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Featured Article

Comorbid amyloid-β pathology affects clinical and imaging features in VCD

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Abstract

Introduction: To date, the clinical relevance of comorbid amyloid-β (Aβ) pathology in patients with vascular cognitive disorders (VCD) is largely unknown.
Methods: We included 218 VCD patients with available cerebrospinal fluid $A\beta_{42}$ levels. Patients were divided into Aβ+ mild-VCD (n = 84), Aβ− mild-VCD (n = 68), Aβ+ major-VCD (n = 31), and Aβ− major-VCD (n = 35). We measured depression with the Geriatric Depression Scale, cognition with a neuropsychological test battery and derived white matter hyperintensities (WMH) and gray matter atrophy from MRI.
Results: Aβ− patients showed more depressive symptoms than Aβ+. In the major-VCD group, Aβ− patients performed worse on attention ($P = .02$) and executive functioning ($P = .008$) than Aβ+. We found no cognitive differences in patients with mild VCD. In the mild-VCD group, Aβ− patients had more WMH than Aβ+ patients, whereas conversely, in the major-VCD group, Aβ+ patients had more WMH. Atrophy patterns did not differ between Aβ+ and Aβ− VCD group.
Discussion: Comorbid Aβ pathology affects the manifestation of VCD, but effects differ by severity of VCD.

Keywords: Vascular cognitive disorders; Vascular dementia; Cognition; Amyloid-β; MRI; White matter hyperintensities; Gray matter atrophy

1. Background

Cerebrovascular pathology is among the most important causes of cognitive impairment and dementia [1]. Vascular cognitive disorders (VCD) are characterized by multiple lacunar infarcts, cortical infarcts, extensive and confluent white matter hyperintensities (WMH), and/or cerebral

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(micro) hemorrhages, leading to cognitive deficits. VCD can be present in isolation but is also frequently seen in combination with amyloid-β (Aβ) pathology [2–4]. To date, the clinical relevance of comorbid Aβ pathology in patients with VCD is largely unknown.

Evidence from neuropathological studies investigating the presence of Aβ in non–Alzheimer's disease (AD) suggests that in some cases Aβ is a secondary pathology in a clinical syndrome primarily driven by non-AD pathologies [5–8]. If comorbid Aβ deposition represents an age-related downstream phenomenon not significantly contributing to the patients' symptoms, its presence in non-AD represents a diagnostic confounder that potentially limits the use and interpretation of Aβ biomarkers in non-AD. Alternatively, if Aβ does contribute to the clinical and biological expression of the disease, then knowledge on the presence of Aβ pathology is important for accurate care and treatment. This is especially important when Aβ-targeted medication becomes available.

Therefore, we investigated the impact of comorbid Aβ deposition on (i) clinical, neuropsychological, and neuropsychiatric features, (ii) the amount and distribution of WMH, and (iii) gray matter atrophy patterns in patients with mild VCD or major VCD.

2. Methods

2.1. Participants

We retrospectively selected all patients from the Amsterdam Dementia Cohort clinically diagnosed with major VCD (n = 66) or mild cognitive impairment (n = 538) between 2000 and 2015. Inclusion criteria were a clinical diagnosis of mild VCD or major VCD based on the VASCOG criteria [9], and availability of a cerebrospinal fluid (CSF) Aβ 1–42 ($A\beta_{42}$) measurement. The clinical diagnosis of VCD was based on consensus within a multidisciplinary team combining clinical and neuropsychological information with presence of significant vascular pathology on MRI [9–11]. Significant vascular pathology on neuroimaging was defined as multiple lacunar infarcts (>2) outside the brain stem, or 1–2 lacunar infarcts when strategically placed or in combination with extensive WMH, or extensive and confluent WMH, or two or more intracerebral (micro) hemorrhages, or the presence of (a) large vessel infarct(s) [9]. Patients with mild VCD have cognitive deficits in one or more cognitive domains, but there is no interference with daily activities [12]. Patients with major VCD were diagnosed with dementia according to the VASCOG criteria [9]. Exclusion criteria were the presence of another brain disease (e.g., brain tumor, multiple sclerosis, encephalitis) or an active psychiatric disorder. We included 218 patients in the study, including all patients with major VCD (n = 66) and 152/538 patients with mild VCD.

CSF $A\beta_{42}$ was determined using Innotest ELISA. To account for increasing $A\beta_{42}$ CSF concentrations over time, we calculated drift-adjusted CSF $A\beta_{42}$ levels for each patient and used a uniform cutoff value [13]. Patients were classified as amyloid-positive (Aβ+) if their drift adjusted CSF $A\beta_{42}$ $\leq$813 pg/mL. Based on clinical diagnosis and Aβ status, patients with VCD were divided into Aβ+ mild-VCD (n = 84), Aβ− mild-VCD (n = 68), Aβ+ major-VCD (n = 31), and Aβ− major-VCD (n = 35).

All patients underwent standard dementia screening, including medical history (including information on vascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, and smoking), physical examination, *APOE* genotyping, lumbar puncture, a structured caregiver interview, Mini–Mental State Examination (MMSE) [14], neuropsychological testing, Geriatric Depression Scale (GDS) [15], and brain MRI. Vascular risk factors were dichotomized into present or absent. A vascular risk factor was deemed to be present based on a positive medical history and/or present medication use. Smoking was dichotomized into never/former or current smoker. We calculated a composite vascular risk factor score based on the sum of these four risk factors. Education was measured using the Verhage scale of educational attainment, ranging from 1 to 7 (7 represents the highest educational attainment) [16]. The study was approved by the VU University Medical Center medical ethics committee. All patients provided written informed consent for their data to be used for research purposes.

