Evidence of Subtle Gray-Matter Pathologic Changes in Healthy Elderly Individuals With Nonspecific White-Matter Hyperintensities

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Objective: To investigate whether additional “occult” tissue changes can be detected in the normal-appearing white matter and gray matter of otherwise normal elderly individuals with nonspecific white-matter hyperintensities on conventional magnetic resonance images of the brain.

Methods: Conventional and magnetization transfer magnetic resonance images were obtained from 12 otherwise normal elderly subjects with white-matter hyperintensities and 11 age- and sex-matched normal individuals. After automatic tissue segmentation, image coregistration, and masking of T2-visible lesions, we obtained magnetization transfer ratio histograms of the normal-appearing white matter and gray matter. For each histogram, the average magnetization transfer ratio, the peak height, and the peak position were measured. We also calculated the percentages of gray-matter and white-matter volumes normalized over the total volume of the intracranial content and the total normalized brain volumes.

Results: Average magnetization transfer ratio (P = .03) and mean peak position (P = .01) of the gray-matter histograms from elderly individuals with white-matter hyperintensities were significantly lower than the corresponding quantities from those without white-matter hyperintensities. The normalized percentages of gray and white matter and normalized brain volume did not differ between the 2 groups. The average gray-matter magnetization transfer ratio was correlated with the average lesion magnetization transfer ratio (r = 0.68; P < .01).

Conclusions: This study shows that brain abnormalities in otherwise normal elderly subjects with nonspecific white-matter hyperintensities extend beyond the macroscopic white-matter lesions visualized on conventional magnetic resonance images.

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NONSPECIFIC white-matter hyperintensities (WMHs) are frequently seen on conventional magnetic resonance (MR) images of the brain from elderly individuals. Although the nature and clinical significance of WMHs in the elderly are still unclear, the most plausible pathological substrate for such changes is thought to be ischemic damage.

In many neurologic diseases associated with focal white-matter (WM) lesions, the use of magnetization transfer (MT) MR imaging has shown that the overall tissue damage extends well beyond that seen on conventional MR images and involves the normal-appearing WM and the gray matter (GM). In these conditions, MT MR imaging has also provided valuable information about the underlying composition of tissue with increased specificity over conventional MR imaging.

Since definitive histopathological correlations are unlikely to be obtained in patients with nonspecific WMHs, we investigated, by means of MT MR imaging and histogram analysis, whether additional “occult” pathologic changes can be detected in the normal-appearing WM and GM of the whole brain of these patients. The aim of the study was not only to provide a more accurate picture of the pathologic changes associated with WMHs in the elderly, but also to gain additional insight into the nature of this condition.

METHODS

Conventional and MT MR images of the brain were obtained from 23 elderly individuals aged 65 years or more with no previous history of neurologic dysfunction and normal results of neurologic examination, who volunteered to take part in this study. They were selected on the basis of the criteria mentioned from a larger group of elderly individuals who served as controls for previous studies conducted at our institution. The study was approved by the local ethical committee, and written informed consent was obtained from all individuals before study entry.
On a single occasion, the following MR sequences of the brain were obtained by means of a 1.5-T machine (Vision; Siemens, Erlangen, Germany) from all individuals: (1) dual-echo turbo spin echo (repetition time, 3300 milliseconds; time to first echo, 16 milliseconds; time to second echo, 98 milliseconds; echo-train length, 5); (2) T1-weighted conventional spin echo (repetition time, 768 milliseconds; echo time, 14 milliseconds); and (3) 2-dimensional gradient echo (repetition time, 640 milliseconds; echo time, 12 milliseconds; flip angle, 20°), with and without an off-resonance radiofrequency saturation pulse (offset frequency, 1.5 kHz; gaussian envelope duration, 16.4 milliseconds; flip angle, 500°). For each pulse sequence, 24 axial, contiguous, 3-mm-thick slices with a 256 × 256 matrix and a 250 × 250-mm² field of view were obtained.

