ORIGINAL RESEARCH

Cerebral Amyloid Angiopathy Is Associated With Emotional Dysregulation, Impulse Dyscontrol, and Apathy

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BACKGROUND: Cerebral amyloid angiopathy (CAA) causes cognitive decline, but it is not known whether it is associated with neuropsychiatric symptoms (NPS).

METHODS AND RESULTS: Participants with CAA, mild cognitive impairment, mild dementia due to Alzheimer's disease, and normal cognition were recruited from stroke and dementia clinics and community advertising. NPS were captured using the Neuropsychiatric Inventory Questionnaire short form. The number and total severity (number multiplied by severity of each symptom [mild, moderate, or severe]) of NPS were analyzed using generalized linear regression with a negative binomial link and multiple linear regression, adjusting for age, sex, and education. A total of 109 participants (43 with CAA, 15 with Alzheimer's disease, 28 with mild cognitive impairment, and 23 with normal cognition) (mean age 71.1 [SD=7.6]; 53.2% male) were included. The most frequent NPS in CAA were depression/dysphoria (48.8%), irritability/lability (37.2%), agitation/aggression (37.2%), apathy/indifference (34.9%), and anxiety (32.6%). In adjusted models, patients with CAA had 3.2 times (95% CI, 1.7–6.0) more NPS symptoms and 3.1 units (95% CI, 1.0–5.1) higher expected severity score. The number of NPS was similar to patients with mild cognitive impairment (3.2 times higher than controls) but less than in patients with Alzheimer's disease dementia (4.1 times higher than controls). Within patients with CAA, there were 1.20 times (95% CI, 1.01–1.32) more NPS per 1% increase in white matter hyperintensity as a percentage of intracranial volume.

CONCLUSIONS: NPS are common in CAA, with a similar prevalence as in mild cognitive impairment. The association of the total number of NPS with higher white matter hyperintensity volume suggests that white matter damage may underlie some of these symptoms.

Key Words: Alzheimer's disease ■ anxiety ■ apathy ■ cerebral amyloid angiopathy ■ depression ■ intracerebral hemorrhage ■ neuropsychiatric symptoms ■ stroke

Cerebral amyloid angiopathy (CAA) is caused by the deposition of amyloid in the cerebral vasculature. In the sporadic age-related form, the amyloid is formed by the Aβ peptide. Patients present with lobar intracerebral hemorrhages, subarachnoid hemorrhages, or transient focal neurological episodes.[1] More recently, CAA has been associated with cognitive impairment. In community-based autopsy studies, CAA is associated with greater decline in global cognition, perceptual speed, and episodic and semantic memory, even after controlling for the degree of accompanying Alzheimer's disease (AD) pathology.[2] Clinic-based studies show that patients with CAA frequently exhibit decreased processing speed, executive function, semantic fluency, and attention.[3,4] A 79% prevalence of mild cognitive impairment (MCI) is reported in CAA.[4]

CLINICAL PERSPECTIVE

What Is New?

- This is one of the first studies to evaluate the prevalence of neuropsychiatric symptoms in people with cerebral amyloid angiopathy, a cerebral small vessel disease that is known to cause cognitive impairment.
- People with cerebral amyloid angiopathy are at risk for having neuropsychiatric symptoms, with emotional dysregulation (including depression and anxiety), apathy, and impulse dyscontrol being most common.

What Are the Clinical Implications?

- Having more neuropsychiatric symptoms was associated with higher volume of cerebral white matter hyperintensities on magnetic resonance imaging, suggesting that ischemic damage to the white matter may cause some of these symptoms.

Nonstandard Abbreviations and Acronyms

CAA	cerebral amyloid angiopathy
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	neuropsychiatric symptoms

Neuropsychiatric symptoms (NPS) are commonly present in neurocognitive disorders and are associated with faster cognitive decline,[5] greater functional impairment,[6] and a faster progression to death.[7] NPS that manifest across the cognitive spectrum are clinically significant and of prognostic utility.