2.2. Neuropsychological assessment

The neuropsychological test battery covered five major cognitive domains [17]: memory (Visual Association Test, total learning, and delayed recall on the Rey Auditory Verbal Learning Test), attention (Digit-Span Forward, Trail Making Test [TMT]-A, Stroop I and II, and Letter-Digit Substitution test), executive functions (frontal assessment battery, Digit-Span Backward, TMT-B, Stroop III, letter fluency [letters DAT]), language (Category Fluency [animals], and Visual Association Test picture naming), and visuospatial ability (Rey figure copy, and the number location test, fragmented letters and dot counting tests of the Visual Object and Space Perception battery).

For patients in whom TMT-B was aborted (n = 23), we estimated the TMT-B score by multiplying TMT-A with the mean TMT-B/A index. The time limit for TMT-A, Stroop I and II was set at 180 seconds, whereas TMT-B and Stroop III were limited at 360 seconds. Scores on these tests were log-transformed because of their skewed distribution.

Supplementary Table 1 shows missing neuropsychological test data across groups. Availability was sufficient to compute cognitive domain scores in 85% of patients. We used an independent reference group of AD biomarker–negative participants with subjective cognitive decline from the Alzheimer Dementia Cohort (n = 533, age = 59.7 ± 9.8 years, 46% male, MMSE

score = 28.9 ± 1.0) to calculate z-scores for each individual test using the mean and standard deviation. Z-scores for the TMT and Stroop tests were inverted (multiplied by −1) so that higher scores implicate a better performance. Z-scores of tests within each cognitive domain were then averaged into a composite score for each domain [17].

2.3. Neuropsychiatric symptoms

To assess neuropsychiatric symptoms, we used the neuropsychiatric inventory (NPI, available in 72%), which is a 12-domain informant-based questionnaire [18]. For each domain, severity and frequency were scored. The domain score was calculated as the product of the severity and frequency. The 12-domain scores were summated to provide the total NPI score. Both the total score (range 0-144) and individual domain scores (range 0–12) were recorded. The GDS-15 (present in 80%) was used to assess depressive symptoms [15].

2.4. Magnetic resonance imaging

2.4.1. Acquisition

MRI scans were acquired on 1T, 1.5 T, or 3T scanners and were available in 195/218 (89%) subjects. Availability of MRI scans across groups were Aβ+ mild-VCD 78/84 (93%), Aβ− mild-VCD 63/68 (93%), Aβ+ major-VCD 24/31 (77%), and Aβ− major-VCD 30/35 (86%). Detailed information regarding imaging parameters used across scanners are provided in Supplementary Table 2. All scans were inspected by a rater who was blinded for all clinical information to provide visual rating scores. Medial temporal lobe atrophy was scored from 0 to 4 on coronal reconstructions of T1-weighted images [19]. We used the Fazekas scale (0–3) to rate WMH on FLAIR images [20]. Microbleeds were defined as small, maximum diameter 10 mm, round hypointense foci located in the brain parenchyma on T2*-weighted images. Lacunes were defined as deep lesions (3–15 mm) with CSF-like signal on all sequences [21]. Presence of infarcts, including territorial and watershed infarctions, was also recorded.

2.4.2. White matter hyperintensities

WMH were automatically segmented with a previously described algorithm using T1-weighted and FLAIR images [22]. Briefly, a Gaussian Mixture Model is used to model healthy tissue and unexpected observations (such as WMH). This model is anatomically constrained by subject-specific tissue anatomical priors [23]. After convergence of the model, a postprocessing step selects candidate WMH voxels and classifies the resulting connected clusters as lesions or artifacts. All WMH segmentations were visually checked by an experienced rater (J.L.). Hyperintensities belonging to a cortical infarct were excluded from the WMH registration (Supplementary Fig. 1). Scans with segmentations producing false positives (such as cortical infarctions, n = 17) or false negatives (n = 8) were segmented a second or a third time (n = 16) with additional rules designed to tackle these cases without affecting the results obtained on other cases. One Aβ+ patient with mild VCD had to be excluded because of excessive motion artifacts.

To visually represent the differences in WMH volumes between Aβ+ and Aβ− patients, a coordinate frame (bullseye) was designed to represent the location of the WMH. The angular segment reflects the lobar location, whereas the radial distance represents the distance to the ventricular surface. The distance from the ventricles to cortex was divided into 4 equidistant layers based on a normalized distance map between the ventricular surface and the cortex. This distance map is obtained by solving the Laplace equation between the two surfaces previously described [24,25]. Beta coefficients of the differences are presented in exponentiated form, corresponding with odds ratios.

2.4.3. Gray matter atrophy

The presence of WMH, infarcts, and infarctions can affect gray matter segmentation [26]. An approach to correct for the presence of WMH is to apply lesion-filling to the T1-weighted images before segmentation. We used a patch-based method implemented in the open-source NiftySeg software to fill the lesion masks with the most plausible T1 texture [27].

After lesion-filling, the structural T1 images were segmented using the "New Segment" toolbox implemented in the Statistical Parameter Mapping 12 software (Welcome Trust Centre for Neuroimaging, UCL, London, UK). To generate a study-specific template, Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra was used to align gray and white matter images nonlinearly to a common space. Gray matter images were spatially normalized to the study-specific template by using individual flow fields. Modulation was applied to preserve tissue volume signal and images were smoothed using an 8 mm full-width-at-half-maximum isotropic Gaussian kernel. After each processing step, the images were visually checked. A total of nine scans (Aβ+ mild-VCD: 2, Aβ− mild-VCD: 2, and Aβ+ major-VCD: 5) were excluded based on these quality checks.

