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RESEARCH ARTICLE

Cognition in (pre)symptomatic Dutch-type hereditary and sporadic cerebral amyloid angiopathy

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Abstract

INTRODUCTION: Cerebral amyloid angiopathy (CAA) is a main cause of cognitive dysfunction in the elderly. We investigated specific cognitive profiles, cognitive function in the stage before intracerebral hemorrhage (ICH), and the association between magnetic resonance imaging (MRI) based cerebral small vessel disease (cSVD) burden in CAA because data on these topics are limited.

METHODS: We included Dutch-type hereditary CAA (D-CAA) mutation carriers with and without ICH, patients with sporadic CAA (sCAA), and age-matched controls. Cognition was measured with a standardized test battery. Linear regression was performed to assess the association between MRI-cSVD burden and cognition.

RESULTS: D-CAA ICH− mutation carriers exhibited poorer global cognition and executive function compared to age-matched controls. Patients with sCAA performed worse across all cognitive domains compared to D-CAA ICH+ mutation carriers and age-matched controls. MRI-cSVD burden is associated with decreased processing speed.

DISCUSSION: CAA is associated with dysfunction in multiple cognitive domains, even before ICH, with increased MRI-cSVD burden being associated with slower processing speed.

KEYWORDS
cerebral amyloid angiopathy, cognitive dysfunction, cerebral small vessel disease burden, Dutch-type hereditary cerebral amyloid angiopathy, hereditary cerebral amyloid angiopathy, intracerebral hemorrhage, magnetic resonance imaging, presymptomatic mutation carriers

Highlights

- Cognitive dysfunction is present in early disease stages of cerebral amyloid angiopathy (CAA) before the occurrence of symptomatic intracerebral hemorrhage (sICH).

- Presymptomatic Dutch-type CAA (D-CAA) mutation carriers show worse cognition than age-matched controls.
- More early awareness of cognitive dysfunction in CAA before first sICH is needed.
- Increased cerebral small vessel disease CAA-burden on magnetic resonance imaging is linked to a decrease in processing speed.

1 | BACKGROUND

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid beta (Aβ) in the cortical and leptomeningeal cerebral vessels. CAA is one of the major causes of intracerebral hemorrhage (ICH), cognitive dysfunction, and vascular dementia in the world.[1–4] Advanced CAA is associated with cognitive dysfunction in multiple domains[5,6] and with a variety of (non-)hemorrhagic injuries of brain tissue, such as lobar cerebral microbleeds (CMBs), white matter hyperintensities (WMHs), and cortical superficial siderosis (cSS).[4,7,8] At the moment, a clear understanding of the cognitive profile in patients with CAA is lacking and the association – and underlying mechanism – between focal brain lesions on magnetic resonance imaging (MRI) and cognitive dysfunction is not known.[4,9] In general, the effects of CAA on cognition are difficult to assess due to age-related comorbidities such as Alzheimer's disease (AD) or vascular risk factor-related arteriolosclerotic small vessel disease (SVD), which are often present in patients with CAA and hamper insight into the contribution of "pure" CAA pathology to cognitive dysfunction. Further, patients often present in a more advanced stage of the disease, and consequently the development of cognitive dysfunction in the early – presymptomatic – phase of the disease cannot be evaluated.

Dutch-type hereditary CAA (D-CAA) is a rare autosomal-dominant disease caused by a point mutation in the Aβ precursor protein (APP) gene.[10] The APP mutation results in extensive amyloid depositions in leptomeningeal arteries and cortical arterioles.[10] The chemical composition and underlying pathology of the amyloid deposits are similar to that in non-hereditary, that is, sporadic, CAA (sCAA).[11,12] D-CAA represents a relatively "pure" form of CAA unaffected by age or other cardiovascular risk factors, as individuals carrying the D-CAA mutation display nearly identical clinical symptoms and radiological signs, albeit approximately 20 years earlier than sporadic patients.[10,13] Previous studies in D-CAA reported that cognitive dysfunction generally develops after the first ICH and progresses between hemorrhages in a stepwise fashion.[2,10,14] However, it has also been reported in some patients that cognitive dysfunction may occur before symptoms are noticed and can precede the first ICH.[15] In contrast to sCAA, D-CAA can be diagnosed during life with certainty by genetic testing. This enables research of the early phase of CAA before the first symptomatic hemorrhage occurs, that is, the presymptomatic phase. We aimed to investigate cognition in presymptomatic and symptomatic D-CAA mutation carriers compared with patients with sCAA and age-matched controls. Our objectives were as follows: (1) to compare cognition across distinct domains for the different groups, (2) to ascertain if cognitive dysfunction could manifest before symptomatic hemorrhage in individuals carrying the D-CAA mutation, and (3) to examine the association of MRI-based cerebral SVD (cSVD) CAA-burden and cognitive (dys)function.

2 | METHODS

2.1 | Participants and study design

For this cross-sectional study, we included D-CAA mutation carriers and patients with sCAA who participated in our ongoing natural history studies on disease progression and biomarkers in D-CAA (AURORA study) and sCAA (FOCAS study) between 2018 and 2022 in the Leiden University Medical Center (LUMC), the Netherlands. Inclusion criteria for the D-CAA mutation carriers were as follows: age ≥18 years and a genetically proven APP mutation, or a medical history of one or multiple lobar ICHs and ≥1 first-degree relative with D-CAA.

Presymptomatic D-CAA was subsequently defined as the phase before the first symptomatic ICH (sICH) (ICH–). sICH was further specified as a symptomatic hemorrhage in which symptoms correspond to the location of the hemorrhage on computed tomography (CT) or MRI.

