Cortical microinfarcts on 3T MRI: Clinical correlates in memory-clinic patients

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Abstract

Background: This is the first study to assess cerebral microinfarcts (CMIs) on 3 tesla (3T) magnetic resonance imaging (MRI) in a memory clinic population.

Methods: We included 238 consecutive patients (aged 72.5 ± 9.1 years) from a memory clinic in Singapore. All patients underwent extensive neurological and neuropsychological testing and 3T MRI on the same day. Cortical CMI rating criteria were adapted from a previous study on 7T MRI. We analyzed the frequency and association of cortical CMIs with demographic, clinical, cognition, and other MRI findings.

Results: Seventy-five patients (32%) had cortical CMIs (median 1, range 1–43). Patients with CMIs showed worse cognitive functioning on MMSE, and in the domains of language and visuoconstruction. The presence of CMIs was related to other markers of small vessel disease, but most strongly larger cortical infarcts. Patients with CMIs were more often diagnosed with vascular dementia.

Conclusion: Cortical CMIs on 3T MRI are a novel marker of cerebrovascular disease in dementia.

Keywords: Dementia; Small vessel disease; Microinfarcts; Atrophy; Alzheimer’s disease; Memory clinic population; MRI

1. Introduction

Cerebrovascular disease is an important contributor to cognitive decline and dementia in the aging population [1]. On autopsy, vascular pathology is found in most patients with clinically diagnosed dementia [2]. This vascular pathology frequently involves the cerebral small vessels. In vivo, signs of cerebral small vessel disease (SVD) on conventional magnetic resonance imaging (MRI) include white matter hyperintensities (WMHs), lacunes, and microbleeds [3,4]. However, these conventional MRI markers do not fully capture the burden of SVD in cognitive decline and dementia. In this context, cerebral microinfarcts (CMIs) have attracted increasing attention [5]. CMIs are regarded as the most widespread form of brain infarction and hence could play an important role in cognitive decline and dementia [5,6]. A systematic review with a pooled analysis of autopsy studies showed that CMIs are observed in 24% of nondemented older subjects, in 43% of patients with Alzheimer’s disease (AD), and in 62% of patients with vascular dementia (VaD) [6]. Moreover, autopsy studies

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link CMIs to ante-mortem cognitive decline, also independent of Alzheimer pathology [7,8]. Recently, it has been shown that cortical CMIs can be visualized in vivo using high-field 7 tesla (7T) MRI [9], and that these CMIs can also be detected on 3T MRI scans [9,10].

In this study, we examined the frequency of cortical CMIs on 3T MRI in a multiethnic Asian memory clinic population with a high vascular burden from Singapore. Furthermore, we investigated their association with vascular risk factors, cognition, and conventional SVD markers.

2. Methods

2.1. Study population

This study involves patients from the National University Health System Memory Ageing and Cognition Centre Cohort recruited from the memory clinics of the National University Hospital and St. Luke’s Hospital in Singapore. Patients were assigned diagnoses by the memory clinic physician before study entry. Five diagnostic categories were eligible for inclusion in this study, which were based on the referral diagnosis. (1) “No cognitive impairment” (NCI): this diagnosis was given to patients visiting the memory clinic who had no objective cognitive impairment on formal neuropsychological tests, or functional loss. (2) “Cognitive impairment no dementia” (CIND), with (2a) or without (2b) a history of stroke was diagnosed in patients who were impaired in at least one cognitive domain of a formal neuropsychological test battery, but did not meet the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition criteria for dementia. Subjects were considered to have failed a test at the memory clinic assessment if they scored lower than age and education-adjusted 1.5 standard deviations (SDs) below established normal means on individual tests. Failure in at least half of the tests in a domain was considered as impairment in that domain. Ischemic stroke was assessed based on medical history, and confirmed by neuroimaging. Patients with a history of hemorrhagic stroke were excluded. (3) AD was diagnosed in accordance with the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINCDS-ADRDA) criteria [11]. (4) VaD was diagnosed in accordance with the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria [12]. Patients with other diagnoses, or significant neurological comorbidities (e.g. Parkinson’s disease), or loss of functional independence (modified Rankin Scale >4), were not included in the cohort.

All study patients underwent a standardized extensive physical, clinical, and neuropsychological assessment (distinct from the initial assessments at the memory clinics before study enrolment) and 3T MRI, all on the same day, at the National University of Singapore. For the present study, we selected all consecutive patients (N = 251) based on the above-mentioned criteria who were admitted in the period between December 2010 and September 2013. Of these 251 subjects, 13 were excluded because of missing T1-, fluid-attenuated inversion recovery (FLAIR), or T2-weighted images, resulting in a total of 238 patients included in the current analyses.