Using the normalized structural T1-weighted images, voxelwise gray matter volume contrasts were performed in Statistical Parameter Mapping 12 between patient groups. Results are presented at $P < .001$ (uncorrected) and we also used a more lenient threshold ($P < .01$ uncorrected) for contrasts between patient groups. The automated anatomical labeling atlas was used to compute predefined composite bilateral regions of interest: medial temporal, lateral temporal, frontal, parietal, and occipital lobe, and cerebellum.

2.5. Statistical analyses

Analyses were performed using SPSS (version 22; IBM, Chicago, IL, USA) and STATA (version 14; StataCorp;

Table 1
Demographics according to diagnostic group

	Mild VCD			Major VCD		
Clinical diagnosis	Aβ+	Aβ−		Aβ+	Aβ−	
Characteristic	N = 84	N = 68	*P*	N = 31	N = 35	*P*
Age, y	70.8 ± 6.6†	67.6 ± 8.5	.010	69.1 ± 8.0	65.9 ± 7.6	.106
Females, n (%)	44 (52)†	21 (31)	.009	10 (32)	9 (26)	.596
Education	5 (4–6)	5 (4–6)	.848	5 (4–6)	4 (3–5)	.105
APOE ε4 carriers n (%)	54 (69)‡	18 (28)	>.001	20 (69)*	10 (35)	.017
MMSE score	26 ± 3	27 ± 2	.294	22 ± 5	23 ± 5	.753
CSF $A\beta_{42}$ levels	636 ± 94‡	1109 ± 197	>.001	604 ± 122‡	1040 ± 148	>.001
NPI total score	6 (3–9.25)	8 (3–20)	.052	12 (4–24)	16 (9.5–23)	.490
GDS	2.3 ± 2.0†	3.8 ± 3.5	.002	2.8 ± 2.9*	5.2 ± 4.1	.030
Vascular risk factors						
Hypertension, n (%)	36 (43)	39 (58)	.103	21 (68)	24 (69)	1.0
Diabetes, n (%)	11 (13)	14 (21)	.272	5 (16)	13 (37)	.095
Hypercholesterolemia, n (%)	19 (23)‡	35 (52)	>.001	14 (45)	8 (23)	.070
Smoking, n (%)	12 (15)	16 (24)	.147	8 (30)	12 (39)	.583
Vascular risk factors (sum)	1 (0–1)	2 (1–2)	.001	2 (1–2)	2 (1–2)	.865
MRI						
Fazekas	2 (1–2)	2 (1–2)	.581	3 (3–3)	3 (1.75–3)	.111
Fazekas ≥2, n (%)	59 (70)	48 (71)	1.0	27 (93)	26 (77)	.092
Lacune ≥2, n (%)	12 (15)	19 (28)	.067	13 (48)	26 (74)	.062
Infarct n (%)	5 (6)	8 (12)	.249	6 (19)	14 (40)	.107
Microbleeds, ≥2, n (%)	33 (42)	21 (31)	.228	16 (70)	12 (41)	.054
GCA	1 (1–1)	1 (1–1.75)	.270	1 (0–1)	1 (1–1.5)	.390
MTA	1 (0–1.5)	1 (0.5–2)	.491	1.75 (1–2.5)	1.5 (1–2)	.258

NOTE. Values are mean ± SD, median (IQR), or count (%). Education is based on Verhage scale (7). Comparisons were stratified on clinical diagnosis.

Availability for incomplete data in Aβ+ mild-VCD group: education: 81/84; *APOE* ε4 carriers: 78/84; MMSE score: 82/84; NPI: 56/84; GDS: 73/84; smoking: 82/84; lacunes: 82/84; GCA and MTA: 83/84; microbleeds: 78/84.

Availability for incomplete data in Aβ− mild-VCD group: *APOE* ε4 carriers: 64/68; NPI: 57/68; GDS 56/68; smoking 66/68; microbleeds: 67/68.

Availability for incomplete data in Aβ+ major-VCD group: education: 27/31; *APOE* ε4 carriers: 29/31; MMSE score: 30/31; NPI: 21/31; GDS: 20/31; smoking: 27/31; Fazekas score: 29/31; lacunes: 27/31; microbleeds: 23/31; GCA: 26/31; MTA: 28/31.

Availability for incomplete data in Aβ+ major-VCD group: education: 30/35; *APOE* ε4 carriers: 29/35; MMSE score: 34/35; NPI: 18/35; GDS: 26/35; Fazekas score: 34/35; microbleeds: 29/35; GCA and MTA: 33/35.

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; GCA, global cortical atrophy; GDS, Global Depression Scale; MMSE, Mini–Mental State Examination; MTA, medial temporal atrophy; NPI, neuropsychiatric inventory; VCD, vascular cognitive disorders.

*$P < .05$ compared Aβ−.

†$P < .01$ compared Aβ−.

‡$P < .001$ compared Aβ−.

College Station, TX, USA). All analyses were stratified based for disease stage (i.e., mild vs. major VCD). Differences in demographical characteristics and neuropsychiatric data were assessed using ANOVA for continuous variables and χ^2 or Mann-Whitney U-tests for dichotomous or categorical data. Differences in cognitive domain scores were assessed using ANOVA, adjusted for age, sex, and education. ANOVA adjusted for age, sex, total intracranial volume, and field strength was used to compare gray matter volumes in the specified regions of interest. To test the effects of cortical infarcts on the gray matter results, we repeated all gray matter assessments after excluding subjects with cortical infarcts (n = 28; Aβ+ mild-VCD: 5, Aβ− mild-VCD: 8, Aβ+ major-VCD: 3, and Aβ− major-VCD: 12).