Patients with sCAA were all diagnosed as "probable CAA" according to the modified Boston criteria 2.0 for CAA.[16] All patients with sCAA had clinical symptoms of CAA as this is mandatory to fulfill the Boston 2.0 criteria. All patients in the sCAA group were primarily diagnosed with CAA, but concomitant AD pathology was not formally excluded with additional diagnostics (eg, amyloid positron emission tomography or cerebrospinal fluid [CSF]). Other common causes of cognitive decline, including acute neurological disease (eg, stroke), and psychiatric comorbidity were excluded. We did not stratify our sCAA group in patients with or without ICH, due to the small numbers with a relatively wide age range and age-related comorbidities and since sCAA does not necessarily result in sICH.

Control participants were recruited from the Early Detection of Angiopathy Network (EDAN) study in 2012 and were individuals at risk of D-CAA but who tested genetically negative, participants' spouses, or extended family members of friends. All control participants underwent genetic testing to rule out D-CAA.[2] Control participants had no history of neurological disease and were all free of subjective cognitive complaints. Controls were excluded if they had radiological evidence consistent with a probable CAA diagnosis. Control participants were divided into <50 (n = 15) years and ≥50 (n = 15) years of age to obtain closely matching age categories for both

D-CAA ICH− mutation carriers, D-CAA ICH+ mutation carriers, and, to a lesser extent, patients with sCAA. The cut-off point of 50 years was based on the mean age of the first sICH in D-CAA and the minimum age criterion in the Boston criteria 2.0.[16,17] Approval for the studies was granted by the local Medical Ethics Committee Leiden Den Haag Delft (AURORA: P17.235; FOCAS: P17.259; EDAN: P11.094). Written consent was obtained from all participants before their enrollment. The data of this study are available upon reasonable request.

2.2 | Data collection

We collected all clinical data, conducted neuropsychological examinations, and performed MRI during a single study visit. Data on demographics, medical history, and clinical symptoms, including history of symptomatic ICH, were prospectively obtained in standardized annual study visits. Information about prior symptomatic ICH was obtained from electronic patient files.

2.3 | Neuropsychological assessment

All neuropsychological tests were administered by trained researchers and according to the testing manual. The comprehensive neuropsychological assessment in D-CAA and sCAA consisted of validated instruments: the Mini-Mental State Examination (MMSE),[18] Montreal Cognitive Assessment (MoCA) version 7.1[19] (corrected for education in accordance with the testing manual), Rey Auditory Verbal Learning Test – 15 words (RAVLT),[20,21] Stroop Color-Word Test (Stroop I, Stroop II, Stroop III), Trail Making Test (TMT-A, TMT-B), Frontal Assessment Battery (FAB), Digit Span Test (forward and backward),[22–25] and category verbal fluency test (animal naming).[26] Due to an amendment of the neuropsychological test battery in June 2019 (AURORA and FOCAS), a subgroup of participants who had their visit before this amendment performed the aforementioned test battery without the RAVLT, Stroop Color-Word Test, and verbal fluency test. Control participants underwent cognitive testing using the MMSE, Hopkins Verbal Learning Test (HVLT),[27] TMT (TMT-A, TMT-B), COWAT FAS (letter fluency test), and verbal fluency test (animal naming).[26,28]

Global cognition was assessed with the MMSE and MoCA (total score); memory encompassed the RAVLT and HVLT (total score on trial 1-5 and number correct on delayed recall); processing speed consisted of TMT-A (time in seconds), Stroop I, and Stroop II (time in seconds); executive function was measured through the TMT B/A-ratio (as a measure for cognitive flexibility),[29] Stroop III/II ratio (as a measure of interference time),[22] and Digit Span test (longest span correct); language was assessed with the verbal fluency test and COWAT FAS (total number correct). An overview of the cognitive domains and tests is shown in Supplementary Table 1. Years of education and education level were retrieved and classified as ranging from 1 (low) to 7 (high) to estimate premorbid intellectual abilities. Level of education was categorized as the highest completed level (1 to 3 low, 4 or 5 middle, 6 or 7 high level): 1: primary education; 2: lower vocational education; 3: low-level secondary education or ≤3 years mid- to high-level secondary education; 4: secondary vocational education; 5: average- or high-level secondary education; 6: university of applied sciences; 7: university degree.[30] By design, neuropsychological testing was performed unblinded to clinical characteristics other than MRI data.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (eg, PubMed) sources. Cerebral amyloid angiopathy (CAA) is a key contributor to intracerebral hemorrhage (ICH) and cognitive dysfunction in the elderly. Dutch-type hereditary CAA (D-CAA) is a rare autosomal-dominant disease with a pathology similar to that in non-hereditary, that is, sporadic, CAA (sCAA). A clear understanding of the cognitive profile and the association between focal brain lesions on magnetic resonance imaging (MRI) and cognitive dysfunction in patients with CAA is lacking.
2. **Interpretation**: Our findings suggest that in the early disease stages, before the occurrence of symptomatic ICH, 20% to 30% of D-CAA mutation carriers already show cognitive dysfunction. Further, patients with sCAA show worse cognition compared with symptomatic D-CAA mutation carriers. Lastly, an increase in focal brain lesions on MRI is associated with decreased processing speed.
3. **Future directions**: More awareness of cognitive dysfunction in the early disease stages is needed, and the relationship between brain lesions on MRI and cognition needs further exploration.