Ethical approval for this study was obtained from the National Healthcare Group Domain-Specific Review Board (DSRB). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained, in the preferred language of the patients, by bilingual study coordinators before recruitment into the study. Consent for patients lacking capacity was provided by their legal representative, as allowed by the DSRB.

The vascular risk profile was recorded for each patient, which included: (a) diabetes mellitus: defined as a history or previous diagnosis of diabetes mellitus, or the use of glucose-lowering medication; (b) hypertension: defined as a history or previous diagnosis of hypertension, or the use of antihypertensive medication; (c) hyperlipidemia: defined as a history or previous diagnosis of hyperlipidemia, or the use of lipid-lowering medication; (d) cardiovascular disease: defined as a previous diagnosis of myocardial infarction, congestive heart failure, atrial fibrillation, or intervention procedures such as angioplasty, or stenting.

2.2. Cognitive assessment

The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) and a formal neuropsychological battery, previously validated for elderly Singaporeans [13], were administered. Seven cognitive domains, with the following subtests were assessed: executive function (Frontal Assessment Battery [14], Maze task [15]; attention (digit span, visual memory span [16], auditory detection [17]); language (Boston naming test [18], verbal fluency [19]); verbal memory (word list recall [20], story recall); visual memory (picture recall, Wechsler memory scale-revised visual reproduction [16]); visuoconstruction (Wechsler memory scale-revised visual reproduction copy task [16], clock drawing [21], Wechsler adult intelligence scale-revised subtest of block design [22]); and visuomotor speed (symbol digit modality test [23], digit cancellation [24]).

The assessment was administered according to the patient’s preferred language (i.e. English, Mandarin, or Malay). All individual raw test scores were transformed to standardized z-scores using the means and SDs of the whole group (N = 238). z-Scores for each domain were calculated by summing up the z-scores of each subtest under that domain, divided by number of subtests. Domain-specific z-scores were used to compute a final composite z-score.

2.3. MRI protocol

All scans were acquired on a 3T Siemens Magnetom Trio Tim system, with a 32-channel receiver head-coil, at the
Clinical Imaging Research Centre of the National University of Singapore. The standardized protocol included a three-dimensional (3D) T1-weighted (1.0 × 1.0 × 1.0 mm³ voxels; repetition time (TR) 2300 ms; echo time (TE) 1.9 ms; inversion time (TI) 900 ms; flip angle 9°; matrix 256 × 256), a 2D multislice T2-weighted (1.0 × 1.0 × 3.0 mm³ voxels; TR 3000 ms; TE 10.1 ms; matrix 247 × 256), a 2D multislice FLAIR (1.0 × 1.0 × 3.0 mm³; TR 9000 ms; TE 82 ms; TI 2500 ms; matrix 232 × 256), and a 2D multislice T2*-weighted image (1.0 × 1.0 × 1.5 mm³ voxels; TR 27 ms; TE 20 ms; flip angle 15°; matrix 192 × 256), for the assessment of markers of SVD. Furthermore, a 3D time of flight MR angiography was used to determine the presence of intracranial stenosis (0.8 × 0.8 × 0.8 mm³ voxels; TR 22 ms; TE 3.4 ms; flip angle 20°; matrix 218 × 256).

2.4. MRI rating

The rating criteria for cortical CMIs were based on a previous study that included histological validation (Fig. 1) [9]. In that study 15 CMIs were found on 7T in 6/22 subjects. A proportion (4/15 = 27%) of those CMIs in two subjects could also be visualized on 3T MRI, especially on the 3D T1-weighted image (Fig. 2) [9]. Based on those results we defined rating criteria for cortical CMIs on 3T for the present study as hypointense on T1, <5 mm in diameter, restricted to the cortex, perpendicular to the cortical surface, and distinct from perivascular spaces. The location of a hypointense cortical lesion found on T1 was explored on FLAIR and T2-weighted images. The lesion was rated as a definite cortical CMI if the location was hyperintense or isointense on FLAIR and T2. The lesion was discarded as a CMI if at the same location a hypointense signal was found on FLAIR or T2, indicating the T1 hypointense lesion was either due to a hemorrhagic lesion, a vessel, or an artifact (Fig. 3). Possible cortical CMIs in tissue affected by larger cortical infarcts were discarded.