To compare WMH volumes, we assessed general linear models adjusted for age, sex, total intracranial volume, and field strength using STATA, with gamma distribution and a log link as the distribution of the WMH volumes was highly skewed.

We additionally adjusted the WMH and gray matter volume analyses for *APOE* ε4 status and the composite vascular risk factor score. We used false discovery rate (FDR) to account for multiple comparisons.

3. Results

3.1. Demographics

Table 1 shows the baseline characteristics of the study participants. Beginning confluent WMH (Fazekas 2), and/or ≥2 microbleeds, and/or ≥2 lacunes (or 1 when strategically placed) was present in 139 (94%) patients with mild VCD and 46 (70%) patients with major VCD. Large-vessel disease in 5 (4%) patients with mild VCD and in 3 (5%) patients with major VCD. A combination of both small vessel disease and large-vessel infarct was present in 8 (5%) patients with mild VCD and in 17 (25%) patients with major VCD.

The patients with mild VCD had a mean age of 69 ± 8 years, a mean MMSE score of 27 ± 2, and 43% of the patients were female. In the mild-VCD group, Aβ− patients were younger than Aβ+, comprised less females and were less often

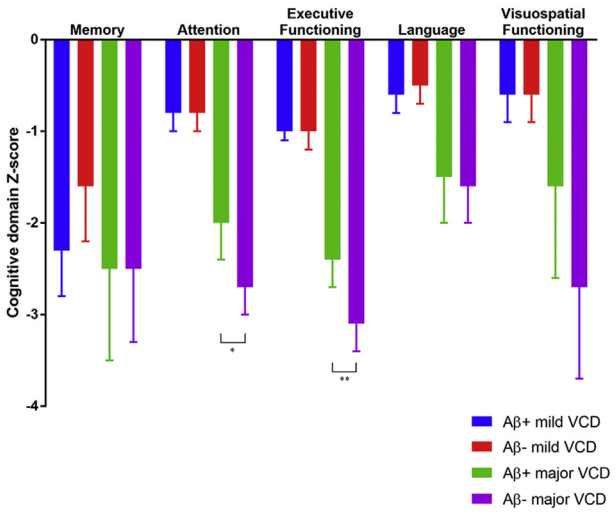

Fig. 1. Neuropsychological performance. Values depicted are estimated marginal mean composite z-scores for cognitive domain scores, adjusted for age, sex, and education, with 95% CI. *Significant difference at $P < .05$, **Significant difference at $P < .01$. Abbreviation: VCD, vascular cognitive disorders.

APOE ε4 carrier. We found a higher prevalence of hypercholesterolemia in the Aβ− mild VCD group compared with the Aβ+ mild VCD group. Furthermore, the Aβ− mild-VCD group had a higher composite vascular risk factor score compared with the Aβ+ mild-VCD group. Finally, Aβ+ did not differ from Aβ− patients with mild VCD on MRI features.

Overall, patients with major VCD had a mean age of 67 ± 8 years, a mean MMSE score of 22 ± 5, and 29% of the patients were female. Aβ− patients with major VCD were less often *APOE* ε4 carriers compared with Aβ+ patients with major VCD. Vascular risk factors did not differ between patients with major VCD. No differences in cerebrovascular brain damage and atrophy were seen between patients with major VCD.

3.2. Neuropsychological examination

We show the raw neuropsychological test results in Supplementary Table 1 and the composite domain z-scores in Fig. 1. Within patients with mild VCD, we found no differences between Aβ+ and Aβ− in cognitive performance.

In the major-VCD group, Aβ− patients with major VCD performed worse than Aβ+ patients with major VCD on attention (−2.7 ± 0.2 vs. −2.0 ± 0.2, $P = .018$, $P_{FDR} = .04$) and executive functioning (−3.1 ± 0.2 vs. −2.4 ± 0.2, $P = .008$, $P_{FDR} = .0045$).

3.3. Neuropsychiatric symptoms

Total NPI and GDS are presented in Table 1, and NPI item scores in Supplementary Table 3. Apathy was reported most often (42%), followed by irritability (39%) and depressive symptoms (23%).

No differences in total NPI scores were seen between Aβ+ and Aβ− patients with VCD. Among patients with mild VCD, Aβ− patients showed more irritability than Aβ+ patients (2.6 ± 2.9 vs. 1.7 ± 2.6, $P = .04$, $P_{FDR} = .34$). Among patients with major VCD, Aβ− patients showed more night-time behavior disturbances than Aβ+ patients (1.8 ± 2.3 vs. 0.4 ± 1.1, $P = .04$, $P_{FDR} = .32$).

We found higher GDS scores in Aβ− patients with mild VCD compared with Aβ+ patients with mild VCD ($P = .002$) and in Aβ+ patients with major VCD compared with Aβ− patients with major VCD ($P = .03$).

3.4. White matter hyperintensities

Fig. 2 shows differences in total WMH volumes within the mild VCD and dementia groups. In the Aβ+ mild VCD group, WMH volumes were smaller compared with Aβ− mild VCD group, predominantly in the basal ganglia and frontal midlayers ($P < .05$, $P_{FDR} > .05$, Fig. 2A and B). By contrast, in dementia, Aβ+ major VCD had a higher WMH load than Aβ− major VCD in all regions except the infratentorial ($P < .05$, $P_{FDR} < .05$). Differences were most pronounced in the occipital and temporal lobes and in periventricular regions (Fig. 2C–F).