2.4 | Radiological assessment

Each marker was scored by two experienced raters independently on 3T-MRI (Philips Achieva, Best, the Netherlands; see Supplemental Methods). In case of discrepancy, a neuroradiologist with over 15 years of experience in the field was consulted. MRI markers were scored in accordance with the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria and with previously described rating scales.[31] We calculated the cSVD CAA burden score as the summary score of lobar CMB (2-4 CMBs: 1 point, ≥5: 2 points), cSS (focal: 1 point, disseminated: 2 points), WMHs (deep WMH Fazekas score 2 or 3 and/or periventricular WMH Fazekas score 3: 1 point), and enlarged perivascular spaces in the centrum semiovale CSO-EPVS (> 20: 1 point) on a 6-point ordinal scale. A higher cSVD CAA-burden score reflects a more severe disease burden on MRI.[32] MRI scans were rated blinded to clinical characteristics and neuropsychological testing

results. Hemorrhagic markers were rated on susceptibility-weighted imaging (SWI), further details about MRI acquisition are given in the Supplemental Methods.

2.5 | Statistical analyses

Data are presented for D-CAA ICH− and ICH+ mutation carriers, patients with sCAA and controls separately. Demographic data and clinical characteristics are displayed as means with standard deviations (SDs) or median with interquartile ranges (IQRs) as appropriate.

For the global cognition domain, we calculated the average of the MoCA and MMSE scores and then adjusted for age, sex, and education level in the regression model. For the memory, processing speed, executive function, and language domains, we calculated age-, sex-, and education-adjusted *z*-scores for the individual neuropsychological tests, using normative data from the Dutch population, and averaged them into domain scores.[21,33,34] Aborted tests were assigned a *z*-score of −3SD. Cognitive dysfunction was defined as an average global cognition score of ≤25/30 or a *z*-score of ≤−1SD on the other four cognitive domains. The cut-off score was set at ≤25 because this is the cut-off in the testing manuals of both the MoCA and the MMSE, and both tests have the same scoring range. This aligns with the criteria set by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; Neurocognitive disorders – mild neurocognitive disorder).[35]

First, we performed global tests to assess any difference in cognition between all five groups. To be specific, these are chi-squared tests on 4 degrees of freedom. Then we conducted multivariable linear regression analysis to compare global cognition between groups (D-CAA ICH−, D-CAA ICH+, sCAA, controls <50 and controls ≥50), adjusted for age, sex, and education level. Then we performed univariable linear regression analysis to compare the other four cognitive domains between groups. Following the statistical significance of these tests, we performed pairwise comparisons of the following groups (uncorrected for multiple testing): (1) D-CAA ICH− mutation carriers versus controls <50 years, (2) D-CAA ICH− versus ICH+ mutation carriers, (3) D-CAA ICH+ mutation carriers versus patients with sCAA, (4) D-CAA ICH+ mutation carriers versus controls ≥50, and (5) patients with sCAA versus controls ≥50. Secondly, we performed linear regression analysis for participants with D-CAA and sCAA to assess the association between cSVD CAA burden score and cognition.

The regression assumptions of linearity, homoskedasticity, and normality were assessed and not violated. By nature, there exists multicollinearity between the different cognitive domains. The influence thereof was reduced by constructing separate regression models for each domain, acknowledging that some over- or underestimation might be induced.

2.6 | Sensitivity analyses

To investigate the cognitive profile of patients with more severe cognitive impairments, we performed a sensitivity analysis in which cognitive dysfunction was defined as an average global cognition score of ≤25/30 or a *z*-score of ≤−2.0 SD on the other four cognitive domains.

3 | RESULTS

We included 159 participants in our study: 44 D-CAA ICH− mutation carriers (mean age 44 years), 25 D-CAA ICH+ mutation carriers (mean age 59 years), 60 patients with sCAA (mean age 71 years), 15 controls <50 years (mean age 37 years), and 15 controls ≥50 years (mean age 59 years) (Table 1, Figure S1, Table S2). Thirty-six (60%) patients with sCAA, 31 (71%) with D-CAA ICH−, and 19 (76%) with D-CAA ICH+ underwent the neuropsychological test battery before the source cohort protocol amendment (ie, prior to June 2019).

Among patients with D-CAA ICH−, seven (16%) had a first presentation due to cognitive complaints, five (13%) had objectified cognitive decline at the cohort visit, and the mean time since onset of cognitive decline was 1(SD:1.5) years. In the sCAA ICH− group, five (18%) presented due to cognitive decline, eight (29%) due to TFNE, and 14 (50%) due to other reasons. Patients with CAA generally had a higher frequency of vascular risk factors than their corresponding controls (Table 1).

An overview of the cognitive function and domain scores is shown in Table 2. There were significant differences between the five groups in global cognition ($X2$ [4, N = 139] = 46.55, p < 0.001), memory ($X2$ [4, N = 71] = 65.26, p < 0.001), processing speed ($X2$ [4, N = 151] = 28.56, p < 0.001), and executive function ($X2$ [4, N = 154] = 114.81, p < 0.001). No differences were found for language ($X2$ [4, N = 69] = 3.15, p = 0.534).

3.1 | Cognitive dysfunction within groups

In D-CAA ICH− mutation carriers, memory dysfunction (ie, ≤−1SD below average of Dutch population) was most common and occurred in 31% of the carriers, followed by dysfunction in executive function speed (21%), processing speed (16%), and global cognition (11%). Dysfunction in language occurred least often (8%). In D-CAA ICH+ mutation carriers, 50% showed dysfunction in memory, followed by 35% in executive function, 25% in language, 24% in global cognition, and 13% in processing speed. In patients with sCAA, the most common dysfunction was found in memory (58%) and processing speed (46%), followed by executive function (33%), global cognition (27%), and language (18%) (Table 3). The cognitive profile of patients with sCAA stratified by history of ICH can be found in Table S2. There were more patients with sCAA ICH+ who had cognitive dysfunction in the domain of executive function, whereas patients with sCAA ICH− more often had dysfunction in the memory domain.