The reliability of these 3T rating criteria was tested, using scans from the database of a previous study [25]. From this data set, 3T scans were selected based on the earlier 7T evaluation by a single rater (SvV). The validation set included 12 subjects with CMIs on the 7T MR images with appropriate 3T MR images, and 11 subjects without CMIs on 7T. Cortical CMIs were identified by one visual rater (SvV) on the 3T FLAIR, T1, and T2 images of these 23 subjects, using the 3T rating criteria as described previously blinded to the 7T results and clinical information. Identified cortical CMI locations on 3T were then compared with the 7T FLAIR, T1, and T2 of the same subject to verify the presence of a CMI. It was found that 7/8 (88%) of the identified cortical CMI locations on 3T in these subjects, matched with CMIs on the 7T MRI. One of the eight CMI locations proved to be a sulcus on the higher resolution 7T images. The seven CMIs identified on 3T represented 27% of the total number of CMIs (N = 26) identified by the same rater on the 7T MRI scans in this data set.

Fig. 1. A cortical microinfarct on 7 tesla (7T) post-mortem magnetic resonance imaging (MRI) and histology, in the brain of an 83-year-old male with pathologically confirmed vascular dementia. A presumed cortical microinfarct (arrow) was identified on post-mortem 7T three-dimensional (3D) T1 (A; 0.4 mm isotropic voxels), which was less conspicuous on post-mortem 7T 3D fluid-attenuated inversion recovery (FLAIR) (B; 0.4 mm isotropic voxels). After the sampling and histological verification of the area indicated with the white square, this cortical lesion was verified as a microinfarct (C; hematoxylin and eosin stain). The adjacent section, immunostained against glial fibrillary acidic protein, confirmed the presence of gliosis (D).
Cortical CMIs were assessed by one experienced rater (SvV). The intrarater agreement for cortical CMIs, as assessed with the intraclass correlation coefficient (ICC) on a representative subset of 3T MRI scans, was excellent (ICC = 0.97) and good, as assessed with Dice’s similarity coefficient (≈0.65) [26]. CMI size was estimated on T1 along the longest axis of the lesion.

Microbleeds were assessed by one rater (SH) on T2*-weighted images using the Brain Observer Micro-Bleeds Scale criteria. The intrarater agreement was excellent (ICC = 0.89).

The presence of any large cortical infarct (>5 mm), any cerebellar infarct, or any subcortical infarct (i.e., a large subcortical infarct and/or a lacunar infarct) was assessed on FLAIR and T1, by two independent raters (SH, NW). Subsequently, both infarct and WMH volume were segmented manually (NW) on FLAIR and T1-weighted images using an in-house developed tool based on MeVisLab (MeVis Medical Solutions AG, Bremen, Germany) [27,28].

Total brain volume and intracranial volume were quantified using a unified segmentation approach as implemented.
in Statistical Parametric Mapping 12b [29]. WMH and infarct volumes were censored in the segmentation using a mask based on the manual delineation of WMHs and infarcts, but were considered as part of total brain volume. Intracranial volume was calculated using total brain volume, intraventricular, and extracortical cerebrospinal fluid volume.

The presence of intracranial stenosis, assessed by one rater (SH) on the time of flight, was defined as a narrowing exceeding 50% of the luminal diameter of the vertebral, basilar, internal carotid, posterior cerebral, middle cerebral, or anterior cerebral artery.

All MRI ratings were performed blinded to clinical information and without knowledge of cortical CMI ratings.

2.5. Statistical analyses

Differences between patients without and with ≥1 or ≥3 (upper tertile) cortical CMIs on MRI were assessed using independent t-tests for continuous variables, chi-square tests for dichotomous variables, and Mann-Whitney U tests for nonparametric data. Linear regression was used for the association of cortical CMIs (determinant) with MMSE, MoCA, cognitive domains, the composite z-score, and diagnosis (outcomes), adjusted for age, gender, and level of education. Linear regression was used for the association of cortical CMIs (determinant) with total brain volume and WMH volume (log transformed) (outcomes), adjusted for age, gender, and intracranial volume. The B from the linear regression models reflects a “mean difference” between patients with cortical CMIs and those without cortical CMIs on MRI. Binary logistic regression was used for the association of cortical CMIs with vascular risk factors (except BMI, which was assessed using linear regression), the presence of intracranial stenosis, (subcortical and cortical) infarcts, (deep and lobar) microbleeds, and the presence of confluent WMHs, adjusted for age and gender. Dummy variables were constructed for the analysis, using chi-square tests, of diagnosis in relation to cortical CMIs. P-values <.05 were regarded as statistically significant. All analyses were performed using IBM SPSS Statistics, version 20.0.

3. Results

3.1. Demographics and vascular risk factor profile

The mean age of the 238 patients in this study was 72.5 ± 9.1 years (range 50–95), including 117 (49%) men. Demographic and vascular risk factor profile characteristics of patients with and without cortical CMIs on MRI are presented in Table 1. Seventy-five patients (32%) had cortical CMIs (Fig. 3), ranging between 1 and 43 CMIs, with a median of 1. Of the patients with cortical CMIs, 39 (52%) had one, 11 (15%) had two, and 25 (33%) had three or more cortical CMIs (in those with ≥3 CMIs: median 5, range 3 and 43). Median size of CMIs was 3 mm, only 8% was larger than 3 mm. Cortical CMIs were found throughout the brain, with a slight predilection for parietal cortical areas (Supplementary Fig. 1). The presence of cortical CMIs was not related to age, gender, race, or level of education. The presence of CMIs was associated with hyperlipidemia, a history of stroke, and cardiovascular disease, but not with other vascular risk factors.