Although CAA has been characterized cognitively, little is known about the NPS profile of CAA. Two case-reports described depression, personality changes, and behavioral problems in patients with CAA.[8,9] However, the NPS profile of CAA in a larger cohort has not been well characterized, nor has it been compared with other clinical populations.

We examined the NPS profile of patients with CAA and compared it to the profile of participants with AD, MCI, and normal cognition (NC). We hypothesized that (1) participants with CAA would present with greater NPS burden compared with NC, similar to MCI and AD with mild dementia; (2) the most common NPS in CAA would be depression, irritability, and apathy; and (3) NPS burden would be higher in participants with more cerebral microbleeds and higher white matter hyperintensity (WMH) volume, which are biomarkers of CAA severity.

METHODS

Study Participants

We analyzed data collected as part of a prospective longitudinal cohort study: FAVR (Functional Assessment of Vascular Reactivity in Small Vessel Disease).[10] The primary aim of the study is to investigate the role of vascular dysfunction in small vessel disease.[9] FAVR participants were recruited by community advertising and through memory, stroke, and geriatric clinics in Calgary, Alberta, Canada. CAA was diagnosed based on a clinical presentation with lobar intracerebral hemorrhage, convexity subarachnoid hemorrhage, cognitive symptoms without dementia, or CAA-related inflammation, with neuroimaging evidence of probable CAA by Boston criteria.[11] AD with mild dementia was diagnosed using the National Institute of Aging-Alzheimer's Association criteria for clinically probable AD,[12] which require the presence of dementia of insidious onset and a typical AD clinical presentation (most commonly, an amnestic presentation) and no evidence of an alternative cause. MCI was diagnosed using the National Institute of Aging-Alzheimer's Association core clinical criteria for amnestic or multiple domain MCI,[13] which require concern regarding a change in cognition, impairment in 1 or more cognitive domains, and preservation of independence in functional abilities. NC controls were interviewed and examined by a neurologist to confirm the absence of previous stroke or other central nervous system diseases.

For all groups, participants were excluded if they were <60 years old, had other central nervous system diseases (eg, Parkinson's disease), had ongoing alcohol or drug abuse, were not fluent in English or French, had a Montreal Cognitive Assessment score of <13, or were unable to go undergo a magnetic resonance imaging (MRI) scan.

All study participants and their informants provided written informed consent to participate. The study was approved by an institutional review board. At the time of publication, de-identified participant data will be made available to the research community on the University of Calgary PRISM dataverse.

Assessments

Clinical Assessments

Age, demographics, and medical history were collecting using standardized case report forms.

Neuropsychiatric Symptoms

NPS were measured using the Neuropsychiatric Interview Questionnaire (NPI-Q) short form administered to an informant.[14] The NPI-Q consists of 12 questions on delusions, hallucinations, agitation/

Table 1. Neuropsychological Test Battery

Domain	Test battery 1	Test battery 2
Memory	California Verbal Learning II Free Delayed Recall	Rey auditory verbal learning
	Rey-Osterrieth Complex Figure delayed recall	Brief Visuospatial Memory Test Revised delayed recall
Executive function	Trail making B	Trail Making B
	Letter fluency (F, A, S)	Letter fluency (F, A, S)
	Category fluency (animals, vegetables)	Category fluency (animals, vegetables)
Processing speed	Trail Making A	Trail Making A
	Digit Symbol Coding (4th ed. of Wechsler Adult Intelligence Scale)	Digit Symbol Coding (3rd ed. of Wechsler Adult Intelligence Scale)

aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor, nighttime behavior, and appetite/eating. For each question the informant answers "Yes" (present) or "No" (absent), and if "Yes" is selected then the informant rates the symptom severity on a 3-point scale, ranging from mild to severe. Because the NPI-Q was a secondary study measure, an informant was not required at the study visit and consequently some participants did not have NPI-Q data because they chose not to be accompanied.