After additional adjustment for *APOE* ε4 presence and composite vascular risk factor score, differences in WMH were no longer significant between Aβ+ and Aβ− patients with mild VCD. In major-VCD, Aβ+ patients showed more WMH in the occipital ($P = .002$, $P_{FDR} = .019$) and temporal ($P = .027$, $P_{FDR} = .084$) lobes and the periventricular region ($P = .006$, $P_{FDR} = .026$).

3.5. Gray matter density

Voxelwise comparisons in mild VCD and major VCD are shown in Fig. 3. Voxelwise comparisons between mild-VCD group revealed no differences at $P < .001$ uncorrected for multiple comparisons. Lowering the threshold to $P < .01$ (uncorrected) revealed reduced gray matter density in the precentral sulcus and temporal pole in Aβ− mild-VCD compared with Aβ+ mild-VCD. We found no differences within major-VCD group.

Region-of-interest analyses showed no differences between Aβ+ and Aβ− patients for both mild and major VCD (Fig. 4). The exclusion of subjects with infarcts resulted in similar group differences (Supplementary Tables 5 and 6).

Both voxelwise and region-of-interest analyses showed similar results after additionally adjusting for *APOE* ε4 and composite vascular risk factor score.

4. Discussion

In the present study, we found that Aβ− patients with major-VCD displayed more nonamnestic cognitive impairments than Aβ+ patients with major VCD. Moreover, independent of disease severity, Aβ− patients showed more depressive symptoms than Aβ+ patients with VCD. Mild

