Mild Cognitive Impairment after Lacunar Infarction: Voxel-Based Morphometry and Neuropsychological Assessment

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Abstract

Background: The aim of the present study was to investigate whether there were differences in neuroradiological features, including white-matter lesions and gray-matter volumes, between patients with lacunar infarction with and without mild cognitive impairment of the vascular type (MCI-V). Methods: A total of 40 patients with lacunar infarction were studied within 1 month after stroke. Results: MCI-V was found in 22 patients, who in comparison with patients without cognitive impairment were significantly older and had fewer years of formal education. MRI subcortical hyperintensities especially in the basal ganglia (putamen and thalamus) were significantly more frequent in the MCI-V group. In the voxel-based morphometric study, patients with MCI-V showed more atrophy bilaterally in the middle temporal gyrus, right and left frontal and posterior bilateral occipitoparietal regions including the posterior cingulate as well as in the cerebellum. A region of interest analysis restricted to the parahippocampi and hippocampi showed further reduced bilateral parahippocampal gyrus and right hippocampus volume reductions in this group of patients. Finally, the amount of white-matter lesions among MCI-V showed negative correlations with gray-matter volume in frontal and temporal areas as well as with the thalamus and mesencephalon. Conclusions: The present findings provide support for an anatomical substrate of the MCI entity in patients with lacunar infarction. Both gray- and white-matter changes seem to contribute to the cognitive impairment of such patients.

Key Words
Lacunar infarction • Mild cognitive impairment • Voxel-based morphometry • Neuropsychological tests

Mild cognitive impairment of the vascular type (MCI-V) identifies a population of nondemented patients exhibiting cognitive impairment mainly as a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease [1, 2]. Epidemiological studies have reported that one fourth of elderly patients meet criteria for dementia 3 months after ischemic stroke [3]. On the other hand, it has recently been reported that brain changes other than those directly related to subcortical cerebrovascular damage, such as global or regional gray-matter shrinkage (i.e. hippocampal atrophy) [4–6], may also account for cognitive deficits in cerebral vascular lesions.

Previous views assumed that lacunar strokes occurring in nondemented patients had no impact on cognitive
functioning [7]. However, an increasing body of evidence indicates that lacunar infarction does influence cognitive performance [8–10]. In this regard, lacunar stroke may be included in the list of vascular diseases causing MCI-V. No previous study has applied the operative criteria for MCI-V [1] among lacunar stroke patients in order to investigate the influence of single or multiple lacunar infarctions or other cerebral changes, including white-matter abnormalities or gray-matter shrinkages on cognitive impairment of the vascular type. Therefore, the study was conducted to determine the neuroradiological features and gray-matter volume characteristics in lacunar stroke patients classified as MCI-V as compared to those without cognitive impairment.

**Patients and Methods**

**Study Population**

Patients with a first-ever stroke presenting as a lacunar infarction were administered first consecutively to the Department of Neurology of Hospital of Sagrat Cor (an acute-care 350-bed teaching hospital in the city of Barcelona, Spain) between January 2003 and February 2005 and were included in the study provided that at least a single symptomatic acute lacunar infarction (>2 and <15 mm in maximal diameter) in the internal capsule, thalamus, basal ganglia, corona radiata, pons or centrum ovale was confirmed by brain MRI. Exclusion criteria were as follows: cortical and/or subcortical nonlacunar infarcts or intracerebral hemorrhage documented by MRI; severe cardiovascular, renal, hepatic, neoplastic or chronic disease; psychiatric comorbidity (DSM-IV); major depression (Hamilton Rating Scale for Depression score ≥18), and dementia [Mini-Mental State Examination (MMSE) score <24]. The definitions of cerebrovascular risk factors and lacunar syndromes, including pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand and atypical lacunar syndrome (patients presenting isolated dysarthria, dysarthria facial paresis or isolated hemiataxia), were those used in previous studies [11–13].

**Neuropsychological Assessment**

All subjects were administered an extensive battery of neuropsychological tests after 1 month of the index admission. The neuropsychological assessment was accomplished with the following tests: Rey Auditory Verbal Learning Test (RAVLT), Visual Reproduction subtest of the Wechsler Memory Scale (WMS-III), Trail Making Test A and B (TMT-A, TMT-B), Stroop Test, Phonetic Verbal Fluency Test, Verbal Category Fluency Test (animal naming), Luria’s Premotor Sequences, Boston Naming Test; Shortened Token Test, Digit Symbol Substitution Test (WAIS-III), Digit Span Forward and Backward Test (WAIS-III), Block Design Test (WAIS-III) and Benton Judgment of Line Orientation Test.