Neuropsychological Assessment Battery

Participants completed a 1.25-hour neuropsychological test battery based on harmonization standards for research on vascular cognitive impairment.[15] For each test, Z scores were derived from published norms and then grouped into domains of memory, executive, function, and processing speed.[4] To harmonize with a national study,[16] in November 2016 some tests were substituted for alternative ones that assessed the same

domains (Table 1). The memory domain Z score was based on the average of the California Verbal Learning Test II delayed recall, Rey Auditory Verbal Learning Test delayed recall,[17] Rey-Osterrieth Complex Figure delayed recall,[17] or the Brief Visuospatial Memory Test Revised delayed recall[18]; executive function was based on the average of Trail Making B,[19] phonemic fluency,[20] and category fluency[20]; and processing speed was based on the average of Trail Making A[19] and the digit symbol coding test of the Wechsler Adult Intelligence Scale (third or fourth edition).[21]

Markers of CAA Severity

MRI was performed on a 3.0 T Signa VH/I or MR750 (General Electric Healthcare, Waukesha, WI). Sequences included 3-dimensional T1-weighted inversion-recovery spoiled gradient recalled (repetition time/echo time=6/2.4 ms, flip angle=8°, voxel size 0.94×0.94×1.0 mm^3, 256×256×180 acquisition matrix); T$_2$-weighted fast spin echo (repetition time/echo time=3500/85 ms, flip angle=125°, echo train length=12, voxel size=0.94×0.94×3.5 mm^3, 39 slices, 256×256 acquisition matrix); T$_2$-weighted fluid attenuated inversion recovery (repetition time/echo time/inversion time=9000/149/2250 ms, voxel size 0.9×0.9×3.5 mm^3, 39 slices, 256×256 acquisition matrix); and 3-dimensional susceptibility-weighted imaging (repetition time/echo time=30/20 ms, flip angle=15°, voxel size 0.5×0.5×1.0 mm^3, 256×256×120 acquisition matrix). WMH was segmented using a custom-designed software application, Quantomo (Cypertrials, Inc, Calgary, Alberta, Canada),[10] and expressed as a percentage of the intracranial volume, which was determined using the Brain Extraction Tool.[22] Cerebral microbleeds and cortical superficial siderosis were assessed on susceptibility-weighted imaging combined phase and magnitude images by a neurologist.[23] Enlarged perivascular spaces were rated on the T2-weighted sequence using a 4-point visual rating scale.[24] The CAA-Small Vessel Disease score was calculated based on the number ofcerebral

Table 2. Characteristics of Participants With and Without NPI-Q information

	Cerebral amyloid angiopathy		Alzheimer's disease		Mild cognitive impairment		Normal cognition	
	Included (n=43)	Excluded (n=17)	Included (n=15)	Excluded (n=8)	Included (n=28)	Excluded (n=13)	Included (n=23)	Excluded (n=27)
Age, y	72.8 (6.8)	76.1 (8.2)	70.3 (7.0)	69.2 (9.4)	72.3 (7.1)	68.3 (6.4)	66.6 (8.9)	69.7 (8.8)
Male, n (%)	25 (58.1)	11 (64.7)	9 (60.0)	5 (62.5)	17 (60.7)	6 (46.2)	7 (30.4)	0 (33.3)
Years of education	13 (12–15)	12 (11–15)	16 (12–18)	15 (13–17)	15 (12–17.5)	16 (14–16)	14 (13–17)	27 (12–17)
Memory	−0.95 (1.11)	−0.87 (1.42)	−2.00 (0.81)	−2.45 (0.62)	−1.07 (1.24)	−0.70 (1.12)	1.04 (1.44)	0.32 (0.95)
Executive function	−1.32 (1.04)	−1.31 (0.91)	−1.55 (0.86)	−1.50 (1.12)	−0.76 (1.01)	−1.54 (0.75)	0.46 (0.93)	0.05 (0.84)
Processing speed	−1.20 (1.12)	−0.81 (0.66)	−1.37 (1.11)	−1.22 (1.05)	−0.28 (1.01)	−0.81 (0.86)	0.89 (0.83)	0.28 (0.85)

Values are mean (SD) or median (quartile 1–quartile 3) unless otherwise noted. Memory, executive function, and processing speed domain scores are expressed as Z scores relative to normative means and SDs provided by the testing manuals. NPI-Q indicates Neuropsychiatric Inventory Questionnaire.