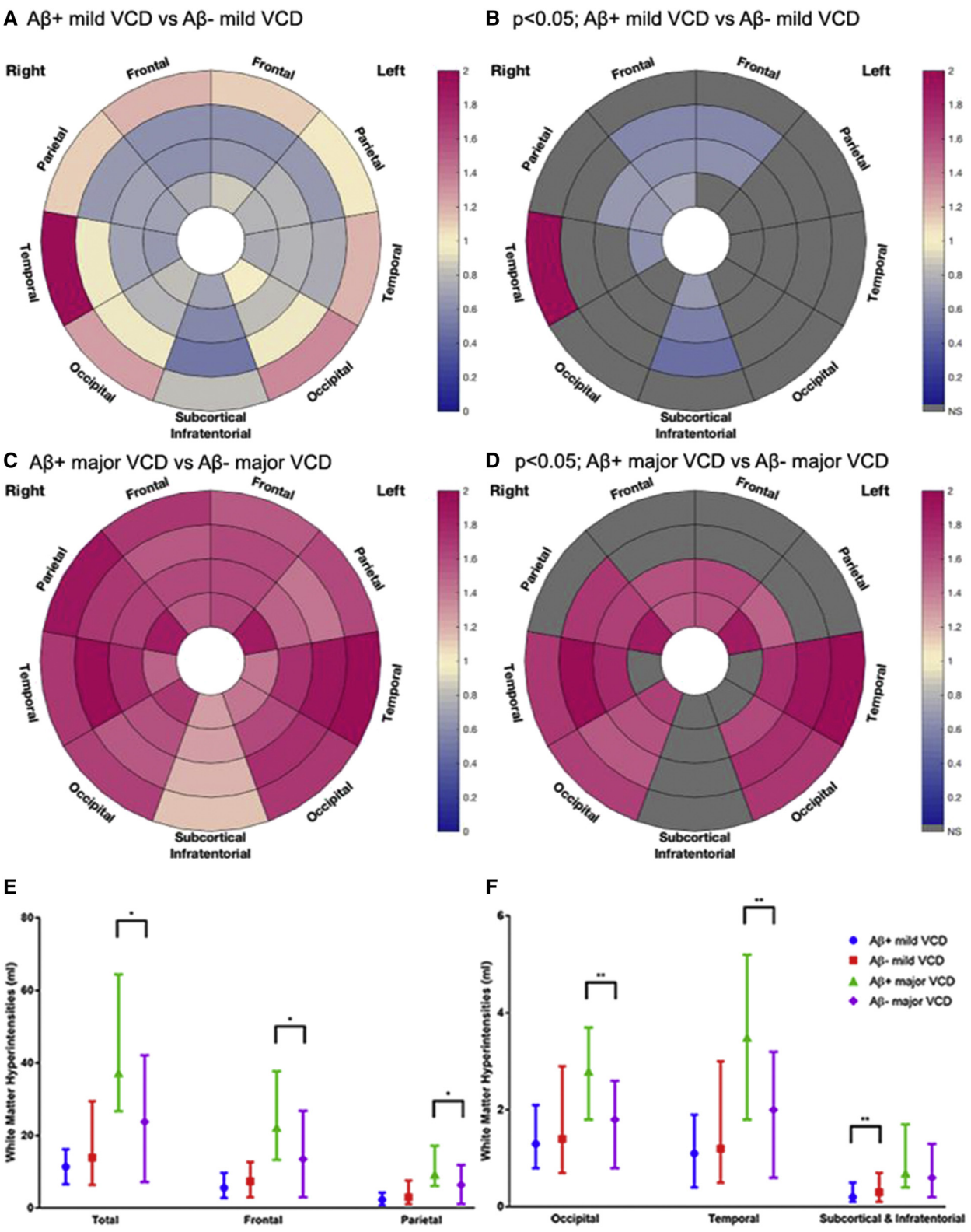

Fig. 2. White matter hyperintensities. Bullseye plot displaying differences in white matter hyperintensity lesion volumes between Aβ+ mild-VCD versus Aβ− mild-VCD group (A and B) and Aβ+ major-VCD versus Aβ− major-VCD group (C and D). The concentric rings of the plot represent four equidistant layers of white matter (center = periventricular and outer = juxtacortical). Pink shades indicate that Aβ+ VCD group have more WMH than Aβ− VCD group and blue shades indicate that Aβ+ VCD group have less WMH than Aβ− VCD group. (A and C) show the beta coefficients of the differences in exponentiated form corresponding with odds ratios and (B and D) only show significant associations. A gray color indicates the difference did not reach statistical significance in that specific anatomical region. (E and F) Values are median white matter hyperintensity volumes with IQR in mL. Right and left hemispheres are combined into one region. Note: The WMH volumes in panel F are shown on a different scale than in panel E. *Difference $P < .01$ compared with Aβ−, ** Difference $P < .05$ compared with major Aβ−, adjusted for age, sex, intracranial volume, and field strength. Abbreviations: Aβ, amyloid-β; VCD, vascular cognitive disorders; WMH, white matter hyperintensities.

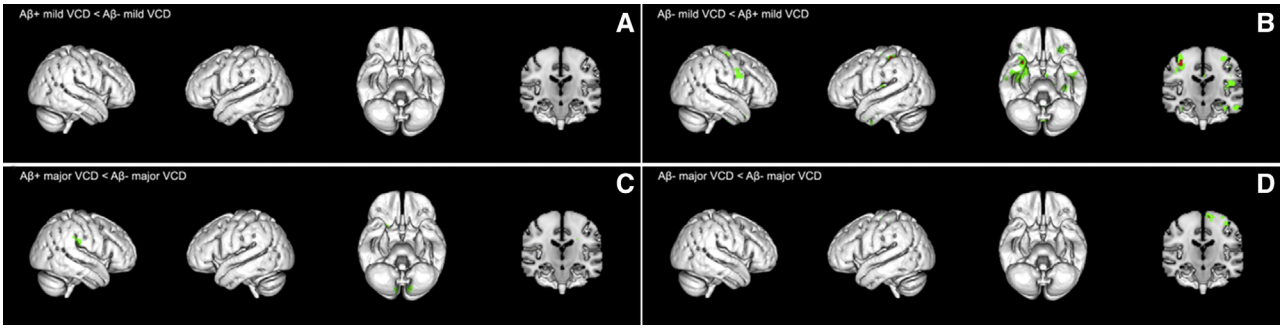

Fig. 3. Gray matter atrophy, voxelwise analyses. Differences in gray matter volumes, adjusted for age, sex, intracranial volume, and field strength between for mild-VCD group (A and B) and major-VCD group (C and D) at $P < .001$ (uncorrected; red) and a more lenient threshold $P < .01$ (uncorrected; green). Abbreviations: Aβ, amyloid-β; VCD, vascular cognitive disorders.

VCD Aβ+ patients showed less WMH than Aβ− patients. However, in patients with major VCD, Aβ+ patients showed higher WMH volumes than Aβ− patients. Voxelwise gray matter analyses showed only minor differences at a very lenient threshold between the Aβ+ mild-VCD group and the Aβ− mild-VCD group. Region-of-interest analyses of gray matter atrophy within mild and within major VCD showed no differences.

We found that patients with major VCD, especially Aβ− patients, were mostly impaired in executive functioning and attention [28–30]. Evidence on the association between Aβ and cognition in patients with VCD is conflicting. Two studies including patients with mild cognitive impairment and severe cerebrovascular disease, and another study including patients with mild subcortical vascular impairment, showed a negative association between Aβ and cognition in patients with VCD [29,31,32]. Another study in cognitive healthy elderly with presence of cerebrovascular disease (defined as extensive WMH and/or presence of (sub) cortical infarcts) found no association between Aβ and cognition [33]. In contrast to the negative association of Aβ seen in some previous studies, in the present study, major-VCD group with comorbid Aβ were less impaired on attention and executive functioning compared with major-VCD group without Aβ pathology. The worse performance in Aβ− major-VCD compared with Aβ+ major-VCD cannot be explained by WMH lesion load, as Aβ− major-VCD group had less WMH than Aβ+ major-VCD group. Although not statistically different, lacunes were more often present in Aβ− patients with major VCD