In controls <50 years, the most common dysfunction was found in language (33%), followed by executive function and memory (both 7%). No dysfunction was present in processing speed or global cognition (both 0%). In controls ≥50 years, the order of most common

TABLE 1 Baseline characteristics.

n	All patients 129	D-CAA ICH− 44	D-CAA ICH+ 25	sCAA 60	Controls <50 years 15	Controls ≥50 years 15
Age, mean, years (SD)	57.3 (14.9)	44.1 (11.3)	59.2 (6.8)	70.7 (6.7)	37.1 (5.7)	58.7 (6.5)
Women, *n* (%)	73 (45.9)	26 (59.1)	10 (40.0)	25 (41.7)	3 (20.0)	9 (60.0)
First CAA-related complaints, *n* (%)						
ICH	51 (40)	0 (0)	22 (88)	29 (48)	–	–
(Subjective) Cognitive decline	12 (9)	7 (16)	0 (0)	5 (8)	–	–
Transient focal neurological episodes	11 (9)	0 (0)	0 (0)	11 (18)	–	–
Seizures	5 (4)	3 (7)	2 (8)	0 (0)	–	–
Convexity subarachnoid hemorrhage	3 (2)	0 (0)	0 (0)	3 (5)	–	–
Other	14 (11)	1 (2)	1 (4)	12 (20)	–	–
None/genetic testing/research	33 (26)	33 (75)	–	–	15 (100)	15 (100)
Time since first complaints, years, median [IQR]	1 [0, 3]	2 [0, 4]	2 [1, 5]	1 [0, 2]	–	–
Reports subjective cognitive complaints, *n* (%)	66 (71)	8 (80)	17 (71)	41 (70)	NA	NA
History of cognitive decline, *n* (%)	30 (35)	5 (56)	8 (36)	17 (32)	NA	NA
Time since start of cognitive decline, years, median [IQR]	0 [0, 2]	NA	0 [0, 2]	0 [0, 1]	NA	NA
History of symptomatic ICH, *n* (%)[a]	63 (39.9)	–	25 (100.0)	32 (53.3)	–	–
No. symptomatic ICH, median [IQR][a]	0 [0, 1]	–	2 [1, 3]	1 [0, 1]	–	–
History of depression, *n* (%)	24 (19.4)	6 (14.0)	4 (16.7)	14 (24.6)	–	–
History of subjective personality change[b], *n* (%)	66 (52.0)	12 (27.9)	16 (64.0)	38 (64.4)	–	–
History of apathy, *n* (%)	20 (16.3)	2 (4.7)	6 (25.0)	12 (21.4)	–	–
Education, years (SD)	13.5 (3.7)	14.2 (2.7)	12.8 (3.7)	13.9 (3.9)	13.1 (3.5)	11.9 (5.3)
Education level, *n* (%)						
High	36 (28)	12 (29)	8 (35)	16 (33)	6 (40)	6 (40)
Average	47 (36)	23 (55)	5 (22)	19 (39)	9 (60)	8 (53)
Low	31 (24)	7 (17)	10 (44)	14 (29)	0	1 (7)
CAA burden score, median [IQR]	3 [1, 5]	1 [0, 3]	4 [4, 5]	4 [3, 6]	0 [0, 0]	0 [0, 1]
Cortical superficial siderosis, *n* (%)						
Focal	12 (8)	4 (9)	6 (24)	2 (3)	0 (0)	0 (0)
Disseminated	27 (17)	1 (2)	6 (24)	20 (33)	0 (0)	0 (0)
Cerebral microbleeds, mean (SD)	160 (271)	61 (144)	332 (398)	156 (234)	0.1 (0.5)	0 (0)
CSO-EPVS grade, median [IQR]	4 [3, 4]	3 [2, 4]	4 [3, 4]	4 [3, 4]	0 [0, 0]	0 [0, 1]
Fazekas DWMH grade, median [IQR]	2 [1, 2]	1 [0, 2]	2 [2, 3]	2 [1, 2]	0 [0, 0]	0 [0, 1]
Hypertension, *n* (%)	53 (33.3%)	10 (22.7%)	6 (24.0%)	31 (51.7%)	0 (0.0%)	6 (40.0%)
Hypercholesterolemia, *n* (%)	44 (27.7%)	5 (11.4%)	10 (40.0%)	27 (45.0%)	0 (0.0%)	2 (13.3%)
Diabetes mellitus type II, *n* (%)	7 (4.4%)	1 (2.3%)	2 (8.0%)	4 (6.7%)	0 (0.0%)	0 (0.0%)
Smoking (ever), *n* (%)	83 (52.2%)	28 (63.6%)	15 (60.0%)	40 (66.7%)	–	–
Alcohol use (ever), *n* (%)	111 (69.8%)	39 (88.6%)	23 (92.0%)	49 (81.7%)	–	–

Note. History of symptomatic ICH for 1/40 of D-CAA ICH− mutation carriers was missing.

Abbreviations: CSO-EPVS centrum semi-ovale enlarged perivascular spaces; D-CAA, Dutch-type cerebral amyloid angiopathy; DWMH, deep white matter hyperintensities; ICH, intracerebral hemorrhage; IQR, interquartile range; sCAA, sporadic cerebral amyloid angiopathy; SD, standard deviation.

[a]Recorded only for patients with history of symptomatic ICH.

[b]Collected as personal experience of change in character in most recent years.