3.2. Cognitive profile

The association of cortical CMIs with cognition is presented in Table 2. The presence of cortical CMIs was associated with lower MMSE score and a lower overall composite z-score, and worse performance on the specific domains, including language and visuoconstruction. The
regression analyses, adjusted for age, gender, and level of education. z-Scores were based on the mean and SDs of the whole patient group (N = 238).

Cortic profiles

Patients without CMIs on MRI (N = 163) | Patients with CMIs (N = 75) | Patients with multiple (≥3) CMIs (N = 25) |
---|---|---|
**P-value** | **OR (95% CI)** | **OR (95% CI)** |

### Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without CMIs</th>
<th>With CMIs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>72.5 ± 9.2</td>
<td>72.4 ± 9.0</td>
<td>.976</td>
</tr>
<tr>
<td>Gender (N male)</td>
<td>76 (47)</td>
<td>41 (55)</td>
<td>.249</td>
</tr>
<tr>
<td>Race (N Chinese)*</td>
<td>130 (78)</td>
<td>55 (73)</td>
<td>.298</td>
</tr>
<tr>
<td>Level of education†</td>
<td>1 [0–3]</td>
<td>1 [0–3]</td>
<td>.960</td>
</tr>
</tbody>
</table>

### Vascular risk factor profile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without CMIs</th>
<th>With CMIs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>14 (9)</td>
<td>10 (13)</td>
<td>.312</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>5 (3)</td>
<td>2 (3)</td>
<td>.504</td>
</tr>
<tr>
<td>Body mass index (BMI) (five missing)</td>
<td>23.7 ± 3.7</td>
<td>24.6 ± 4.6</td>
<td>.118</td>
</tr>
<tr>
<td>Hypertension</td>
<td>120 (74)</td>
<td>60 (80)</td>
<td>.304</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>56 (34)</td>
<td>34 (45)</td>
<td>.104</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>103 (63)</td>
<td>65 (87)</td>
<td>.000</td>
</tr>
<tr>
<td>History of stroke†</td>
<td>53 (33)</td>
<td>39 (52)</td>
<td>.005</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>25 (15)</td>
<td>28 (37)</td>
<td>.000</td>
</tr>
</tbody>
</table>

### Abbreviations

CMI, cerebral microinfarcts; MRI, magnetic resonance imaging; OR, odds ratio; CI, confidence interval; n/a, not available.

NOTE. Data are presented as mean ± standard deviation, number (percentage), or median [range].

Bold text indicates P < .05.

*Chinese (N = 185), Malay (N = 33), Indian (N = 15), mixed (N = 2), others (N = 3).

^NIl (N = 52), primary (N = 88), secondary (N = 69), tertiary (N = 28).

^Based on self-reported stroke. Odds ratio in binary logistic regression, adjusted for age and gender, compared with patients without CMIs.

^Mean difference in BMI between groups, adjusted for age and gender.

The presence of ≥3 cortical CMIs was also associated with impaired executive function.

### 3.3. MRI findings

The association of cortical CMIs with other MRI findings is presented in Table 3.

The presence of cortical CMIs was associated with the presence of both large cortical and subcortical infarcts, and both deep and lobar microbleeds. In patients with a large cortical infarct, cortical CMIs were not always restricted to the same hemisphere as the infarct. The relation between cortical CMIs with hyperlipidemia and cardiovascular disease did not alter when we adjusted for presence of large cortical infarcts.

The presence of cortical CMIs was associated with smaller brain volume, and larger WMH volume. The association of the presence of cortical CMIs with brain volume did not alter when we subsequently adjusted for WMH volume, presence of infarcts, or presence of microbleeds.

The presence of cortical CMIs was associated with the presence of any intracranial stenosis. Of note, the location of the CMI and the stenosis appeared to be interrelated. Cortical CMIs in the right middle cerebral artery (MCA) territory were more common in patients with a right MCA stenosis (patients with a right MCA stenosis, presence of any intracranial stenosis).