Table 3. Sample Characteristics

	Overall (n=109)	Cerebral amyloid angiopathy (n=43)	Alzheimer's disease (n=15)	Mild cognitive impairment (n=28)	Normal (n=23)	*P* value
Age, y	71.1 (7.6)	72.8 (6.8)	70.3 (7.0)	72.3 (7.1)	67.0 (8.6)	0.02
Male, n (%)	58 (53.2)	25 (58.1)	9 (60.0)	17 (60.7)	7 (30.4)	<0.01
Years of education	14 (12–16)	13 (12–15)	16 (12–18)	15 (12–17.5)	14 (13–17)	0.18
NPI-Q total	2 (0–3)	2 (1–3)	4 (1–5)	2 (1–4)	0 (0–1)	<0.01
NPI-Q severity total	2 (0–4.5)	3 (1–4)	5 (1–7)	3 (1–5)	0 (0–2)	<0.01

Values are mean (SD) or median (quartile 1–quartile 3) unless otherwise noted. *P* values were based on chi-square tests or Fisher's exact test (if any cell number was <5) for categorical variables, and the Kruskal-Wallis test for continuous variables. NPI-Q indicates Neuropsychiatric Inventory Questionnaire-Short Version.

microbleeds, cortical superficial siderosis, WMH, and enlarged perivascular spaces, as in a previous study.[25]

Statistical Analysis

The number (also referred to as rate) of NPS was calculated as the sum of all "yes" responses (range 0–12). The total severity was calculated as the sum of all severity scores (range 0–36), calculated by adding the severity scores (0–3 points based on none, mild, moderate, or severe symptoms) for the 12 symptoms. Chi-square, Fisher's exact, Mann-Whitney *U*, and Kruskal-Wallis tests were used to compare NPS and other characteristics among CAA, AD, MCI, and NC groups; and, within CAA, among those with and without history of intracerebral hemorrhage (ICH). Spearman correlation was used to determine whether the NPI-Q total number and severity were correlated with WMH volume and number of cerebral microbleeds at baseline. Generalized linear regression with a negative binomial link function was used to estimate the association between clinical group status and the

number of NPS, using NC as a reference. These models produce incidence rate ratios, which are interpreted as the ratio of the rate of NPS in patients to the rate of NPS in controls, after controlling for other covariates. Multiple linear regression was used estimate the association between group status and the total NPS severity, using NC as a reference. Both models were adjusted for age, sex, and years of education. These covariates for adjustment were selected before building the models, based on prior literature showing that age,[26] sex,[27] and education[28] are associated with the prevalence of mood and behavioral symptoms. Similar models were used to determine if MRI markers of CAA severity were associated with the number/severity of NPS, restricted to the participants with CAA only. Logistic regression was used to explore whether markers of CAA severity were associated with the presence or absence of each of the 12 NPS symptoms, adjusting for age, sex, and education. Data were missing for some participants for NPS total severity (n=1), memory domain score (n=2), executive function domain score (n=1), neuropsychological processing speed domain score (n=1), and MRI

Table 4. NPS Prevalence in CAA, AD, MCI, and Controls

Symptom type	Overall (n=109)	CAA (n=43)	AD (n=15)	MCI (n=28)	NC (n=23)	*P* value*
Agitation	34 (31.2)	16 (37.2)[†]	7 (46.7)	10 (35.7)	1 (4.4)	0.02
Anxiety	30 (27.5)	14 (32.6)[†]	4 (26.7)	11 (39.3)	1 (4.4)	0.03
Apathy	29 (26.6)	15 (34.9)[†]	6 (40.0)	5 (17.9)	3 (13.0)	0.10
Appetite	28 (25.7)	11 (25.6)	9 (60.0)	6 (21.4)	2 (8.7)	<0.01
Delusions	6 (5.5)	2 (4.7)	3 (20.0)	1 (3.6)	0	0.08
Depression	39 (35.8)	21 (48.8)[†]	6 (40.0)	9 (32.1)	3 (13.0)	0.03
Disinhibition	20 (18.4)	8 (18.6)	6 (40.0)	4 (14.3)	2 (8.7)	0.11
Elation	3 (2.8)	0	1 (6.7)	1 (3.6)	1 (4.4)	0.24
Hallucinations	0	0	0	0	0	0.99
Irritability lability	39 (35.8)	16 (37.2)[†]	7 (46.7)	14 (50.0)	2 (8.7)	0.01
Motor disturbance	10 (9.2)	5 (11.6)	2 (13.3)	3 (10.7)	0	0.32
Nighttime behaviors	24 (22.0)	6 (14.0)	4 (26.7)	10 (35.7)	4 (17.4)	0.16