MCI-V [1] was considered in nondemented patients exhibiting cognitive impairment mainly as a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease.

According to the criteria of Frisoni et al. [1] for MCI-V which emphasize impairment in executive function whereas the memory dysfunction may be considered as mild, MCI-V patients were those showing dysfunction in at least one of the following tests assessing executive functions: Verbal Fluency, TMT-A and TMT-B, and Stroop Test and in one of the following declarative memory tests: immediate, delayed recall or recognition of RAVLT and Visual Reproduction of WMS-III. We defined cognitive dysfunction in our study using a cutoff of –1.5 SD for executive functions because this cutoff point is employed in ‘nonvascular’ MCI to define impairment in the declarative memory domain [14]. On the other hand, since the memory dysfunction might be mild in MCI-V [1], we used a less strict cutoff for memory impairment set to –1 SD so as to include individuals with mild impairment. Previously published normative data in healthy elderly people with similar demographic characteristics were used to determine the cutoff value for each neuropsychological test [15–17].

**MRI Examination**

MRI acquisitions were obtained using a General Electric 1.5-tesla Sigma system. To distinguish between acute and chronic silent lacunar infarcts and to rate the degree of white-matter hyperintensities, MRI was performed in the following sequences: 3D/FSPGR (TR = 13.1 ms, TE = 4.2 ms, FOV 24 × 18, slice thickness 3.0 mm, gap 0.0), TRA/SE/T1 (TR = 460 ms, TE = 14 ms, FOV 24 × 18, slice thickness 5.0 mm, gap 2.5), TRA/DUAL DP-T2 (TR = 3.980 ms, TE 20/100, FOV 24 × 18, slice thickness 5.0 mm, gap 2.5), fluid-attenuated inversion recovery (FLAIR; TR = 10,002 ms, TE = 148.5 ms, FOV 24 × 24, slice thickness 5.0 mm, gap 2.5) and diffusion sequences (TR = 10,000 ms, TE = 125.7 ms, FOV 34 × 25.5, slice thickness 5.0 mm, gap 0.0). The comparison between T1-weighted and FLAIR sequences was used to reduce the possibility of confounding lacunar infarctions with Virchow-Robin spaces since these only appear in FLAIR as hypointensities but not in T1-weighted images. The presence of acute or chronic, single and/or multiple silent lacunar infarcts and its location were determined by two senior neuroradiologists (J.C.S. and M.R.) by means of visual inspection using the T1-weighted, FLAIR and T2-weighted sequences of MRI scans. The neuroradiologists were unaware of the results of neuropsychological tests with regard to the patients’ cognitive status. White-matter lesions were evaluated from T2-weighted images, and periventricular, white-matter, subcortical and infratentorial hyperintensities were evaluated in axial slices according to the scale of Scheltens et al. [18]. Scores of ratings were established by consensus.

**Voxel-Based Morphometry**

Optimized voxel-based morphometry was performed using the SPM2 (Statistical Parametric Mapping) software and following the procedure described by Good et al. [19]. This procedure allows the automatic detection of whole-brain morphological differences by assigning each brain voxel a probability of being gray matter, white matter and cerebrospinal fluid (CSF). t-Statistic maps were obtained from the analyses of smoothed images with 1 × 1 × 1 mm voxel size and thresholded at p < 0.001 (uncorrected for multiple comparisons). Since previous studies have indicated that medial temporal lobe regions are compromised in cerebrovascular patients [4–6], a subsequent hypothesis-driven region of interest (ROI) analysis was performed using the Wake Forest University of School of Medicine Pickatlas software (WFU Pickatlas) [20,21].
Pickatlas v2) comprising the hippocampi and the parahippocampal gyri. Results derived from the ROI analyses were thresholded at \( p < 0.05 \) voxel level with a false discovery rate (FDR) correction for multiple comparisons. For all analyses, in addition to the threshold set at a voxel level, a given cluster was considered as significant by taking into account only clusters showing a corrected value of \( p \leq 0.05 \) and with an extent threshold of 20 voxels. To interpret the specific brain regions that emerged from the voxel-based morphometry analyses into the Talairach coordinates space, SPM coordinates, given in Montreal Neurological Institute, were corrected (http://www.mrc-cbu.cam.ac.uk/Imaging/mnisspace.html). Total intracranial volume and gray-matter volumes were calculated using the ‘segment’ option provided in SPM2. We started the analyses beginning with the raw images correctly oriented (AC-PC origin) in the native space. The second step included the automated partition of the original image into separate images representing probability maps for gray matter, white matter and CSF using the combined pixel intensity and a priori knowledge approach integrated in SPM. The resultant images were inspected for adequate segmentation into the different tissue types, and no gross abnormalities could be appreciated despite the fact that lacunar infarcts were frequently misclassified as CSF. Following this process we used the routine ‘seg-vol’ implemented in MATLAB which calculates the volume of each tissue separately. The last step was adding the value of the 3 compartments to obtain total intracranial volume. For each segmented subject we checked gray-matter, white-matter and CSF compartments to obtain total intracranial volume. For each segmented subject we checked gray-matter, white-matter and CSF compartments to obtain total intracranial volume.

### Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 11.0). Clinical variables and the ratings of lacunar infarcts and white-matter hyperintensities in the 2 groups of patients were analyzed with Student’s \( t \) test or the Fisher’s exact probability test (when appropriate) for categorical variables. Comparisons of gray-matter volumes and correlations between white-matter hyperintensities and gray-matter atrophy derived from the statistical maps were analyzed with the ‘two-sample \( t \) test’ and ‘simple regression (correlation)’ models provided by SPM2.

### Results

During the study period, 60 patients with first-ever lacunar stroke were diagnosed. However, 20 patients were excluded from the study for the following reasons: cortical and/or subcortical nonlacunar infarcts documented by MRI (n = 13); normal MRI findings (n = 2); cavernous angioma (n = 1); major depression (n = 1); dementia (n = 1); retained shrapnel particles in the head (n = 1), and MRI contraindication (cardiac pacemaker; n = 1).

The lacunar study population finally included 40 patients, 19 men and 21 women, with a mean age of 70.8 years (standard deviation, SD, 12.2). The clinical syndromes included 12 patients with pure motor hemiparesis, 9 with pure sensory stroke, 8 with dysarthria-clumsy hand/ataxic hemiparesis, 8 with atypical lacunar syndrome and 3 with sensorimotor stroke. Twenty-two patients (55%) met criteria for diagnosis of MCI-V. Patients in the MCI-V group compared with patients without cognitive impairment were older (mean age 77.4 ± 11 vs. 65.9 ± 11.9 years, \( p = 0.02 \) and less educated (mean years attending school 8.1 ± 2.6 vs. 11 ± 4.6, \( p = 0.03 \)). The mean MMSE score was 27.6 (SD 1.8) in the MCI-V group and 29.4 (0.8) in the non-MCI-V group (\( p < 0.001 \)). The mean number of infarctions was 3.7 (1.9) in the MCI-V group and 2.9 (2.5) in the non-MCI-V group (\( p = 0.28 \)). The percentage of cases showing 1 vs. multiple infarcts in both groups did not reach statistical significance (MCI-V group vs. non-MCI-V group, single lacunar infarction 18.2 vs. 44.4%; multiple lacunar infarctions 81.8 vs. 55.5%; \( \chi^2 = 3.570, p = 0.061 \)).

As shown in table 1, overall subcortical and basal ganglion hyperintensities were significantly more frequent in the MCI-V group. The specific regions where MCI-V showed increased hyperintensities were the putamen and the thalamus. Differences between the study groups with regard to MRI hyperintensities remained after adjusting for age and years attending school.

### Table 1. Significant differences on MRI hyperintensities between lacunar stroke patients with and without MCI-V (means with SD in parentheses)