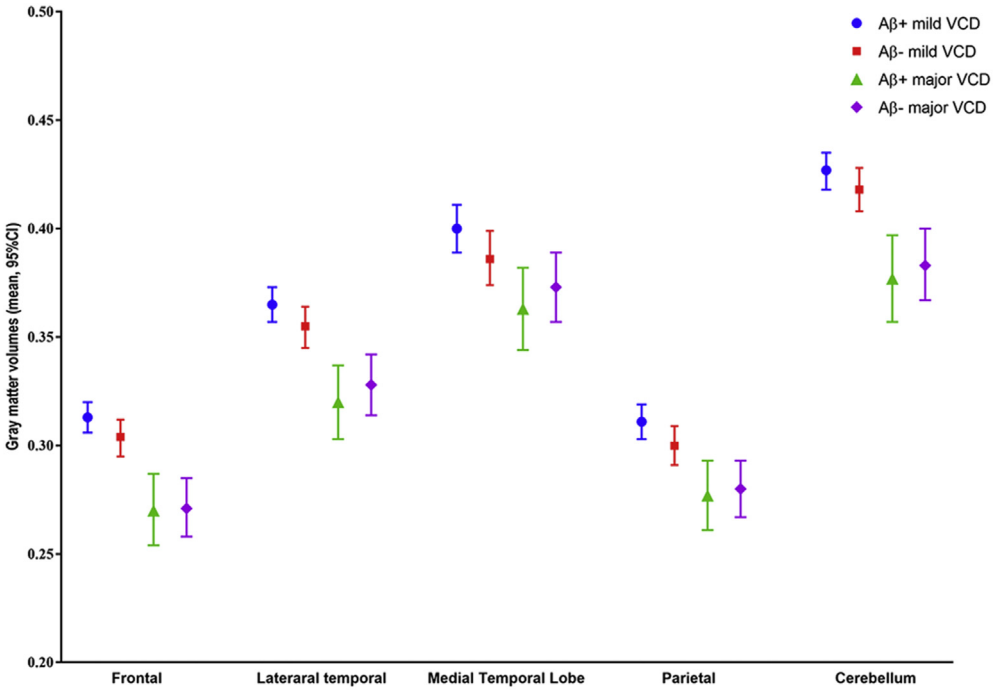

Fig. 4. Gray matter atrophy, region-of-interest analyses. Estimated marginal mean scores of gray matter volumes, adjusted for age, sex, intracranial volume, and field strength. Differences were analyzed stratified by diagnosis. Abbreviations: Aβ, amyloid-β; VCD, vascular cognitive disorders.

than in Aβ+ patients with major VCD. Lacunes have been associated with executive dysfunctioning and attention, without affecting memory [29,34]. In major-VCD group, presence of lacunes was associated with lower attention ($P = .026$). This might be an explanation for the attentional differences observed between Aβ+ and Aβ− major-VCD group. Alternatively, differences in lesion location of WMH might have influenced the cognitive profiles of the major-VCD group. It has been shown that the impact of location of the WMH is greater than total WMH load. Lesions in the anterior thalamic radiation and the forceps minor, for example, have been associated with poor executive functioning [35]. Furthermore, lesions in specific white matter tracts, such as the forceps minor and the cortical spinal tract, have also been associated with depressive symptoms [36]. Future studies on the association between lesion location and neuropsychological and neuropsychiatric symptoms in patients with VCD should replicate our findings.

WMH are thought to reflect small-vessel disease caused by vascular risk factors and might also be caused by blood brain barrier leakage [37–39]. In healthy individuals, the presence of Aβ and cerebrovascular disease are not predictive of each other and might be caused by different processes [40]. Our results in mild-VCD group support these findings, as Aβ+ mild-VCD group had lower WMH volumes and less vascular risk factors than Aβ− mild-VCD group. This might suggest that in Aβ+ patients with mild VCD, Aβ and cerebrovascular disease have an additive effect on cognitive impairment and that both pathologies are necessary to cross the threshold of normal cognitive function, whereas in Aβ− patients with mild VCD, the cerebrovascular disease is sufficient. We hypothesized a priori that the same would be true for major-VCD group, assuming that in Aβ+ major-VCD group, less cerebrovascular disease is needed to cause dementia compared with Aβ− major-VCD group, where only a single pathology is present. However, somewhat to our surprise, Aβ+ patients with major VCD had the highest volumes of WMH. This supports the idea that cerebrovascular disease and Aβ pathology are interconnected in more advanced disease stages. Cerebrovascular disease may cause reduced Aβ clearance, whereas Aβ may lead to disruption of cerebrovascular disease [41]. A recent neuropathological study suggested that in patients with AD, WMH are associated with neurodegenerative changes occurring secondary to AD (hyperphosphorylated tau and Aβ) through Wallerian degeneration, whereas in controls, WMH are due to small-vessel disease [42]. In our patients with major VCD, the presence of Aβ pathology may also have led to the high volumes of WMH, meaning that the WMH seen in our Aβ+ patients with major VCD could also be due to neurodegenerative changes instead of vascular pathology. In addition, both Aβ+ mild-VCD and Aβ+ major-VCD groups were more frequently *APOE* ε4 carriers than Aβ− mild-VCD and Aβ− major-VCD groups. *APOE* ε4 has shown to be associated with occipital distribution of WMH, a location known to be affected by cerebral amyloid angiopathy [43,44]. The higher volumes of occipital WMH in the Aβ+ major-VCD group might thus also be partially cerebral amyloid angiopathy mediated. Overall, our study supports the notion that WMH is not only caused by cerebrovascular disease but occurs also secondary to neurodegeneration and (vascular) Aβ pathology.

In patients with VCD, comorbid Aβ pathology does not seem to influence atrophy patterns in mild-VCD or in major-VCD group, as no differences in atrophy pattern were seen between VCD patients with comorbid Aβ+ and those without. It seems that cerebrovascular disease and Aβ are independently associated with cortical volumes loss and do not interact to potentiate neurodegeneration, in accordance with previous studies [33,45]. Recent literature showed that the atrophy pattern of small-vessel disease partially overlaps with AD-specific regions and that atrophy is not only associated with neurodegeneration but is also vulnerable to cerebrovascular disease [46–50]. Based on the present study and existing literature, we constructed a hypothetical model (Fig. 5), where Aβ and vascular