Values are N (%). AD indicates Alzheimer's disease; CAA, cerebral amyloid angiopathy; MCI, mild cognitive impairment; NC, normal cognition; and NPS, neuropsychiatric symptoms.

P value based on the chi-square tests for differences according to group.
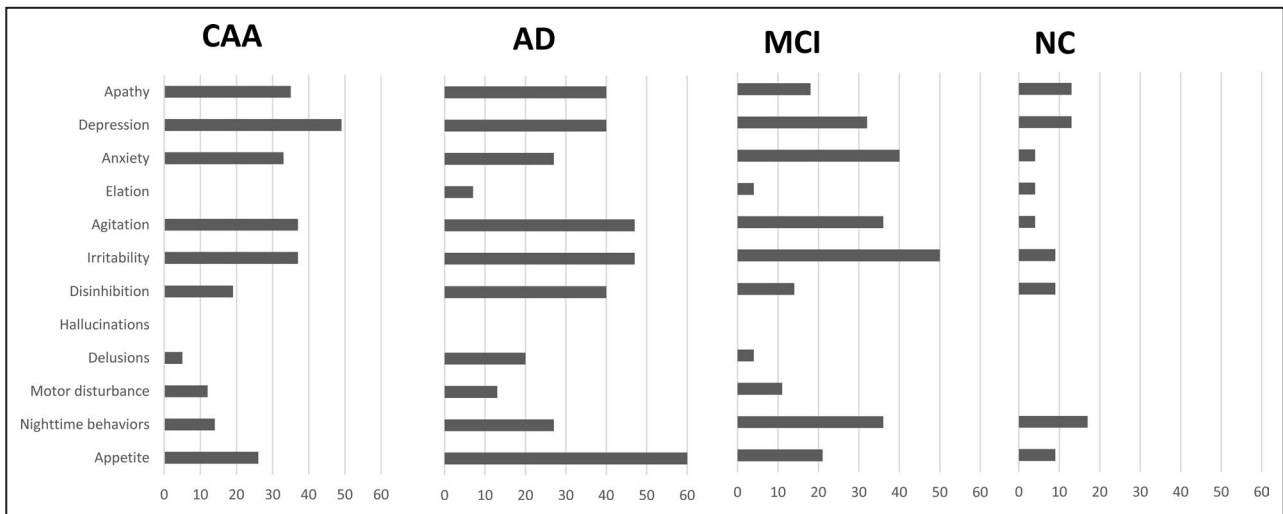
[†]*P*<0.05 for comparison of CAA with NC.

Figure. Frequency of neuropsychiatric symptoms in cerebral amyloid angiopathy (CAA) and comparison groups of Alzheimer's disease (AD) with mild dementia, mild cognitive impairment (MCI), and normal controls (NC).

(n=2). Results were considered statistically significant with a 2-sided *P*<0.05. All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

NPS in CAA

A total of 174 participants were enrolled in the study (60 with CAA, 23 with AD, 41 with MCI, 50 with NC) but because an informant (required for NPI-Q assessment) was not mandatory there were 109 with NPI-Q information (43 with CAA, 15 with AD, 28 with MCI, and 23 with NC). Characteristics of participants with and without NPI-Q data are shown in Table 2. Participants with NC were more likely to attend without an informant; otherwise, age, sex, years of education, and neuropsychological test performance were similar between those with and without NPI-Q data.

