lesion volume (Pearson r=0.40, P<.002; P<.005) both before and after age adjustment. However, BCR (Spearman r=0.20, P=.12; P=.47, respectively), total hyperintense T2 parenchymal lesion load (Spearman r=0.22, P=.08), or T1 black hole lesion volume (Spearman r=0.20, P=.14) did not significantly correlate with the EDS5 score. Similarly, BCR (P=.86 by logistic regression), T1 black hole lesion volume (P=.82 by individual samples t test), and total hyperintense T2 parenchymal lesion load (P=.21 by individual samples t test) did not differ between the patients with relapsing-remitting MS and those with secondary progressive MS. No significant correlation was found between the BCR and the caudate volume either with (P=.08) or without (Pearson r=-0.39, P=.06) adjustment for total brain volume in the subgroup of 24 patients with MS. The Table summarizes associations between BCR and clinical and/or MRI variables in the patients with MS.

This study indicates that increased BCR is associated with MS, is related to delayed cognitive processing speed, and correlates with the MRI disease burden of T1 and T2 parenchymal plaque lesion load volumes. The increased BCR in patients with MS is caused by the widening of the intercaudate distance, but is not significantly related to caudate volume. Thus, the BCR may be closely related to frontal horn ventricular enlargement due to atrophy of deep frontal subcortical white matter. This atrophy appears in patients with relapsing-remitting MS and patients with secondary progressive MS and across a range of physical disabilities, corroborating recent findings that atrophy begins early in the disease process of MS.57 Most im-

**Figure 1.** Fluid-attenuated inversion-recovery magnetic resonance imaging scan of a patient with multiple sclerosis showing the technique of determining the bicaudate ratio (BCR). The BCR is the minimum intercaudate distance (solid line) divided by brain width along the same line (dashed line).

**Figure 2.** Box plots showing bicaudate ratio (BCR) in 60 patients with multiple sclerosis (MS) vs 50 age- and sex-matched healthy control subjects. Boxes indicate 1 SD from the mean. Vertical bars indicate the total range of scores. The BCR was higher in patients with MS (mean [SD] 0.11 [0.03]) than in the controls (0.09 [0.02]) (P<.001), indicating subcortical atrophy in the patients with MS. This difference persisted after adjusting for age (P<.001). The difference in BCR between controls and the patients with MS was attributable to differences in the intercaudate distance (numerator of the BCR). The mean distance between the caudate nuclei in the patients with MS (11.88 mm [3.94 mm]) was significantly higher than in the controls (9.67 mm [2.67 mm]) (P<.001), while the brain width along the same line (denominator of the BCR) did not differ between the 2 groups (P=.89).

BCR remained statistically significant after adjusting for whole-brain atrophy (P<.03). Further regression modeling with age adjustment indicated that the BCR was significantly predictive of the SDMT score (P<.02), while neither T1 black hole lesion volume (P=.65) nor total hyperintense T2 parenchymal lesion load (P=.33) were predictive of the SDMT score. Also, regression modeling selected BCR as the better predictor of the SDMT score (P=.03) over caudate volume (P=.45) after adjusting for age and total brain volume. Thus, the BCR was independently predictive of the SDMT score, after considering all of the other MRI measures. The BCR also correlated positively and significantly with the total hyperintense T2 parenchymal lesion load (Pearson r=0.56, P<.001) and with T1 black hole lesion volume (Pearson r=0.40, P<.002; P<.005) both before and after age adjustment. However, BCR (Spearman r=0.20, P=.12; P=.47, respectively), total hyperintense T2 parenchymal lesion load (Spearman r=0.22, P=.08), or T1 black hole lesion volume (Spearman r=.20, P=.14) did not significantly correlate with the EDS5 score. Similarly, BCR (P=.86 by logistic regression), T1 black hole lesion volume (P=.82 by individual samples t test), and total hyperintense T2 parenchymal lesion load (P=.21 by individual samples t test) did not differ between the patients with relapsing-remitting MS and those with secondary progressive MS. No significant correlation was found between the BCR and the caudate volume either with (P=.08) or without (Pearson r=-0.39, P=.06) adjustment for total brain volume in the subgroup of 24 patients with MS. The Table summarizes associations between BCR and clinical and/or MRI variables in the patients with MS.

**Table**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=50)</th>
<th>MS (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT Score</td>
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<td></td>
</tr>
<tr>
<td>50th percentile</td>
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<td>41</td>
</tr>
<tr>
<td>Median</td>
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<td>46</td>
</tr>
<tr>
<td>90th percentile</td>
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<td>63</td>
</tr>
<tr>
<td>Range</td>
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<td>18</td>
</tr>
</tbody>
</table>

**Figure 3.** Scatterplot of bicaudate ratio (BCR) vs Symbol Digit Modalities Test (SDMT) score of cognitive function in 23 patients with multiple sclerosis. The BCR was significantly inversely correlated with the SDMT score both before (Pearson r=-0.42, P=.04) and after (P<.01) age adjustment, indicating that greater subcortical atrophy was associated with poorer cognitive function.
Importantly, increased BCR shows a close relationship to cognitive dysfunction, a relationship that exists despite accounting for caudate volume, total brain T1 and T2 MRI parenchymal plaque lesion load, and whole-brain atrophy. Thus, increased BCR appears to show clinical relevance independent of general MRI measures. This highlights the close relationship between subcortical atrophy and cognitive dysfunction in patients with MS.