TABLE 2 Cognitive profile in (D-)CAA.

n	D-CAA ICH− 44	D-CAA ICH+ 25	sCAA 60	Controls < 50 years[a] 15	Controls ≥50 years[a] 15
Global cognition, mean (SD)	**28.0 (1.7)**	**27.2 (2.1)**	**25.8 (3.0)**	**29 (0.9)**	**29 (0.5)**
Domain score based on tests, *n* (%)	44 (100)	25 (100)	60 (100)	15 (100)	15 (100)
MMSE, median [IQR]	29 [28, 30]	28 [27, 30]	28 [27, 29]	30 [29, 30]	29 [29, 30]
MoCA, median [IQR]	28 [26, 29]	27 [24, 29]	25 [23, 27]	–	–
Memory, *z*-score mean (SD)	**−0.6 (1.0)**	**−0.5 (1.7)**	**−1.0 (0.8)**	**0.7 (0.9)**	**0.9 (0.6)**
Domain score based on tests, *n* (%)	13 (30)	4 (16)	24 (40)	15 (100)	15 (100)
RAVLT immediate recall, median [IQR]	44 [36, 49]	30 [23, 46]	27 [21, 34]	–	–
RAVLT delayed recall, median [IQR]	9 [6.5, 12]	6 [5, 11]	5 [3, 7]	–	–
Processing speed *z*-score mean (SD)	**0.0 (1.0)**	**0.0 (1.1)**	**−1.0 (1.5)**	**0.2 (0.7)**	**−0.1 (1.0)**
Domain score based on tests, *n* (%)	43 (98)	23 (92)	55 (92)	15 (100)	15 (100)
TMT-A, s, median [IQR]	26 [20, 34]	35 [25, 43]	49 [32, 70]	27 [20, 29]	39 [26, 49]
Stroop I, s, median [IQR]	44 [43, 52]	45 [41, 58]	56 [50, 65]	–	–
Stroop II, s, median [IQR]	57 [52, 61]	65 [53, 85]	79 [65, 86]	–	–
Executive function *z*-score mean (SD)	**−0.4 (0.6)**	**−0.6 (0.8)**	**−0.6 (0.8)**	**1.1 (1.2)**	**1.5 (1.2)**
Domain score based on tests, *n* (%)	44 (100)	23 (92)	57 (95)	15 (100)	15 (100)
Cognitive flexibility (TMT B/A), mean (SD)	2.8 (0.5)	2.6 (1.1)	2.6 (1.0)	2.0 (0.5)	2.0 (0.6)
TMT-B, s, median [IQR]	57 [43,76]	81 [50, 134]	105 [62, 161]	46 [37, 61]	70 [51, 96]
Stroop interference (Stroop III/Stroop II), mean (SD)	1.4 (0.2)	1.8 (0.4)	1.9 (0.4)	–	–
Stroop III, s, median [IQR]	78 [73, 82]	97 [84, 192]	131 [112, 189]	–	–
Digit span forwards, median [IQR]	6 [5, 7]	5 [5, 6]	5 [5, 6]	–	–
Digit span backwards, median [IQR]	4 [4, 6]	4 [3, 5]	4 [3, 5]	–	–
FAB, median [IQR]	18 [17, 18]	16 [14, 18]	16 [14, 18]	–	–
Language *z*-score mean (SD)	**−0.1 (0.7)**	**−0.5 (1.1)**	**−0.3 (0.8)**	**−0.5 (0.8)**	**−0.5 (0.6)**
Domain score based on tests, *n* (%)	13 (30)	4 (16)	22 (37)	15 (100)	15 (100)
Category fluency, words, median [IQR]	25 [22, 29]	19 [16, 27]	20 [17, 22]	23 [17-29]	20 [19, 22]

Abbreviations: CAA, cerebral amyloid angiopathy; D-CAA, Dutch-type cerebral amyloid angiopathy; FAB, frontal assessment battery; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey-Auditory Verbal Learning Test; TMT, trial making test; sCAA, sporadic cerebral amyloid angiopathy; STROOP, STROOP Color-Word Test.

[a]Cognitive domain scores of control subjects consist of different cognitive tests, see Table S1.

dysfunction was processing speed (27%), language (20%), and executive function (7%), all without dysfunction in memory or global cognition (both 0%).

3.2 | Cognitive dysfunction between different groups

D-CAA ICH− mutation carriers performed worse on global cognition (mean difference in domain score [95% CI] = −1.35 [−2.67, −0.04]; $p = 0.044$), memory (mean difference [95% CI] = −1.27 [−1.91, −0.63]; $p < 0.001$), and executive function (mean difference [95% CI] = −1.48 [−1.97, 0.98]; $p < 0.001$) compared with controls <50 years. Performance on processing speed did not differ between the two groups. D-CAA ICH+ mutation carriers did show worse performance on global cognition (mean difference [95% CI] = −2.27 [−3.72, −0.82]; $p = 0.002$) and memory (mean difference [95% CI] = −1.41 [−2.36, −0.46]; $p = 0.004$) compared with controls ≥50 years. Global cognition, processing speed, and executive function were more affected in D-CAA ICH+ mutation carriers; none of these differences were significant compared with mutation carriers with D-CAA ICH−.

Patients with sCAA showed worse performance on global cognition (mean difference [95% CI] = −1.43 [−2.54, −0.33]; $p = 0.011$) and processing speed (mean difference [95% CI] = −1.0 [−1.57, −0.43]; $p < 0.001$) compared with D-CAA ICH+ mutation carriers and performed significantly worse in all cognitive domains compared with controls ≥50 years (Table 4 and Figure 1; univariate comparison in Table S3).

TABLE 3 Prevalence of cognitive dysfunction in (D-)CAA and controls.