### Table 2

Cognitive profile

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without CMIs</th>
<th>With CMIs (N = 75)</th>
<th>B (95% CI)</th>
<th>P-value</th>
<th>With CMIs (N = 25)</th>
<th>B (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>21.0 ± 6.2</td>
<td>19.5 ± 5.9</td>
<td>-1.49 [-2.89; -0.08]</td>
<td>.038</td>
<td>18.8 ± 6.2</td>
<td>-2.17 [-4.37; 0.04]</td>
<td>.054</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>16.5 ± 7.2</td>
<td>15.2 ± 6.9</td>
<td>-1.38 [-2.96; 0.20]</td>
<td>.086</td>
<td>14.2 ± 6.2</td>
<td>-2.19 [-4.63; 0.25]</td>
<td>.078</td>
</tr>
<tr>
<td>Composite z-score (12 missing)</td>
<td>0.08 ± 1.05</td>
<td>-0.17 ± 0.10</td>
<td>-0.20 [-0.42; 0.01]</td>
<td>.067</td>
<td>-0.37 ± 0.79</td>
<td>-0.38 [-0.74; -0.03]</td>
<td>.036</td>
</tr>
<tr>
<td>Executive function (seven missing)</td>
<td>0.06 ± 1.00</td>
<td>-0.13 ± 1.00</td>
<td>-0.18 [-0.41; 0.05]</td>
<td>.133</td>
<td>-0.36 ± 1.05</td>
<td>-0.39 [-0.76; -0.01]</td>
<td>.042</td>
</tr>
<tr>
<td>Attention (six missing)</td>
<td>0.03 ± 1.00</td>
<td>-0.07 ± 1.02</td>
<td>-0.11 [-0.34; 0.13]</td>
<td>.375</td>
<td>-0.19 ± 1.06</td>
<td>-0.21 [-0.59; 0.17]</td>
<td>.282</td>
</tr>
<tr>
<td>Language (seven missing)</td>
<td>0.09 ± 1.04</td>
<td>-0.21 ± 0.89</td>
<td>-0.28 [-0.53; -0.04]</td>
<td>.023</td>
<td>-0.44 ± 0.62</td>
<td>-0.48 [-0.87; -0.09]</td>
<td>.017</td>
</tr>
<tr>
<td>Verbal memory (10 missing)</td>
<td>0.05 ± 1.05</td>
<td>-0.11 ± 0.88</td>
<td>-0.13 [-0.37; 0.10]</td>
<td>.268</td>
<td>-0.24 ± 0.78</td>
<td>-0.21 [-0.59; 0.17]</td>
<td>.273</td>
</tr>
<tr>
<td>Visual memory (nine missing)</td>
<td>0.07 ± 1.06</td>
<td>-0.15 ± 0.84</td>
<td>-0.21 [-0.45; 0.03]</td>
<td>.086</td>
<td>-0.34 ± 0.55</td>
<td>-0.37 [-0.77; 0.02]</td>
<td>.063</td>
</tr>
<tr>
<td>Visuoconstruction (nine missing)</td>
<td>0.10 ± 1.03</td>
<td>-0.21 ± 0.89</td>
<td>-0.30 [-0.52; -0.08]</td>
<td>.008</td>
<td>-0.44 ± 0.77</td>
<td>-0.51 [-0.87; -0.15]</td>
<td>.005</td>
</tr>
<tr>
<td>Visuomotor speed (eight missing)</td>
<td>0.07 ± 1.06</td>
<td>-0.15 ± 0.83</td>
<td>-0.19 [-0.40; 0.01]</td>
<td>.067</td>
<td>-0.27 ± 0.87</td>
<td>-0.25 [-0.60; 0.09]</td>
<td>.153</td>
</tr>
</tbody>
</table>

### Abbreviations

CMI, cerebral microinfarcts; MRI, magnetic resonance imaging; CI, confidence interval.

NOTE. Data are presented as mean ± standard deviation (SD). B: Mean difference between patients with cortical CMIs and patients without, from linear regression analyses, adjusted for age, gender, and level of education. z-Scores were based on the mean and SDs of the whole patient group (N = 238).
Table 3
MRI findings

