Lobar Distribution of Cerebral Microbleeds

The Rotterdam Scan Study

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Objective: To investigate the distribution of lobar microbleeds over the different lobes, taking into account lobar volume and clustering effects of multiple microbleeds.

Design: Population-based, cross-sectional analysis.

Setting: The Rotterdam Scan Study.

Participants: A total of 198 persons (age range, 61-95 years) with lobar microbleeds.

Main Outcome Measures: Distribution of microbleeds over different lobes.

Results: We found that lobar cerebral microbleeds occurred significantly more often in the temporal lobe, a region known to be more affected in cerebral amyloid angiopathy.

Conclusion: This study corroborates the presumed association of lobar microbleeds with cerebral amyloid angiopathy.

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CEREBRAL MICROBLEEDS (CMBs) can be detected with T2*-weighted gradient-echo magnetic resonance imaging (MRI) and are associated with presence and risk of intracerebral hemorrhage. Previous articles found that microbleeds in deep or infratentorial regions were associated with hypertension, whereas lobar microbleeds share risk factors with cerebral amyloid angiopathy (CAA). Little is known, however, about the spatial distribution of these lobar microbleeds. An imaging study of patients with CAA showed that microbleeds as well as intracerebral hemorrhage occurred more often in the temporal and occipital lobes, which fits autopsy studies describing a posterior predilection of vascular pathology in CAA.

Knowledge of the spatial distribution of lobar CMBs in the general population might contribute to our understanding of their pathophysiology and may corroborate the presumed association of lobar microbleeds with CAA.

To date, only 1 population-based study of elderly persons examined spatial distribution of lobar bleeds and found that microbleeds occur more often in the parietal lobe. However, merely counting the number of microbleeds per lobe might give a distorted interpretation because volumetric differences between lobes are not taken into account. Furthermore, in persons with multiple microbleeds, consecutive microbleeds tend to occur in proximity of a preceding bleed.

Therefore, in the population-based Rotterdam Scan Study, we investigated the spatial distribution of lobar microbleeds, taking into account the volume of the separate lobes and clustering effects of multiple microbleeds.

METHODS

SETTING

This study is based on the Rotterdam Scan Study. We previously described the prevalence and risk factors of cerebral microbleeds in a population of 1062 persons without dementia. Of these, 250 had, in total, 1151 microbleeds. Microbleeds that were located in the deep or infratentorial brain region were discarded from our present analysis, as we aimed to investigate the spatial distribution of lobar microbleeds, leaving 838 lobar microbleeds in 198 persons for the analyses.

BRAIN MRI

We performed a multisequence MRI protocol on a 1.5-T scanner (GE Healthcare, Milwaukee, Wisconsin). A custom-made, accelerated, 3-dimensional, T2*-weighted, gradient-
recalled echo sequence with high spatial resolution and long echo time was used for microbleed detection. The other sequences in the imaging protocol consisted of 3 high-resolution axial scans, ie, a T1-weighted sequence, a proton density–weighted sequence, and a fluid-attenuated inversion recovery sequence. Slice position of the T1- and T2*-weighted gradient-recalled echo scans was matched.

RATING OF CEREBRAL MICROBLEEDS

Microbleeds were defined as focal areas of very low signal intensity. All scans were reviewed by 1 of 2 trained raters, as described previously. In brief, they recorded the presence, number, and slice location of all microbleeds. Intraobserver and interobserver agreement was good, with k values of 0.87 and 0.85 respectively.

Subsequently, all microbleeds were manually labeled by a single trained rater using the Montreal Neurological Institute tool Display (http://www.bic.mni.mcgill.ca/ServicesSoftwareVisualization/HomePage).

ASSESSMENT OF LOBAR DISTRIBUTION OF MICROBLEEDS

For assessment of lobar distribution of microbleeds, we first created a template scan in which the lobes were labeled according to a slightly modified version of the segmentation protocol as described by Bodke et al into left and right frontal, parietal, temporal, and occipital lobes. Subsequently, we used validated nonrigid registration to map this template to each scan, in which microbleeds were manually labeled. By combining this lobar segmentation with the labeled microbleeds, we obtained the microbleed distribution per lobe.

STATISTICAL ANALYSIS

We analyzed the distribution of lobar microbleeds in 4 groups: (1) participants with lobar CMBs (with or without microbleeds located in a deep or infratentorial brain region); (2) participants with multiple lobar CMBs (>1 microbleeds with or without microbleeds located in a deep or infratentorial brain region); (3) participants with strictly lobar microbleeds (without microbleeds located in a deep or infratentorial brain region); and (4) multiple, strictly lobar CMBs (>1 lobar microbleeds without CMBs located in a deep or infratentorial brain region). These groups meet with varying degrees the criteria for the presumed underlying CAA pathology. A possible limitation of our study is misclassification according to the tendency of microbleeds to cluster. Furthermore, we also took into account lobar volumes when analyzing spatial distribution of microbleeds, and thus different a priori probabilities for microbleed occurrence. We found in the general population that lobar microbleeds show a predilection for the posterior brain regions, particularly the temporal lobes.