	D-CAA ICH− 44	D-CAA ICH+ 25	sCAA 60	Controls < 50 years 15	Controls ≥ 50 years 15
Global cognition					
No. tests	44	25	60	15	15
Cognitive dysfunction	11.4%	24.0%	26.7%	0.0%	0.0%
Memory					
No. tests	13	4	24	15	15
Cognitive dysfunction	30.8%	50.0%	58.3%	6.7%	0.0%
Processing speed					
No. tests	43	23	55	15	15
Cognitive dysfunction	16.3%	13.0%	45.5%	0.0%	26.7%
Executive function					
No. tests	44	23	57	15	15
Cognitive dysfunction	20.5%	34.8%	33.3%	6.7%	6.7%
Language					
No. tests	13	4	22	15	15
Cognitive dysfunction	7.7%	25.0%	18.2%	33.3%	20.0%

Note. Data represent *n* (%) of participants with cognitive dysfunction defined as a global cognitive function score of ≤25/30 as a score of ≥1 SD below Dutch normative data for the other domains.
Abbreviations: D-CAA, Dutch-type cerebral amyloid angiopathy; sCAA, sporadic cerebral amyloid angiopathy.

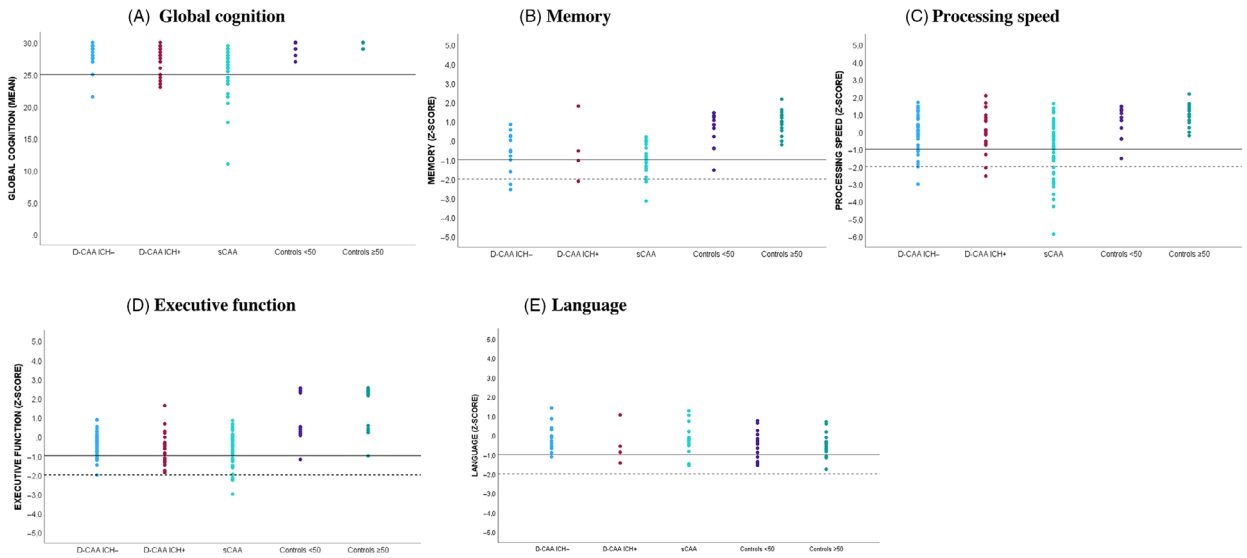

FIGURE 1 Cognitive performance in D-CAA and sCAA.

3.3 | cSVD CAA burden score and cognition

In the total patient population, a higher cSVD CAA burden score was associated with worse cognitive performance on processing speed (unstandardized β [95% CI] = −0.20 [−0.33, −0.07]; p = 0.003). No association was observed with the other four cognitive domains: global cognition (β [95% CI] = −0.02 [−0.39, 0.44]; p = 0.909), memory (β [95% CI] = 0.01 [−0.22, 0.23]; p = 0.949), executive function (β [95% CI] = −0.05 [−0.13, 0.02]; p = 0.171), and language (β [95% CI] = 0.09 [−0.07, 0.25]; p = 0.252) (Figure 2; univariate analysis in Table S4).

3.4 | Sensitivity analyses

The sensitivity analysis that restricted the cut-off for cognitive dysfunction to ≤−2.0 SD yielded similar results as the main analysis, albeit with altered proportion estimates (Table S5)

TABLE 4 Comparison of mean domain scores.

Group comparison	Domain	Mean difference [95% CI]	*p*-value
D-CAA ICH− versus controls < 50 years	Global cognition	−1.35 [−2.67, −0.04]	**0.044**[a]
	Memory	−1.27 [−1.91, −0.63]	**<0.001**[a]
	Processing speed	−0.18 [−0.87, 0.51]	0.613
	Executive function	−1.48 [−1.97, 0.98]	**<0.001**[a]
	Language	0.44 [−0.89, 0.97]	0.103
D-CAA ICH+ versus D-CAA ICH−	Global cognition	−0.85 [−1.99, 0.28]	0.141
	Memory	0.14 [−0.82, 1.11]	0.770
	Processing speed	−0.06 [−0.66, 0.54]	0.839
	Executive function	−0.21 [−0.64, 0.22]	0.332
	Language	−0.36 [−1.19, 0.47]	0.393
D-CAA ICH+ versus controls ≥50 years	Global cognition	−2.27 [−3.72, −0.82]	**0.002**[a]
	Memory	−1.41 [−2.36, −0.46]	**0.004**[a]
	Processing speed	0.07 [−0.70, 0.84)	0.859
	Executive function	−2.08 [−2.63, −1.53]	0.194
	Language	0.01 [−0.78, 0.80]	0.972
sCAA versus D-CAA ICH+	Global cognition	−1.43 [−2.54, −0.33]	**0.011**[a]
	Memory	−0.54 [−1.46, 0.37]	0.245
	Processing speed	−1.0 [−1.57, −0.43]	**<0.001**[a]
	Executive function	−0.01 [−0.42, 0.40]	0.964
	Language	0.12 [−0.67, 0.90]	0.764
sCAA versus controls ≥50 years	Global cognition	−3.70 [−4.99, −2.41]	**<0.001**[a]
	Memory	−1.95 [−2.51, −1.40]	**<0.001**[a]
	Processing speed	−0.93 [−1.60, −0.26]	**0.007**[a]
	Executive function	−2.09 [−2.57, −1.61]	**<0.001**[a]
	Language	0.14 [−0.33, 0.60]	0.573