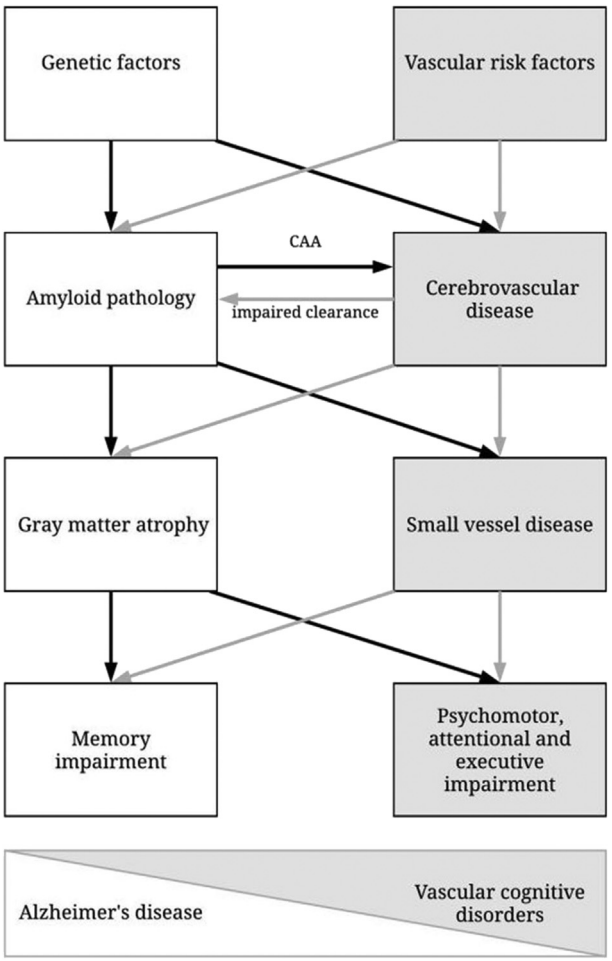

Fig. 5. Interactions between amyloid-β and vascular pathways in dementia. Arrows show effects and possible interactions. Gray arrows represent effects of vascular pathology and black arrows represent effects of Aβ pathology. Abbreviation: CAA, cerebral amyloid angiopathy.

pathways have independent effects and each contribute to the cognitive profile in a distinct manner, and vascular and Aβ pathways interact at multiple levels. First, risk factors known to be associated with AD pathology, for example, *APOE*, have been associated with cerebrovascular disease [43]. Moreover, vascular risk factors have also been associated with Aβ deposition [51,52]. Second, Aβ and vascular pathologies might mutually interact. On one hand, it has been shown that small vessel disease can impair the perivascular clearance of Aβ [53,54]. This may cause an abundance of Aβ, causing gray matter atrophy. On the other hand, Aβ pathology may cause small-vessel disease such as WMH and microbleeds, in turn leading to disruption of subcortical white matter tracts [41]. Through the interactions between cerebrovascular disease and Aβ, and the resulting effects on gray matter, and white matter, cognitive domains may be affected on various degrees.

Strengths of the study include the combined assessment of cognition, atrophy, and cerebrovascular disease on MRI, and the relatively large sample size of patients with VCD. To our knowledge, this is the first study investigating the associations of comorbid Aβ in patients with VCD, including patients with large vessel disease in contrast to previous studies only including subcortical VCD. The spectrum of VCD represents a promising candidate to investigate the impact of comorbid Aβ pathology on the clinical expression of VCD because the diagnosis depends on objective measurements (i.e., cognitive function and radiological characteristics). Another strength of the study is that we accounted for the effect of white matter lesions in tissue segmentation through lesion-filling [27]. Lesion-filling of WMH is a common approach in the field of multiple sclerosis, but not (yet) in the dementia field. High volumes of white matter lesions, as present in our patients with VCD, can influence the segmentation and analyses of gray matter; thus it is of the utmost importance to correct for this [26].

There are also several limitations that need to be addressed. First, we collected information over a period of 15 years to include enough patients in each subgroup. As a result, different neuropsychological protocols and multiple different MRI scanners were used. Second, MRI segmentation procedures failed in 5% and these patients could not be included in the gray matter analyses. The segmentation failed mostly in the Aβ+ major-VCD group (21%). This is a problem for all studies including patients with a high burden of WMH, as this can frequently lead to segmentation failure. Furthermore, the presence of cortical infarcts in the VCD groups could have negatively influenced the total gray matter volumes of the patients with VCD. However, when repeating the gray matter analyses, after excluding patients with cortical infarcts, the results for gray matter atrophy remained largely the same. Finally, the cross-sectional design of the study does allow any causal inferences, and longitudinal studies are required to investigate whether Aβ+ mild-VCD group show a more rapid change in WMH volumes over time.

The development of positron emission tomography and CSF biomarkers to measure Aβ pathology *in vivo* has substantially improved the early and differential diagnosis of AD. However, their clinical utility in patients with non-AD dementia is potentially limited by the increasing proportion of patients exhibiting positive Aβ biomarkers with advancing age. While longitudinal assessment is needed to confirm the effects of Aβ on the clinical and neurobiological manifestation of the disease in VCD patients, we demonstrate here that presence of Aβ in patients with VCD should not be disregarded (and we speculate that these findings extrapolate to other non-AD types of dementia). Therefore, it is of utmost importance that therapeutic approaches targeting either VCD or AD should consider possible interactions between Aβ and cerebrovascular disease on multiple levels. Future studies should investigate whether targeting amyloid pathology in early stages of VCD affects the clinical and biological manifestation of the disease.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.08.190.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using PubMed for articles regarding vascular cognitive disorders and amyloid-β (Aβ) pathology. Although the development of positron emission tomography and CSF biomarkers to measure Aβ pathology *in vivo* have substantially improved the early and differential diagnosis of Alzheimer's disease, the impact of Aβ pathology in patients with vascular cognitive disorders (VCD) is not well known.
2. Interpretation: Our findings show that presence of Aβ in VCD affects the clinical and radiological manifestation of VCD, but effects vary as a function of VCD severity. This article demonstrates that presence of Aβ in VCD provides important information.
3. Future directions: Future longitudinal studies should investigate how the presence of Aβ affects the natural disease course of patients with VCD. Furthermore, future studies should investigate whether targeting amyloid pathology in early stages of VCD affects the clinical and biological manifestation of the disease.

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