<table>
<thead>
<tr>
<th>MRI hyperintensities</th>
<th>MCI-V present n = 22</th>
<th>MCI-V absent n = 18</th>
<th>t</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcortical, overall</td>
<td>18.1 (10.4)</td>
<td>11.9 (8.9)</td>
<td>2.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Periventricular, total</td>
<td>3.3 (1.5)</td>
<td>3.2 (2.3)</td>
<td>0.21</td>
<td>0.84</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.0 (0.7)</td>
<td>0.9 (0.9)</td>
<td>0.23</td>
<td>0.82</td>
</tr>
<tr>
<td>Frontal</td>
<td>1.2 (0.6)</td>
<td>1.0 (0.8)</td>
<td>0.78</td>
<td>0.44</td>
</tr>
<tr>
<td>Periventricular</td>
<td>1.2 (0.6)</td>
<td>1.3 (0.8)</td>
<td>0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>White matter, total</td>
<td>7.4 (6.9)</td>
<td>4.3 (4.5)</td>
<td>1.64</td>
<td>0.12</td>
</tr>
<tr>
<td>Frontal</td>
<td>2.4 (2.2)</td>
<td>1.8 (2.2)</td>
<td>0.89</td>
<td>0.38</td>
</tr>
<tr>
<td>Parietal</td>
<td>2.3 (2.5)</td>
<td>1.1 (1.6)</td>
<td>1.85</td>
<td>0.07</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.9 (2.1)</td>
<td>1.0 (1.1)</td>
<td>1.58</td>
<td>0.12</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.8 (1.7)</td>
<td>0.3 (0.6)</td>
<td>1.31</td>
<td>0.20</td>
</tr>
<tr>
<td>Basal ganglia, total</td>
<td>5.5 (2.9)</td>
<td>3.0 (2.6)</td>
<td>2.84</td>
<td>0.007</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.7 (0.8)</td>
<td>0.7 (1.0)</td>
<td>0.10</td>
<td>0.92</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.4 (1.1)</td>
<td>0.5 (0.6)</td>
<td>3.17</td>
<td>0.003</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>1.4 (1.1)</td>
<td>0.7 (1.2)</td>
<td>1.96</td>
<td>0.06</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.2 (1.3)</td>
<td>0.2 (0.4)</td>
<td>3.36</td>
<td>0.002</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>1.2 (0.8)</td>
<td>1.1 (1.8)</td>
<td>0.12</td>
<td>0.88</td>
</tr>
<tr>
<td>Infratentorial, total</td>
<td>1.9 (2.3)</td>
<td>1.4 (2.0)</td>
<td>0.61</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Total intracranial volume did not differ between the MCI-V and the non-MCI-V groups (mean 1,511.47 ± 160.50 vs. 1,594.88 ± 167.84 mm$^3$, p = 0.12), but patients with cognitive impairment showed reduced whole gray-matter volume (628.41 ± 74.63 mm$^3$) compared with patients without cognitive impairment (mean 728.79 ± 77.82 mm$^3$; p < 0.001). This difference remained when age was used as a covariate (p < 0.001) and when the index gray-matter/total intracranial volume was compared instead of only comparing gray-matter values (p < 0.005). The interpretation of the statistical parametric maps showed that, regionally, MCI-V patients were characterized by shrinkage of gray-matter volume bilaterally at the temporal and frontal lobes, a posterior region including the right parietal-occipital and posterior cingulate region and the left cerebellum (table 2, fig. 1). The ROI analyses focused on the hippocampi and parahippocampal gyri further revealed a more atrophic bilateral parahippocampal gyrus (x, y, z: 36, –26, –25; cluster size 9,485 voxels, $P_{\text{FDR-corrected}}$: 0.026; x, y, z: –32, –10, –11; cluster size 8,326 voxels, $P_{\text{FDR-corrected}}$: 0.026) and right hippocampus (x, y, z: 27, –20, –12; cluster size 1,003 voxels, $P_{\text{FDR-corrected}}$: 0.030, fig. 2) in the MCI-V group.

Significant inverse correlations between subcortical hyperintensities and regional gray-matter volumes were observed among the MCI-V group in frontal and temporal regions such as the medial frontal gyrus (BA 9, x, y, z: –15, 43, 20; cluster size 1,524 voxels, and BA 6, x, y, z: –33, 15, 55; cluster size 2,246), the left posterior thalamus (x, y, z: –22, –27, 9; cluster size 1,218 voxels) and in right areas including the precentral and paracentral gyri (BA 4/5, x, y, z: 7, –35, 68; cluster size 8,273 voxels, and BA 6, x, y, z: 44, 0, 46; cluster size 2,256 voxels) as well as the right mesencephalic region (x, y, z: 10, –27, –4; cluster size 1,526 voxels; fig. 3). In patients without cognitive impairment, no negative correlations between gray-matter volume and subcortical hyperintensities were observed.