Baseline characteristics are shown in Table 3. The participants with CAA presented with lobar ICH (19),

transient focal neurological episodes (15), or cognitive symptoms without dementia (9). Most participants with CAA (36/43, 84%) had evidence of cognitive impairment, defined as *Z* scores more than 1 SD below the mean in one or more cognitive domains. The median number of NPS in patients with CAA was 2 (interquartile range [IQR], 1–3) and median total severity was 3 (IQR, 1–4). Comparing CAA with ICH to CAA without ICH, the number of NPS were similar (median 3 [IQR, 0–5] versus median 2 [IQR, 1– 3]; *P*=0.58) and the median total severity was similar (median 2.5 [IQR, 0–6] versus median 3 [IQR, 1–3]; *P*=0.86). Most controls (16/23, 70%) did not have any NPS (median number 0 [IQR, 0–1]; median severity was 0 [IQR, 0–2]).

The 5 most frequent NPS in CAA were depression/ dysphoria (48.8%), irritability/lability (37.2%), agitation/ aggression (37.2%), apathy/indifference (34.9%), and anxiety (32.6%) (Table 4). The patterns of NPS are graphically displayed in Figure. Comparing CAA with ICH to those without ICH, the proportion with each type of NPS was similar (depression/dysphoria 52.6%

Table 5. Multivariable-Adjusted Associations of CAA With Neuropsychiatric Symptoms Number and Total Severity

	Number of NPS		NPS total severity	
	Incidence rate ratio (95% CI)	*P* value	Estimate (95% CI)	*P* value
Group				
CAA vs NC	3.18 (1.69 to 5.99)	<0.01	3.07 (1.01 to 5.13)	<0.01
AD vs NC	4.08 (2.04 to 8.17)	<0.01	4.18 (1.73 to 6.64)	<0.01
MCI vs NC	3.23 (1.68 to 6.22)	<0.01	2.70 (0.55 to 4.86)	0.01
Age	0.97 (0.95 to 0.99)	0.03	−0.13 (−0.23 to −0.03)	0.01
Male	1.38 (0.94 to 2.03)	0.10	1.04 (−0.45 to 2.53)	0.17
Years education	0.98 (0.92 to 1.04)	0.41	−0.03 (−0.26 to 0.19)	0.77

AD indicates Alzheimer's disease; CAA, cerebral amyloid angiopathy; MCI, mild cognitive impairment; and NPS, neuropsychiatric symptoms.

Table 6. Comparing NPS Number and Severity Between CAA, MCI, and AD, Adjusted for Age, Sex, and Education

	Number of NPS		NPS total severity	
	Incidence rate ratio (95% CI)	P value	Estimate (95% CI)	P value
Group				
CAA vs MCI	0.98 (0.63 to 1.53)	0.94	0.37 (–1.41 to 2.15)	0.68
CAA vs AD	0.79 (0.46 to 1.31)	0.35	–1.11 (–3.34 to 1.12)	0.33
AD vs MCI	1.26 (0.73 to 2.18)	0.40	1.48 (–0.84 to 3.80)	0.21

AD indicates Alzheimer's disease; CAA, cerebral amyloid angiopathy; MCI, mild cognitive impairment; and NPS, neuropsychiatric symptoms.

versus 45.8%; irritability/lability 42.1% versus 33.3%; agitation/aggression 42.1% versus 33.3%, apathy/indifference 36.8% versus 33.3%; all *P*>0.05) with the possible exception that the frequency of anxiety was numerically higher but not statistically significant (anxiety 47.4% versus 20.8%; *P*=0.10).

Associations between NPS and group status are shown in Table 5, adjusted for age, sex, and education. Compared with patients with NC, patients with CAA had a higher rate of NPS symptoms (incidence rate ratio, 3.18; 95% CI, 1.69–5.99). Patients with CAA had higher total NPS severity compared with NC (mean difference 31, 95% CI, 1.01–5.13). In additional analyses comparing NPS number and severity between CAA, MCI, and AD, there were no significant differences (Table 6). However, the number and severity of NPS in CAA were most similar to MCI and were numerically lower than in AD dementia (Table 6).