Note. Data represent mean difference scores and 95% CI's resulting from age, sex, and education adjusted analyses. These values represent how much the Z-scores of the cognitive domains differs between CAA phenotypes and controls.
Abbreviations: D-CAA, Dutch-type cerebral amyloid angiopathy; sCAA, sporadic cerebral amyloid angiopathy.
[a]Statistical significance.

4 | DISCUSSION

The key findings from this study can be summarized in three main points. First, we found that 20% to 30% of the D-CAA mutation carriers without symptomatic hemorrhage showed executive and memory dysfunction. Second, both symptomatic D-CAA mutation carriers and patients with sCAA demonstrated a decrease in cognitive function, most pronounced in the domains of global cognitive performance and memory. Third, higher cSVD-CAA burden as assessed by MRI was related to a decrease in processing speed.

Our finding that cognitive dysfunction is prevalent among D-CAA mutation carriers in the presymptomatic stage has implications for clinical practice. This new insight highlights the importance of awareness of cognitive dysfunction in the years leading up to the first sICH, as individuals may encounter work-related limitations or experience CAA-related cognitive effects, often associated with stress or even burnout, without recognizing that they are already affected cognitively. Early awareness can enable timely counseling and support. This is, in our experience, also in line with patients with sCAA who often report problems at work years before CAA diagnosis. Our results are not consistent with an earlier study from our institute in presymptomatic D-CAA mutation carriers that found no cognitive changes on testing in the presymptomatic stage of the disease. This could be due to the smaller sample size ($n = 12$) and younger age of D-CAA mutation carriers (34.4 years) in that study.[2]

Overall, cognitive function decreased in both D-CAA ICH+ and ICH− mutation carriers and patients with sCAA compared with controls ≥50 years. Furthermore, patients with sCAA exhibited a more pronounced decrease in cognitive function compared with D-CAA ICH+ mutation carriers. Although we corrected for age in our analyses, it was not feasible to correct for all age-related pathology, and this probably resulted in the more pronounced cognitive dysfunction in patients with sCAA.[36] The observed decrease in cognitive function in D-CAA ICH+ mutation carriers, compared with age-matched controls,

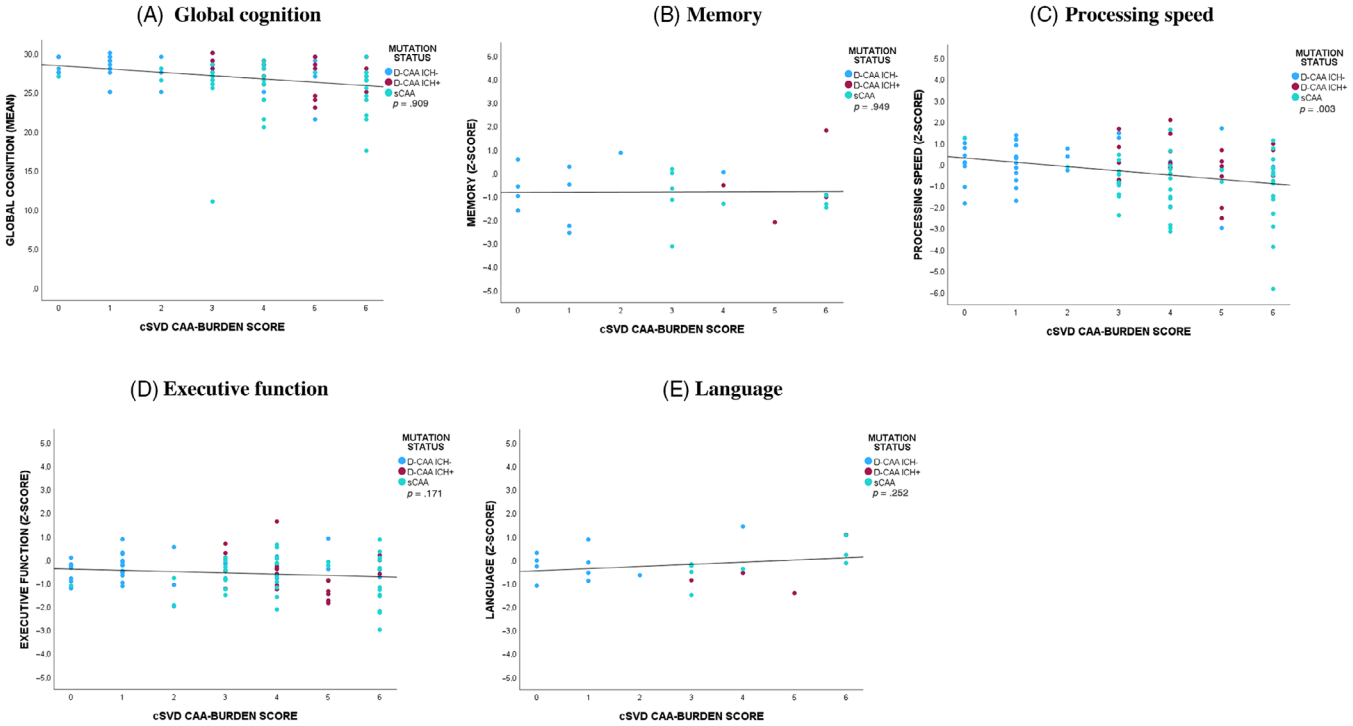

FIGURE 2 Association between cognitive performance and cSVD CAA burden.