Dual-echo images from all subjects were reviewed in a random order by consensus by 2 experienced observers (D.M.M. and M.A.R.), unaware of subjects’ identity, to identify the presence of WMHs. According to the presence or absence of WMHs, the subjects were divided into 2 groups: the study group (12 individuals; mean age, 69 years; range, 65-73 years; 6 women, 6 men) and the control group (11 individuals; mean age, 68 years; range, 65-74 years; 6 women, 5 men). In the former group, WMHs were scored according to the scale of Fazekas et al. The scale provides 2 different scores rated on a 3-point scale according to the following criteria: periventricular score: 0 (absence), 1 (caps or pencil-thin lining), 2 (smooth halo), or 3 (irregular periventricular hyperintensities extending into the deep WM); and WM score: 0 (absence), 1 (punctate foci), 2 (beginning clusur of foci), or 3 (large confluent areas). This scale was chosen because it has been validated histopathologically and is characterized by an acceptable reliability.

The volume of WMHs was measured by a semiautomated technique based on local thresholding. With the use of statistical parametric mapping 99 and maximum image homogeneity correction, brain GM, WM, and cerebrospinal fluid were automatically segmented from T2- and proton-density-weighted images. Each pixel was classified as either GM, WM, or cerebrospinal fluid, depending on which mask had the greatest probability (maximum likelihood) at that location. This generated mutually exclusive masks for each tissue. The figure shows a typical example of this procedure, indicating how well the segmentation technique worked. At this stage, the percentages of GM and WM volumes normalized over the total volume of the intracranial content were calculated. Maps of the MT ratio (MTR) were obtained as previously described. After WMHs were automatically superimposed onto the coregistered MTR map, average MTR of the WMHs was calculated, as extensively described elsewhere. Then, the MTR maps (from which the WMHs had been automatically removed) were superimposed onto the GM and WM masks, and MTR histograms (with bins 1% in width) of normal-appearing WM and GM were obtained. To correct for the between-patient differences in brain volumes, each histogram was normalized by dividing it by the total number of pixels included. For each histogram, the average MTR, the peak height (ie, the proportion of pixels at the most common MTR value), and the peak position (ie, the most common MTR value) were measured.

On T1-weighted images, normalized volumes of the whole of the brain were obtained by means of the cross-sectional version of the SIENA (Structural Imaging Evaluation of Normalized Atrophy) software. This is a fully automated and accurate method that performs segmentation of brain from nonbrain tissue in the head, estimates the outer skull surface, and uses these results to drive the spatial transformation to a standard template. This software is extensively described elsewhere. A Mann-Whitney test was used to compare MTR-derived metrics, normalized brain volume, normalized percentage of GM, and normalized percentage of WM from the 2 groups of subjects. Univariate correlations were assessed by means of the Spearman rank correlation coefficient. Bonferroni correction for multiple comparisons was not used in the present study because of its exploratory nature.

In the 12 subjects with WMHs, the mean lesion load volume was 6.0 mL (SD, 7.1 mL). In all of these subjects, WMHs were scored as grade 1 or grade 2 for both the periventricular (mean, 1.4) and the WM (mean, 1.2) scores, according to the scale of Fazekas et al. The average lesion MTR was 39.3% (SD, 1.1%). No macroscopic GM abnormalities were seen on the brain MR images of any of the individuals. The normalized percentage of WM, the percentage of GM, and the normalized brain volume did not differ between the 2 groups (Table 1).

Average MTR (P = .03) and mean peak position (P = .01) of the GM histograms from elderly individuals with WMHs were significantly lower than the corresponding
quantities from those without (Table 2). The MTR histogram metrics of the normal-appearing WM were not significantly different between the 2 groups (Table 2).

The average MTR of the GM histogram was correlated with the average lesion MTR ($r=0.68; P<.01$). No significant correlation was found between MTR metrics of the GM histograms and the volume of WMHs.

### COMMENT

This preliminary study shows that brain pathologic changes in otherwise normal elderly subjects with nonspecific WMHs extend beyond the macroscopic abnormalities visualized on conventional MR images. Using MTR histogram analysis, we detected a subtle involvement of the brain GM of these individuals. This finding not only provides a more complete picture of brain changes in elderly individuals with nonspecific WMHs but also, and more important, may improve our understanding of the pathophysiology of this condition, which is unlikely to be obtained from histopathological studies. Since we are aware that cortical and brain atrophy can cause a GM MTR decrease due to partial volume effects associated with the inclusion of voxels contaminated by cerebrospinal fluid, we measured normalized brain volume and normalized percentage of GM in the 2 groups of elderly individuals (ie, those with and those without WMHs). Since there was no difference of either of these 2 quantities between the 2 groups, we can reasonably exclude that GM MTR decrease in individuals with WMHs is attributable to cortical and brain atrophy. It remains to be established whether these subtle GM changes in otherwise normal individuals might evolve into cortical atrophy and be the basis of the mild cognitive deficits that have been reported in some individuals with WMHs.19