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients without CMIs on MRI (N = 163)</th>
<th>Patients with CMIs (N = 75) B [95% CI]</th>
<th>P-value</th>
<th>Patients with multiple (≥3) CMIs (N = 25) B [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume (ml) (two missing)</td>
<td>1434 ± 137</td>
<td>1459 ± 152</td>
<td>.506</td>
<td>1497 ± 166</td>
<td>.298</td>
</tr>
<tr>
<td>Brain volume (ml) (two missing)</td>
<td>918 ± 114</td>
<td>897 ± 109</td>
<td>.001</td>
<td>905 ± 117</td>
<td>.017</td>
</tr>
<tr>
<td>WMH volume (ml) (four missing)</td>
<td>15.4 ± 16.7</td>
<td>21.6 ± 21.1</td>
<td>.008</td>
<td>27.8 ± 26.9</td>
<td>.035</td>
</tr>
<tr>
<td>Intracranial stenosis (nine missing)</td>
<td>31 (20)</td>
<td>24 (34)</td>
<td>.027</td>
<td>11 (46)</td>
<td>.009</td>
</tr>
<tr>
<td>Presence of infarcts</td>
<td>56 (34)</td>
<td>48 (65)</td>
<td>.000</td>
<td>21 (84)</td>
<td>.000</td>
</tr>
<tr>
<td>Cortical infarcts</td>
<td>12 (7)</td>
<td>27 (36)</td>
<td>.000</td>
<td>18 (72)</td>
<td>.000</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>42 (26)</td>
<td>33 (44)</td>
<td>.009</td>
<td>11 (44)</td>
<td>.163</td>
</tr>
<tr>
<td>Presence of microbleeds (four missing)</td>
<td>83 (51)</td>
<td>52 (72)</td>
<td>.004</td>
<td>21 (84)</td>
<td>.005</td>
</tr>
<tr>
<td>Deep microbleeds</td>
<td>28 (17)</td>
<td>25 (35)</td>
<td>.006</td>
<td>10 (40)</td>
<td>.017</td>
</tr>
<tr>
<td>Lobar microbleeds</td>
<td>70 (43)</td>
<td>45 (63)</td>
<td>.009</td>
<td>19 (76)</td>
<td>.003</td>
</tr>
<tr>
<td>Presence of WMHs* (one missing)</td>
<td>101 (62)</td>
<td>56 (75)</td>
<td>.044</td>
<td>21 (84)</td>
<td>.037</td>
</tr>
</tbody>
</table>

Abbreviations: CMI, cerebral microinfarcts; WMH, white matter hyperintensities; OR, odds ratio; MRI, magnetic resonance imaging; CI, confidence interval.

NOTE. Data are presented as mean ± standard deviation, or number (percentage). B: mean difference between patients with cortical CMIs and patients without, from linear regression analyses, adjusted for age, gender, and intracranial volume. Odds ratio in binary logistic regression, adjusted for age and gender, compared with patients without CMIs.

*Presence of WMHs is defined as beginning confluence or large confluent area, on Fazekas scale.

1Based on the log transformed WMH volume.

N = 16; 50% CMIs in right MCA territory; patients without a right MCA stenosis, N = 213; 17% CMIs in right MCA territory; P = .001). The same was true for the left MCA stenosis (patients with a left MCA stenosis, N = 14; 36% CMIs in left MCA territory; patients without a left MCA stenosis, N = 215; 12% CMIs in left MCA territory; P = .010).

The association of the presence of cortical CMIs with MMSE was independent of the presence of infarcts, attenuated after adjusting for WMH volume, the presence of microbleeds, and after adjustment for brain volume (as percentage of intracranial volume), a marker for brain atrophy. The association of the presence of cortical CMIs with the domain language was independent of the presence of infarcts and microbleeds, and attenuated after adjusting for WMH volume, and after adjustment for brain volume. The association of the presence of cortical CMIs with the domain visuoconstruction was independent of the presence of infarcts, microbleeds, and WMH, and attenuated after adjustment for brain volume (Table 4).

3.4. Clinical diagnosis

The presence of cortical CMIs was linked to the assigned referral diagnoses (Supplementary Table 1). Patients with cortical CMIs on MRI were less often diagnosed with NCI (0.27 [0.09; 0.85] P = .025) or CIND without stroke (0.34 [0.12; 0.92] P = .033), whereas patients with cortical CMIs were more often diagnosed with VaD (2.86 [1.17; 6.99] P = .021), compared with patients without cortical CMIs (Supplementary Table 1).

4. Discussion

This study showed that cortical CMIs are a common finding on 3T MRI in a memory clinic population. The presence of CMIs was associated with several distinct clinical features, including reduced performance in the domains of

Table 4
Association of cortical CMIs with cognition, adjusted for other MRI markers