Association of NPS With Imaging Markers of CAA Severity and Cognition

Patients with CAA had median 36 cerebral microbleeds (IQR, 6–87), median WMH 1.9% of intracranial volume (IQR, 0.8–3.3%), and median 3.5 CAA-Small Vessel Disease score (IQR, 3–5); and 61% had cortical superficial siderosis. Adjusted associations of imaging markers with NPS number and severity are shown in Table 7. Only higher WMH volume was associated with more NPS symptoms. Additional exploratory analyses showed that higher WMH volume was associated with agitation (odds ratio, 1.69; 95% CI, 1.05–2.75) and apathy (OR, 2.00; 95% CI, 1.16–3.46), with a nonsignificant trend toward an association with depression (OR, 1.62;

95% CI, 0.97–2.70). Among patients with CAA, we failed to find associations between cognitive domain scores (memory, executive function, and processing speed) and NPS (including the number of symptoms and total severity) (Table 8).

DISCUSSION

We found that patients with CAA had more NPS and more severe NPS than healthy controls. The proportion of controls with NPS (30%) was similar to that described in the general population.[29] The number and severity of NPS in patients with CAA were similar to patients with MCI but somewhat less than patients with mild dementia due to AD, although this difference was not statistically significant. NPS symptoms were associated with higher WMH volume but not other CAA markers. An awareness that CAA is associated with NPS might lead to better recognition of symptoms, some of which may be treatable to improve quality of life.

NPS are noncognitive features of neurodegenerative disorders such as agitation, anxiety, apathy, depression, disinhibition, delusions, and hallucinations. NPS are important in neurocognitive disorders, as they are associated with faster cognitive decline,[5] greater functional impairment,[6] higher rates of institutionalization,[30] increased caregiver burden,[31] lower quality of life[32] and a faster progression to death.[7] In addition to being present in neurocognitive disorders, NPS can emerge in predementia populations, such as in subjective cognitive decline and MCI.[33,34] NPS in the predementia populations are associated with greater

Table 7. Adjusted Association of Neuropsychiatric Symptoms With MRI Markers of CAA Severity

Marker	NPS number			NPS total severity		
	Incidence rate ratio	95% CI	P value	Estimate	95% CI	P value
Cerebral microbleed count	1.00	0.97 to 1.02	0.77	0.001	–0.01 to 0.01	0.87
White matter hyperintensity	1.16	1.01 to 1.32	0.03	0.74	–0.03 to 1.51	0.06
Presence of cortical superficial siderosis	1.15	0.66 to 2.00	0.63	0.48	–2.38 to 3.34	0.74
CAA-SVD score	1.10	0.85 to 1.42	0.46	0.22	–0.98 to 1.42	0.72

Adjusted for age, sex, and education. CAA indicates cerebral amyloid angiopathy; CAA-SVD score indicates cerebral amyloid angiopathy small vessel disease score; MRI, magnetic resonance imaging; NPS, neuropsychiatric symptoms.

Table 8. Adjusted Association of Cognitive Domain Scores With NPS Number and Total Severity in Patients With CAA, Adjusted for Age, Sex, and Education

Cognitive domain	NPS number			NPS total severity		
	Incidence rate ratio	95% CI	P value	Estimate	95% CI	P value
Memory	0.82	0.63 to 1.07	0.14	−0.98	−2.19 to 0.22	0.11
Executive function	0.90	0.69 to 1.17	0.44	−0.64	−2.00 to 0.71	0.34
Processing speed	0.84	0.66 to 1.06	0.15	−1.05	−2.30 to 0.21	0.09

Adjusted for age, sex, and education. CAA indicates cerebral amyloid angiopathy; and NPS, neuropsychiatric symptoms.

caregiver burden,[31] a higher likelihood of presenting to a clinical setting,[35] increased risk of progression to dementia,[33,34] and dementia biomarkers.[36–38] NPS that manifest across the cognitive spectrum, including those with preclinical, prodromal, and dementia syndromes are clinically significant and of prognostic utility.[39] Therefore, identifying NPS in CAA is important.