With this in mind, the major issue to be addressed is to elucidate the origin of such GM changes. Since these individuals had WMHs, the most readily apparent explanation for the MTR decrease found in their brain GM is to interpret this finding as the result of a passive upstream effect secondary to the damage of fibers transversing WM lesions. Although we cannot exclude a contribution of this mechanism to the observed GM changes, we believe that retrograde neuronal degeneration is unlikely to play an important role because of the scarcity of the macroscopic WM lesions seen in these patients and the lack of occult damage in the normal-appearing WM. This interpretation fits with the lack of a correlation between the volume of WMHs and MTR histogram-derived metrics, as well as with previous MR spectroscopy data,20 which did not show a decrease in N-acetylaspartate in WMHs of otherwise healthy elderly individuals.

An alternative, although not mutually exclusive, explanation of the GM occult changes seen in these individuals is the presence of small GM lesions that go undetected when conventional MR imaging is used. There are several possible reasons that can explain why these lesions are not seen on conventional MR images; these include the fact that GM lesions may be small, have relaxation characteristics that result in poor contrast with normal GM, and, in the case of cortical lesions, because of partial volume effects with the surrounding cerebrospinal fluid.

The nature of WMHs in elderly individuals is still unclear. However, one of the most plausible explanations for these abnormalities is supposed to be an ischemic injury occurring during episodes of cerebral hypoperfusion.5 The susceptibility of deep WM to systemic or focal decreases of cerebral blood flow is most likely a consequence of the unique pattern of its blood supply through long penetrating end-arterial vessels.21 Since it is known that damage secondary to cerebral hypoperfusion can also cause small cortical infarcts to vascular watershed zones,22 it is tempting to suggest a similar mechanism as the pathologic basis of both WMHs and GM MTR decrease in otherwise normal elderly individuals. Arteriosclerosis or cerebral amyloid angiopathy might well be additional factors that can concur with the anatomic susceptibility in the genesis of both WMHs and cortical watershed microinfarcts.23-25

This interpretation of the results of the present study fits with the absence of diffuse occult WM changes of the brain, and it is supported by the correlation found between average lesion MTR and average GM MTR, which suggests that the severity of WMHs and GM abnormalities are not independent of each other. In this context, it is also worth noting that, with the use of MTR, occult GM involvement has also been reported in patients with WM vascular abnormalities, such as those with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.9

In conclusion, the preliminary evidence presented herein suggests that brain pathologic changes in these individuals extend beyond the classic deep WM areas, suggesting a diffuse whole-brain disorder. Larger studies are now warranted to confirm the present findings.

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**Author contributions:** Study concept and design (Drs Mezzapesa and Filippi); acquisition of data (Drs Mezzapesa and Rocca); analysis and interpretation of data (Drs Mezzapesa, Rocca, and Pagan); drafting of the manuscript (Drs Mezzapesa and Filippi); critical revision of the manu-

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Table 2. GM and WM MTR Histogram-Derived Metrics in Elderly Individuals With and Without White-Matter Hyperintensities

<table>
<thead>
<tr>
<th></th>
<th>Study Group</th>
<th>Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) GM average MTR, %</td>
<td>35.51 (1.23)</td>
<td>37.37 (2.07)</td>
<td>.03</td>
</tr>
<tr>
<td>Mean (SD) GM average MTR, %</td>
<td>77.31 (12.89)</td>
<td>85.44 (10.18)</td>
<td>.17</td>
</tr>
<tr>
<td>histogram peak height, %</td>
<td>31.33 (1.07)</td>
<td>32.36 (2.00)</td>
<td>.01</td>
</tr>
<tr>
<td>Mean (SD) WM average MTR, %</td>
<td>41.07 (1.13)</td>
<td>42.43 (2.62)</td>
<td>.12</td>
</tr>
<tr>
<td>histogram peak position, %</td>
<td>141.77 (22.41)</td>
<td>153.62 (35.44)</td>
<td>.26</td>
</tr>
<tr>
<td>MTR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) WM average MTR, %</td>
<td>35.58 (1.00)</td>
<td>37.09 (2.17)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviations: GM, gray matter; MTR, magnetization transfer ratio; WM, white matter.
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REFERENCES