**Discussion**

In the present clinical study of 40 patients with first-ever lacunar infarction, 22 of them (55%) fulfilled the criteria of MCI-V. Accordingly, patients suffering from a lacunar stroke may constitute a relevant subgroup of the general vascular patients identified as MCI-V. The higher percentage of patients with lacunar infarction showing cognitive impairment in our series compared with previous reports in similar patients may be explained not only by the definition of cognitive impairment, but also by differences in the battery of neuropsychological tests used for the assessment of cognitive domains. In our study, cognitive function was assessed with a comprehensive and accurate battery of neuropsychological tests to maximize the homogeneity of our sample. It should be noted that published neuropsychological controls were used to determine the cutoff value for each neuropsychological test. This may be considered a limitation because, ideally,
Fig. 1. Cerebral horizontal slices displaying decreased gray-matter volumes in MCI-V relative to non-MCI-V patients (for anatomical localization of significant regions, see Table 2). Statistical parametric maps are represented according to neurological convention (left corresponding to the left hemisphere). The color bar represents t values derived from the voxel-based analysis. Clusters are scaled with the yellow-white regions being more significant than the red ones. Depicted results are representative of the group comparison but are displayed on a normalized brain image of a single subject.
**Fig. 2.** ROI analysis result showing reduced right hippocampus volume in MCI-V as compared to the group without cognitive impairment. See main text for precise anatomical localization of the significant cluster. Statistical parametric maps are represented according to neurological convention (left corresponding to the left hemisphere). The color bar represents t values derived from the voxel-based analysis. Clusters are scaled with the yellow-white regions being more significant than the red ones. Depicted results are representative of the group comparison but are displayed on a normalized brain image of a single subject.

**Fig. 3.** Significant negative correlations between subcortical ratings (Scheltens’ scale) and gray-matter volumes among MCI-V. See main text for precise anatomical localization of all significant clusters. Statistical parametric maps are represented according to neurological convention (left corresponding to the left hemisphere). The color bar represents t values derived from the voxel-based analysis. Clusters are scaled with the yellow-white regions being the ones showing the highest negative correlations. Depicted results are representative of the group comparison but are displayed on a normalized brain image of a single subject.
it would be better to use data from a control population matched to the study group in which the risk factor profile was known. In a lacunar infarction cohort of 200 patients, Yamamoto et al. [20] found cognitive impairment and dementia in 40 (20.5%) of cases. In that study however, the Clinical Dementia Rating Scale and Hasegawa’s Dementia Rating Scale Revised were used as measures of cognitive function and no neuropsychological evaluations were included. In other studies [3, 21] cognitive impairment in small-vessel disease patients have only been assessed with a general screening as MMSE. Loeb et al. [21] found that 23.1% of the patients with lacunar infarcts developed dementia after 4 years of follow-up. Although classical descriptions of clinical lacunar syndromes are presumed to imply preserved cognitive functioning [7], our findings add further evidence to the accumulating knowledge using formal neuropsychological testing indicating that the clinical manifestations of a first-ever lacunar infarct are frequently associated with some degree of neuropsychological impairment [8, 10, 22–24].

Despite the poor correlation between radiological and pathological findings observed in previous investigations [25], it seems feasible that most of the rating scores attributed to the subcortical nuclei (thalamus, putamen, globus pallidus, internal capsule) correspond to lacunar infarcts. In this regard, our findings would be consistent with recently published neuropathological and imaging data showing that lacunes in the thalamus and the basal ganglia strongly correlated with cognitive status [25–27], suggesting that cognitive deterioration in patients with lacunar infarcts may result from the disruption of subcortical-frontal circuits.

Using voxel-based morphometry to assess gray-matter atrophy, we were able to show gray-matter shrinkages in our cognitively impaired patients mainly affecting bilaterally the temporal lobes, parietal and frontal regions and the left cerebellum as well as bilaterally the parahippocampal gyri and the right hippocampus, although these latter structures only emerged when a hypothesis-driven ROI analysis restricted to these specific regions was performed. These findings might be interpreted as corroborating and extending findings from the functional neuroimaging literature on the remote effects of subcortical damage beyond the immediate area of infarction [28, 29]. Hence, in addition to the aforementioned subcortical abnormalities in the basal ganglia, our results indicate that regional gray-matter damage contributes to the cognitive picture of MCI-V. However, it should be noted that some of our findings might be related to particular characteristics of the operational criteria used to define MCI-V. Besides a typical subcortical cognitive pattern of brain dysfunction (e.g. executive function), a mild impairment of declarative memory was also required [1]. Because secondary memory is related to the medial and lateral temporal lobe integrity [30–32], the present findings of reduced volumes in these areas may be reflecting the specificity of the classification criteria. In this regard, further studies assessing anatomical correlates of vascular cognitive impairment based just on subcortical functions may show different results.