Despite the importance of NPS in neurodegenerative disorders, there has been limited research on NPS in the population with CAA. Three case reports have described patients with CAA presenting with NPS of personality changes, behavioral disturbances, irritability, aggression, reduced drive, and depression.[8,9,40] In an autopsy series of patients diagnosed with dementia due to AD or Lewy body disease, the presence of advanced CAA was associated with delusions and hallucinations.[41]

NPS have been found to be common in patients following stroke, with depression, irritability, eating disturbances, agitation, apathy, and anxiety being the most prevalent.[42,43]

The pattern of NPS in CAA, with prominent apathy and depression, is similar to the pattern seen after stroke. Agitation and irritability were somewhat less common in CAA than in AD or MCI. However, the small sample size of our study prevented us from statistically comparing the frequency of individual NPS across groups. Additionally, larger cohorts of patients with CAA will be needed to determine if the different CAA-related clinical syndromes vary in NPS severity and pattern. It would be of great interest to test whether asymptomatic CAA in the general older population is associated with later life NPS, similar to the association between clinically unrecognized CAA and cognition. Ideally, this would be ascertained in community-based autopsy studies with premortem assessment of NPS.

Most patients with CAA have cognitive dysfunction that meets criteria for MCI. Interestingly, the frequency and severity of NPS in CAA was similar to that of our MCI comparison group. CAA can cause cognitive dysfunction in the absence of clinically evident hemorrhage[2]; in a similar fashion, it is possible that clinically unrecognized CAA could cause NPS. The syndrome of mild behavioral impairment is defined as later life new onset NPS and is proposed to be an early marker of neurodegeneration and risk for dementia.[44] CAA may be the cause of a subset of mild behavioral impairment and MCI, but more research is needed on how to recognize CAA in these settings, including whether the pattern of NPS in CAA differs from that of AD or ischemic vascular disease, which can also cause mild behavioral impairment and MCI.

Participants with CAA and higher WMH volume had more NPS and a trend toward more severe NPS. In additional exploratory analyses, we found that higher WMH volume was associated with increased odds of agitation and apathy, with a trend toward increase odds of depression. This suggests that white matter disconnection may underlie these symptoms. Apathy has been described previously in patients with cerebral autosomal dominant arteriopathy with subcortical leukoencephalopathy and after stroke.[45] Later life onset depression has been associated with higher WMH.[46] Further research is needed on the mechanisms by which WMH contribute to agitation, apathy, and depression. Additionally, more research is needed on other potential mechanisms by which vascular amyloid could lead to NPS, including the roles of altered vascular reactivity, brain connectivity, and atrophy.

We did not find associations between NPS and cognitive scores in patients with CAA, except for a borderline nonsignificant association between better memory and lower NPS severity. This suggests that the mechanisms that lead to cognitive impairment may differ from those that lead to neuropsychiatric symptoms.

The strengths of this study are the inclusion of comparison groups with AD and MCI and the use of an informant-based questionnaire. The main limitation is the relatively small sample size. Another limitation is the use of a brief NPS questionnaire, the NPI-Q, that is usually used in people with dementia and may not be as sensitive to NPS in outpatients with milder cognitive impairment. In future work we will use the Mild Behavioral Impairment Checklist,[47,48] which is designed to be more applicable to predementia states and more clearly differentiates later life acquired NPS from those related to longstanding psychiatric or personality disorders.[49,50]

CONCLUSIONS

Based on these findings, clinicians should be aware that NPS are common in CAA and should probably

be screened for using a validated tool such as the NPI-Q or the Mild Behavioral Impairment Checklist (freely available at www.mbitest.org). Many of these NPS—such as depression, anxiety, and agitation—are potentially amenable to pharmacological and nonpharmacological treatments, which could improve the quality of life of patients with CAA. In addition to studies of NPS treatment, future studies should also explore the incidence of new NPS in CAA in association with different CAA-related clinical syndromes and explore the neuropathological and neuroimaging correlates of NPS in CAA.

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