<table>
<thead>
<tr>
<th>MRI markers included in the model</th>
<th>B (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (in points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMIs alone</td>
<td>−1.49 [−2.89; −0.08]</td>
<td>.038</td>
</tr>
<tr>
<td>CMIs + presence of infarcts</td>
<td>−1.61 [−3.07; −0.15]</td>
<td>.031</td>
</tr>
<tr>
<td>CMIs + WMH volume</td>
<td>−1.22 [−2.63; 0.18]</td>
<td>.087</td>
</tr>
<tr>
<td>CMIs + presence of microbleeds</td>
<td>−1.34 [−2.79; 0.11]</td>
<td>.070</td>
</tr>
<tr>
<td>CMIs + brain volume (% ICV)</td>
<td>−0.68 [−2.00; 0.65]</td>
<td>.015</td>
</tr>
<tr>
<td>Language (z-score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMIs alone</td>
<td>−0.28 [−0.53; −0.04]</td>
<td>.023</td>
</tr>
<tr>
<td>CMIs + presence of infarcts</td>
<td>−0.28 [−0.53; −0.02]</td>
<td>.034</td>
</tr>
<tr>
<td>CMIs + WMH volume</td>
<td>−0.24 [−0.49; 0.01]</td>
<td>.057</td>
</tr>
<tr>
<td>CMIs + presence of microbleeds</td>
<td>−0.27 [−0.52; −0.02]</td>
<td>.038</td>
</tr>
<tr>
<td>CMIs + brain volume (% ICV)</td>
<td>−0.15 [−0.38; 0.08]</td>
<td>.196</td>
</tr>
<tr>
<td>Visuoconstruction (z-score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMIs alone</td>
<td>−0.30 [−0.52; −0.08]</td>
<td>.008</td>
</tr>
<tr>
<td>CMIs + presence of infarcts</td>
<td>−0.26 [−0.49; −0.03]</td>
<td>.027</td>
</tr>
<tr>
<td>CMIs + WMH volume</td>
<td>−0.26 [−0.48; −0.04]</td>
<td>.019</td>
</tr>
<tr>
<td>CMIs + presence of microbleeds</td>
<td>−0.28 [−0.51; −0.05]</td>
<td>.015</td>
</tr>
<tr>
<td>CMIs + brain volume (% ICV)</td>
<td>−0.18 [−0.38; 0.03]</td>
<td>.086</td>
</tr>
</tbody>
</table>

Abbreviations: CMI, cerebral microinfarcts; MRI, magnetic resonance imaging; CI, confidence interval; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities; ICV, intracranial volume.

NOTE. B: mean difference between patients with cortical CMIs and patients without, from linear regression analyses, adjusted for age, gender, level of education, and for each of the individual MRI marker indicated in the corresponding row.
language and visuoconstruction, domains that are not typically related to other MRI markers of vascular disease. On MRI, the presence of cortical CMIs was related to markers of SVD and large vessel disease.

Until recently, cortical CMIs could not be visualized on MRI, giving rise to the term “the invisible lesion” [5]. Recently, it was shown that cortical CMIs can be visualized with 7T MRI, but also with 3T MRI [9]. In this study we show that CMIs are a common finding on 3T MRI scans from a memory clinic population. This is important because 3T is more widely available than 7T, allowing a more widespread evaluation of the clinical relevance of CMIs in the context of aging, cerebrovascular disease, and dementia in future clinical studies. In the present cohort, cortical CMIs were more common in patients with dementia (36%) compared with patients without dementia (27%), which is in line with neuropathological findings [6] and a previous 7T MRI study [30]. It should be acknowledged, however, that 3T MRI only detects the larger CMIs. Neuropathological studies report that sizes of CMIs vary between 50 μm and 5 mm [6]. The vast majority of CMIs that are captured on 3T MRI are 2–3 mm. Hence, these CMIs on MRI are likely to represent only a small fraction of the largest lesions from a much larger underlying total CMI burden. The same applies, albeit to a lesser extent, for 7T, as again only the larger CMIs are detected. Indeed, estimates from neuropathological studies indicate that CMI counts are much higher than observed in the present study [31]. Nevertheless, as shown here, the CMIs that are detected by MRI do have important clinical correlates.

Of the demographic and vascular risk factors examined in this study, only hyperlipidemia, a history of stroke, and a history of cardiovascular disease were associated with the presence of cortical CMIs. Relatively few autopsy studies have systematically examined the relation between CMIs and demographic or vascular risk factors. Some autopsy studies found an association of CMIs with advanced age at death [32,33], but other studies did not [8]. No relation with gender has been found [8,32,34], which is in line with our findings. Severe hypertension was identified as a risk factor for microscopic infarcts on autopsy in one population-based study [34]. Another population-based autopsy study found only an association between higher systolic blood pressure and CMIs in individuals younger than 80 years of age at entry [35]. As far as we know, the relation between CMIs and dyslipidemia has not been explored in post-mortem studies. The strong association of hyperlipidemia, rather than hypertension, with cortical CMIs in our study is remarkable, as hypertension is the most important risk factor for the conventional markers of SVD (i.e., lacunar infarcts, microbleeds, WMHs). This implies that CMIs may also occur in the context of other etiological processes.

We found that cortical CMIs were associated with worse cognitive performance, in particular tasks assessing cortical function (i.e., language and visuoconstruction). Interestingly, tasks that are known to be related to vascular damage in subcortical regions (e.g., attention, visuomotor speed) were relatively less affected. The significant association with MMSE score in contrast to MoCA score further underlines this finding, as the MoCA incorporates more tests of executive function. Few autopsy studies have looked into the relation of CMIs and specific cognitive domains. A relation between cortical CMIs and worse performance on semantic memory, perceptual speed, and visuospatial abilities was found in one study, whereas subcortical CMIs were not associated with any of the cognitive domains [8].