Some strengths of our study are its population-based setting, high response rate, and large sample size. Moreover, an important strength of our article compared with previous articles is that we took into account lobar volume when analyzing spatial distribution of microbleeds, and thus different a priori probabilities for microbleed occurrence. Furthermore, we also took into consideration the tendency of microbleeds to cluster.

A possible limitation of our study is misclassification of cerebral microbleeds, as small blood vessels and calcification may resemble cerebral microbleeds. However, mimics of cerebral microbleeds can usually be dis-

Table 1 presents the characteristics of the study population. The mean age was 72.5 years, and 96 (48.5%) were women. The Figure illustrates the spatial distribution of all lobar microbleeds. The CMBs were not uniformly distributed throughout the brain (P = .04). Table 2 shows the distribution of lobar microbleeds in all participants (n = 198) and in participants with multiple lobar (n = 81), strictly lobar (n = 134), and multiple strictly lobar microbleeds (n = 35). Most microbleeds were located in the temporal lobe, ie, 32.6% in participants with lobar microbleeds, 32.9% in participants with multiple lobar microbleeds, and 31.4% in participants with multiple strictly lobar microbleeds (after correction for random effects). Compared with the expected distribution based on the volume of the lobes, lobar cerebral microbleeds occurred significantly more often in the temporal (P < .001) and parietal lobes (P = .04). The CMBs occurred significantly less often than expected in the frontal lobe (P < .001). Moreover, temporal and parietal CMBs (Figure) did not appear to be uniformly distributed in these lobes, but rather appear primarily in the posterior part of the temporal and parietal lobes.

Similar results were found in participants with multiple lobar microbleeds and (multiple) strictly lobar microbleeds.

**Table 1.** Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>72.5 (8.3)</td>
</tr>
<tr>
<td>Women</td>
<td>96 (48.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>146.1 (19.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>79.6 (11.0)</td>
</tr>
<tr>
<td>Mild hypertension</td>
<td>97 (49.7)</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>48 (24.6)</td>
</tr>
<tr>
<td>Smoking, ever</td>
<td>151 (77.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (8.6)</td>
</tr>
<tr>
<td>Serum total cholesterol, mean (SD), mg/dL</td>
<td>214.7 (37.8)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mean (SD), mg/dL</td>
<td>54.4 (15.1)</td>
</tr>
<tr>
<td>APOE ε2 allele carrier</td>
<td>27 (14.3)</td>
</tr>
<tr>
<td>APOE ε4 allele carrier</td>
<td>69 (36.5)</td>
</tr>
<tr>
<td>Cortical infarct on MRI</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>Lacunar infarct on MRI</td>
<td>36 (18.2)</td>
</tr>
<tr>
<td>White matter lesions on MRI, median (IQR), mL</td>
<td>5.0 (2.4-10.8)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein cholesterol; IQR, interquartile range; MRI, magnetic resonance imaging.

SI conversion factors: To convert total and HDL cholesterol to millimoles per liter, multiply by 0.0259.

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regarded based on location and shape. Furthermore, as the high spatial resolution of our MRI sequence enabled us to distinguish the linear shape of sulcal vessels from the typical round or ovoid, blind-ending shape of CMBs, we believe that we did not label any more structures than there are microbleeds.

We found lesions preferentially in the temporal and parietal lobe but not in the occipital lobe, as has been described in previous studies that investigated the distribution of CMBs or amyloid burden in patients with CAA and AD. There may be 3 reasons for the absence of occipital predilection in our study. First, most studies that describe the distribution of CMBs or amyloid burden are done in patients with CAA or AD, whereas our study was done in the general elderly population. It may be that CMBs occur preferentially in occipital regions in patients with severe CAA, whereas persons with mild CAA do not share this predilection. Only one other population-based study assessed the lobar location of microbleeds and suggested that lobar microbleeds show a predilection for the parietal brain area; they also did not find an overrepresentation of CMBs in the occipital brain area. Second, although the evidence of the relationship between lobar CMBs and CAA is accumulating, we cannot exclude that some factor other than CAA might account for the distribution of CMBs in this general elderly population.