implies an independent contribution of amyloid pathology to cognitive dysfunction.[37]

Surprisingly, we did not find differences in cognitive function between D-CAA ICH+ and ICH− mutation carriers. This may be due to the relatively advanced age of presymptomatic D-CAA mutation carriers in our sample and, therefore, a relatively limited difference in age and disease stage compared with the symptomatic carriers. Additionally, selection bias might have occurred, since it is more likely that relatively healthy D-CAA ICH+ mutation carriers participated in our study. Notably, prior research showed an association between CAA and cognitive dysfunction before the occurrence of sICH.[38] This association emphasizes that sICH is not the sole mechanism contributing to cognitive dysfunction in CAA and highlights the importance of underlying small vessel mechanisms.[36] Further, we considered ICH to be symptomatic when the participant had suffered from symptoms and/or signs that could directly be attributed to the ICH. This definition might be debated, since asymptomatic ICH has been observed in presymptomatic D-CAA mutation carriers and probably also contributes to cognitive dysfunction. Non-hemorrhagic CAA-related changes might already affect cognition at an earlier stage of disease before the onset of hemorrhagic changes.[4] Although we observed similar WMH and CSO-EPVS grades across all patient groups, we could not further assess the influence of non-hemorrhagic markers (eg, vasoreactivity, cortical microinfarcts, or changes in diffusion tensor imaging) on cognition. This awaits further investigation. Nonetheless, by including patients with D-CAA ICH− who all had limited hemorrhagic CAA burden (63% without hemorrhagic burden), we were able to capture some of the early CAA-related changes in cognition in our study. Our results highlight the need for additional research to better understand the mechanisms of CAA on cognitive (dys)function.

We found an association between increased cSVD-CAA burden score on MRI and diminished processing speed at testing. Because of our cross-sectional design, no statements about causality of this association could be made. The finding is in line with a study with 189 patients at risk of cSVD that showed associations between higher cSVD burden on MRI and decreased performance of processing speed and overall cognition.[39] Moreover, it has been found that multiple types of brain lesions in CAA can together affect cognition through disruption of the brain connectivity.[9] The observed association between cSVD-CAA burden and diminished processing speed may be a reflection of the broader impact of CAA-related macrovascular pathology on cognitive function. Therefore, macrostructural alterations can be considered a link between vascular pathology and clinical manifestations. At the same time, we note that the processing speed of patients and controls were similar and that the clinical relevance of our observation should be further evaluated in future studies.

We note several methodological considerations about neuropsychological testing. There is considerable pathophysiological overlap between CAA and AD.[40] Therefore, we cannot exclude the possibility that some of our patients also had AD pathology. While such copathology is seldom present in D-CAA, this might have influenced our findings in patients with sCAA. As concomitant AD might affect all the cognitive domains under investigation, the directionality of this potential bias is uncertain.[41] At the same time, a previous study in sCAA did not observe differences in global cognition or the type

of affected cognitive domain(s) between patients with and without concomitant AD based on CSF markers.[42] The impact of concomitant AD on the cognitive profile of patients with CAA remains to be further evaluated in future studies. Further, we note that the measures used to assess language function are all time-dependent tests and might, therefore, also be confounded by general psychomotor slowness and executive function. This might also have played a role in our assessment of memory, which was evaluated with the RAVLT/HVLT. In extension, this might explain why 33% of control participants had language dysfunction, although that might also be a consequence of the −1SD cut-off being too conservative (dysfunction absent in the sensitivity analysis with cut-off −2SD). Next, we acknowledge that the scores for cognitive performance might have been influenced by somatic impairments, such as motor or coordination deficits (5% of all patients in our study; 24% unknown due to COVID-19 restrictions). This might have introduced a slight measurement error in our study.

The strengths of our study are its unique, well-defined hereditary CAA population including D-CAA ICH− mutation carriers with limited coexisting age-related pathology. Second, data for patients with sCAA and D-CAA mutation carriers were prospectively collected using a standardized neuropsychological assessment and high-quality 3T imaging performed at the same study visit. Our study also has limitations. We excluded participants without neuropsychological assessment, resulting in selection bias, so we potentially underestimated the true severity of cognitive dysfunction. In addition, our inferences about the language and memory domains are limited by high missingness of cognitive tests for these domains. Another important limitation is that there were some differences in neuropsychological assessment between the CAA groups and controls, which could have influenced the comparability of the results. Next, some over- or underestimation effect might exist in the regression model coefficients, even though we attempted to reduce the influence of multicollinearity by attempting to maximize the sample size and by constructing separate models for the different cognitive domains. This might be further assessed in future replication studies.

In summary, our study shows that even in the early disease stages, a substantial part of presymptomatic D-CAA mutation carriers show dysfunction in executive function and worse cognitive function in multiple domains compared with age-matched controls. Moreover, patients with sCAA show worse global cognition and processing speed compared with symptomatic D-CAA mutation carriers. More awareness is needed of cognitive dysfunction in the years before the first sICH. Lastly, an increase in cSVD CAA burden on MRI is linked to a decrease in processing speed. Further exploration of this relationship in future studies is warranted.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants provided informed consent before their enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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