Cortical CMIs were strongly associated with larger cortical infarcts. They were not solely found in cortical areas surrounding the infarct, but also in other cortical areas and the other hemisphere. This suggests global underlying vessel pathology instead of a more local manifestation of cerebrovascular disease. Cortical CMIs are generally considered as manifestations of cerebral SVD [5]. Our results suggest that CMIs are likely to be attributable to different pathologies. The strong associations of cortical CMIs with larger cortical infarcts and the spatial relation with the presence of intracranial stenosis suggest that they are also related to large vessel disease. Possibly CMIs downstream from a large vessel stenosis are due to hypoperfusion, but microemboli might also be a causative factor. Neuropathological studies indeed confirm that CMIs are related to SVD, in particular cerebral amyloid angiopathy [33,34,36–39], but can also be attributed to large vessel disease [40]. The present study cohort was enriched for patients with ischemic stroke, but patients with hemorrhagic stroke were excluded. In future studies it would be interesting to assess CMI burden also in patients with hemorrhagic stroke, for example, in the context of cerebral amyloid angiopathy, because CMIs appear to be common in such patients [37–39,41].

This study further showed that cortical CMIs are related to brain atrophy. Neuropathological studies have suggested that a single CMI on routine pathological examination indicates the presence of hundreds up to a thousand CMIs in a single brain [31]. It could be argued that this lesion burden by itself contributes to volume loss. With our current scan protocol, only the largest of the whole CMI spectrum can be captured. Extending the neuropathological findings, several CMIs on MRI could therefore indicate the presence of many more smaller CMIs. Nevertheless, whether many CMIs in a single brain by themselves explain global brain atrophy remains to be determined. Even hundreds of CMIs still only account for a total lesion volume of less than 1 ml, which is still only a fraction of the total cortical volume. The relation of cortical CMIs with worse cognitive performance in this study lost statistical significance when we adjusted for atrophy measured by brain volume as part of intracranial volume. Apparently, cortical atrophy and CMIs may be linked through shared aetiologies or risk factors. The interrelation between
atrophy, CMIs, and cognition should be a topic of future studies.

There are some limitations to this study that need to be considered. Cortical CMI rating criteria have been developed and validated with histology on 7T MRI. The current 3T rating criteria proved to be very consistent with 7T MRI, in the sense that 88% of 3T MRI CMIs proved to be CMIs on 7T in our validation study. However, it needs to be acknowledged that the sensitivity of 3T to detect cortical CMIs is much lower than 7T (27% of CMIs on 7T are detected by 3T). The current translation of cortical CMI rating that was developed on 7T MRI to conventional MRI is of importance, as it allows the assessment of this novel marker of cerebrovascular disease in much larger groups of patients and in the general population. Longitudinal studies are needed to further unravel the clinical importance of cortical CMIs. To further improve cortical CMI rating, we suggest scan protocol improvements, including the use of 3T 3D FLAIR images. Finally, it remains to be investigated if the current findings are generalizable to non-Asian populations and patients from other memory clinics, or comparable in those with a different vascular risk factor profile.

4.1. Conclusion

Our 3T MRI study showed that cortical CMIs are a common finding in an Asian memory clinic population. Cortical CMIs are associated with cerebral SVD, but most strongly with cortical infarcts. In contrast with subcortical SVD, cortical CMIs are particularly related with worse language and visuoconstructive abilities, domains considered cortical in nature. Hence, CMIs may be regarded as a distinct marker of cerebrovascular disease in dementia.

Acknowledgments

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2014.12.010.

RESEARCH IN CONTEXT

1. Systematic review: Earlier, we published a systematic review on neuropathological studies of cerebral microinfarcts (CMIs) (Brundel et al.). This review indicated that CMIs are common and a potential contributor to aging related cognitive decline and dementia. To identify emerging magnetic resonance imaging (MRI) studies that were published hereafter, we searched PubMed until September 2014, with the search term “microinfarcts”.

2. Interpretation: Our findings support insights from the neuropathological literature on CMIs. Furthermore, we point out the relevance of studying CMIs with 3 Tesla (3T) MRI. CMIs proved to be common, were associated with distinct vascular risk factors, and a specific cognitive profile.

3. Future directions: The present study is one of the first in vivo 3T MRI studies on CMIs and underlines the potential clinical importance of this previously called “invisible lesion” in a memory clinic population. Longitudinal studies, also in other cohorts, would provide more insight in the value of CMIs.

References