Recently, patients with lacunar infarction have shown a decrease in the N-acetyl-aspartate/creatine ratio of the centrum semiovale at a distance from the infarct in both the ipsilateral and contralateral hemispheres and this decrease has been related to a reduced cognitive capacity [10]. Moreover, MRI studies using manual delimitations of regional volumes reported hippocampal, frontal and cortical gray-matter atrophy as predictors of cognitive impairment [5, 6, 33, 34]. In agreement with previous studies [5, 35–37], we found significant correlations between gray-matter volume reduction in the frontal, parietal and temporal lobes, as well as in the thalamus and overall subcortical hyperintensities, especially in the basal ganglion region. In addition, correlations between scores of subcortical hyperintensities and gray-matter volumes were limited to the group of lacunar stroke patients with MCI-V.

With regard to quantification of white-matter hyperintensities, two limitations should be acknowledged. Firstly, a visual semiquantitative method based on T2-weighted and FLAIR sequences was only used. This method is probably less accurate than measuring white-matter high-signal volume. High correlations between both procedures have been reported [38, 39] but volume measurements have higher reliability [39] and sensitivity [38, 39]. In our study, volume measurements would have been inaccurate because T2*-weighted and FLAIR images had interslice gaps of 2.5 mm. Secondly, recent studies provided evidence that white-matter damage assessed by diffusion tensor imaging showed better correlations with cognitive function than T2-weighted or FLAIR sequences [40, 41]. However, this technique was not used in the present study. Thus, the use of diffusion tensor images could have led to the detection of further differences in white-matter damage observed in two groups that differed as a function of their cognitive profile. A further related limitation in white-matter quantification is inherent to the automatic segmentation procedure used by SPM. Specifically, lacunar infarcts and white-matter hyperintensities were found to be misclassified mostly as CSF due to their
intensity characteristics. However, these limitations may have little relevance for the gray-matter analysis.

Whether gray-matter volume reductions correspond to neuron loss or a specific neuropathological process in our patients cannot be determined by the methodological approach used in the present study. It is of note however that most brain regions we found to be atrophied in our MCI-V patients have also recently been reported to be affected in ‘nonvascular’ MCI patients [42–44]. This pattern of gray-matter loss in mild cognitive impairment is highly consistent with the course of neurofibrillary tangles across aging and Alzheimer’s disease [44] and has been evidenced in a voxel-based study mapping the rapid conversion of MCI to Alzheimer’s disease [45]. In that study, regions, such as the hippocampus, the inferior and middle temporal gyrus as well as the posterior cingulate and precuneus, that were found to be reduced among MCI-V in our report were the ones showing greater gray-matter loss in MCI patients evidencing rapid conversion to Alzheimer’s disease.

Additionally, in the recent literature, one report found that patients with vascular dementia exhibited neuron loss of the CA1 region comparable to that observed in Alzheimer’s disease [46], whereas other results indicate that the number of neurons is significantly reduced in Alzheimer’s disease as compared to ischemic vascular disease patients but that it correlates with MRI volumes of the structure [47]. Thus, despite the fact that evidence derived from close conditions suggests that it is possible that gray-matter atrophy in our study reflects neuronal loss or some type of neuropathological findings, future MRI studies combined with autopsy data are needed to clarify this issue.

In summary, our data provide evidence suggesting that a significant percentage of patients presenting clinically with a lacunar infarct may be identified as MCI-V patients. The MRI correlates that best explained cognitive performance among these patients were abnormalities found in the basal ganglion region as well as total gray-matter volume reductions but additional shrinkages in the hippocampus, lateral temporal and parietal cortices as well as in the cerebellum were also observed when compared to patients without cognitive dysfunction. The nature of the correlations found between cerebrovascular subcortical damage and gray-matter atrophy in these patients needs to be established in clinicopathological studies.

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