The BCR was shown to correlate with caudate volume in diseases primarily affecting the caudate nuclei, such as Huntington disease. However, it has shown only a weak association with caudate volume in normal aging and in patients with certain psychiatric illnesses, such as autism and obsessive-compulsive disorder. Thus, increases in BCR may represent different processes across disease states. In this study, BCR was not significantly related to caudate volume. In light of this finding, it is important to consider what the increased BCR may represent in patients with MS and how this relates to the clinical findings. We found that the difference in BCR between the controls and the patients with MS could be accounted for by a larger numerator of the BCR (ie, a larger intercaudate distance) in patients with MS. This suggests that atrophy of white matter tracts and ventricular enlargement in the vicinity of the caudate nuclei are responsible for the increased BCR in MS. Conversely, the lack of difference in BCR denominator between the controls and the patients with MS suggests that increased BCR in MS is not due to a lower brain width at this level, such as might be caused by opercularfrontal cortical atrophy. It is likely that the increased BCR represents the caudate nuclei moving apart due to adjacent white matter atrophy and ventricular enlargement present in MS. However, the correlation between BCR and caudate volume was tested in a limited subset of 24 patients with MS; therefore, it is possible that a relationship between caudate volume and BCR was not detected because of the sample size and other methodological limitations of the current study.

Atrophy of white matter axonal tracts in the frontal subcortical and periventricular region, including those connecting to the caudate nuclei, could explain the link between increased BCR and cognitive dysfunction. Frontal-subcortical circuits, many of which eventually relay through the caudate nucleus, are known to play a role in informational processing speed that contributes to the SDMT. Interruption of the dorsolateral-prefrontal circuit has been demonstrated in diseases affecting the caudate, including stroke, Huntington disease, and neuroacanthocytosis. Disruptions of this pathway have produced deficiencies in retrieval and verbal fluency. None of the MRI variables examined were associated with physical disability (EDSS score) or a relapsing-remitting vs secondary progressive clinical course. The poor relationship between conventional MRI findings and physical disability has been reviewed in 1999. Possible reasons for this poor correlation include the heavy weighting of EDSS toward motor symptoms, its nonlinearity, and the pathologic nonspecificity of lesions on conventional MRI scans. The lack of correlation between BCR and EDSS score could be explained by some of the reasons outlined earlier. Interruption of the subcortical circuits that are pertinent to increased BCR may not cause visual, motor, sensory, and gait impairments that contribute to the EDSS score. Whole-brain atrophy and other general atrophy measures have shown better correlations with the EDSS score. Recent studies have demonstrated that atrophy in MS occurs early in the disease course and is present in a large number of patients with relapsing-remitting MS. Patients with relapsing-remitting MS who have only mild physical disability suffer continual brain volume loss that underlies their otherwise episodic disease course. In the present study BCR did not differ significantly between patients with relapsing-remitting MS and those with secondary progressive MS, in agreement with these previous findings that atrophy is not limited to late-stage disease.

The SDMT scores in this study are similar to the scores in a larger cohort (N=103) of patients with MS from a different geographical area, suggesting external validity of our patient sample. Our MRI measurements were highly reliable and were obtained quantitatively. Our controls showed a high degree of internal validity accounting for caudate volume, total brain T1 and T2 MRI variables in patients with multiple sclerosis (MS).

### Associations Between Bicaudate Ratio and Clinical and Magnetic Resonance Imaging Variables in Patients With Multiple Sclerosis (MS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients With MS</th>
<th>Regression Model in the Group With MS, P Value</th>
<th>Correlation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60</td>
<td>.45   .001</td>
<td></td>
</tr>
<tr>
<td>Symbol Digit Modalities Test score</td>
<td>23</td>
<td>-.04</td>
<td></td>
</tr>
<tr>
<td>Expanded Disability Status Scale score</td>
<td>60</td>
<td>.20</td>
<td>.12</td>
</tr>
<tr>
<td>Lesion load volume</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total hyperintense T2</td>
<td>60</td>
<td>.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total T1 black hole</td>
<td>60</td>
<td>.40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Caudate volume</td>
<td>24</td>
<td>-.39</td>
<td>.06</td>
</tr>
</tbody>
</table>

*Either the Pearson product moment correlation or Spearman rank correlation was used to calculate these values. For a complete explanation, see the “Statistical Methods” subsection of the “Subjects and Methods” section.

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plaque lesion load or whole-brain atrophy. The BCR demonstrates high reliability and excellent scan-rescan reproducibility. Future work should determine the sensitivity of BCR in longitudinal studies and the use of BCR compared with other regional atrophy measures, such as cortical atrophy,\textsuperscript{7} corpus callosum area, or third ventricular width.\textsuperscript{9} While the recent trend has been toward measuring whole-brain atrophy in MS, regional atrophy measures may be useful for understanding specific clinical aspects of the disease. The BCR may be useful as a surrogate marker to complement parenchymal plaque lesion load assessments and whole-brain atrophy measures, helping to understand cognitive dysfunction in MS.

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Author contributions: Study concept and design (Mr Bermel and Drs Bakshi and Jacobs); acquisition of data (Messrs Bermel and Tjoa and Dr Puli); analysis and interpretation of data (Mr Bermel and Dr Bakshi); drafting of the manuscript (Mr Bermel and Dr Bakshi); critical revision of the manuscript for important intellectual content (Mr Bermel and Drs Bakshi and Jacobs); statistical expertise (Mr Bermel and Dr Bakshi); obtaining funding (Mr Bermel and Drs Bakshi and Jacobs); administrative, technical, and material support (Mr Tjoa and Dr Puli); and study supervision (Drs Bakshi and Jacobs).

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