Lastly, differences across studies in the definition of the border between the occipital, parietal, and temporal lobes may play a role. Because there is no clear sulcal landmark between the 3 lobes except for the parieto-occipital sulcus, the definition between the occipital and parietal lobes is somewhat arbitrary. As we especially found a predilection to microbleeds in the surrounding

Figure. Sagittal (A) and axial (B) image of the distribution of all lobar microbleeds. Each spot represents a single microbleed (uniform size representation).

Table 2. Distribution of Lobar Cerebral Microbleeds

<table>
<thead>
<tr>
<th>Location</th>
<th>Lobar Microbleeds (n=198)</th>
<th>Multiple Lobar Microbleeds (n=81)</th>
<th>Strictly Lobar Microbleeds (n=134)</th>
<th>Multiple Strictly Lobar Microbleeds (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>40.6% 237/28.3% 0.70</td>
<td>28.8% 0.71 78/28.5% 0.70 51</td>
<td>28.5% 1.31 55/31.4% 1.38</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>22.8% 273/32.6% 1.43</td>
<td>32.8% 1.44 82/29.8% 1.31 55</td>
<td>29.8% 1.38 55/31.4% 1.38</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>22.6% 212/25.8% 1.12</td>
<td>24.3 1.08 77/28.1% 1.24 46</td>
<td>28.1% 1.24 46/26.3% 1.16</td>
<td></td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>13.9% 116/13.8% 0.99</td>
<td>14.0 1.01 37/13.8% 0.97 23</td>
<td>13.5% 0.97 23/13.5% 0.94</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>838/721</td>
<td>721/274</td>
<td>175/721</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: O/E, observed divided by expected.

a Lobar microbleeds with or without microbleeds in a deep or infratentorial region (median, 1; interquartile range, 1-3).
b More than 1 lobar microbleed with or without microbleeds in a deep or infratentorial region (median, 4; interquartile range, 2-8).
c Lobar microbleeds without microbleeds in a deep or infratentorial region (median, 1; interquartile range, 1-2).
d Small differences in the number of participants with strictly lobar microbleeds between this article and our previous article2 are caused by differences in labeling procedures (automatic labeling vs visual rating scale).
e More than 1 lobar microbleed without microbleeds in a deep or infratentorial region (median, 2; interquartile range, 2-5).
f Percentages corrected for clustering effects by added random effects for within subject variation.
g P < .05 for observed vs expected distribution, based on lobar volume percentages.
h P < .01 for observed vs expected distribution, based on lobar volume percentages.

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areas of these borders, the setting of the border may influence lobar predilection.

Our finding that microbleeds are found preferentially in the posterior regions of the brain and are underrepresented in the frontal lobes is consistent with previous studies that described the lobar distribution of microbleeds.\textsuperscript{3,6,18} The only population-based study that studied the lobar location of microbleeds suggested that lobar microbleeds show a predilection for the parietal brain area.\textsuperscript{6} However, the authors did not correct for lobar volume and therefore their results may have been driven by volume differences between the lobes.\textsuperscript{6} Only one clinical study in patients with CAA took lobar volume into account in the same way as we did and found lesions preferentially in the temporal and occipital lobes.\textsuperscript{3}

The posterior predilection of microbleeds in CAA has been hypothesized to relate to pattern of β-amyloid accumulation. It is thought that decreased pulse pressure and interstitial fluid pumping may lead to lower clearance of vascular β-amyloid.\textsuperscript{10} In the posterior lobes, these processes may be most clearly reduced, resulting in more vascular pathology and, consequently, more microbleeds.

Cerebral amyloid angiopathy–related CMs are thought to be multiple and to occur primarily in lobar brain regions.\textsuperscript{2,12} In our study, the distribution pattern of lobar CMs in participants with multiple lobar CMs was similar to the distribution in participants with multiple, strictly lobar CMs. Moreover, we found, on average, more CMs per person in the group with multiple lobar CMs compared with the group with multiple, strictly lobar CMs (Table 1). Taken together, this suggests that multiple lobar CMs might be as indicative of CAA as multiple, strictly lobar CMs.

In conclusion, our findings show that lobar microbleeds occur more often in the temporal lobe and are underestimated in the frontal lobe. This corroborates the presumed association of lobar microbleeds with CAA in the general population.

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Author Contributions: Drs Mesker and Poels contributed equally to the study. Study concept and design: Hofman and Breteler. Acquisition of data: Mesker, Poels, Ikram, and Vrooman. Analysis and interpretation of data: Mesker, Poels, Ikram, Vernooij, van der Lugt, and Breteler. Drafting of the manuscript: Mesker, Poels, and Ikram. Critical revision of the manuscript for important intellectual content: Vernooij, Hofman, Vrooman, van der Lugt, and Breteler. Statistical analysis: Mesker, Poels, and Ikram.

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