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Prevalence and Association of Basal Ganglia Calcifications and Depressive Symptoms in Patients With Mild Cognitive Impairment or Dementia

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Aim: The aim of this study is to investigate the association between basal ganglia calcification (BGC) and depressive symptoms within older adults with mild cognitive impairment (MCI) or dementia.

Methods: For this cross-sectional study, we included patients with MCI or dementia who visited the memory clinic between April 2009 and April 2015. All patients underwent a standard diagnostic workup, including assessment of depressive symptoms with the Geriatric Depression Scale and computed tomography imaging of the brain. Computed tomography scans were assessed for presence and severity of BGC. To analyse the association between BGC and depressive symptoms, binary logistic regression models were performed with adjustment for age, sex, cardiovascular risk factors, and cardiovascular diseases.

Results: In total, 1054 patients were included (median age: 81.0 y; 39% male). BGC was present in 44% of the patients, of which 20% was classified as mild, 20% as moderate, and 4% as severe. There were 223 patients (21%) who had a Geriatric Depression Scale score indicative of depressive symptoms. No association was found between the presence or severity of BGC and depressive symptoms.

Conclusions: Although both BGC and depressive symptoms were common in patients with MCI or dementia, no association was demonstrated between the presence or severity of BGC and depressive symptoms.

Key Words: basal ganglia calcification, dementia, mild cognitive impairment, depression

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Depression is common in patients with mild cognitive impairment (MCI) and dementia. In a large American cohort, depressive symptoms were reported in 20% of MCI patients.[1] Around 20% to 30% of patients with Alzheimer disease have depression, and these rates are even higher in other types of dementia.[2] However, it is unclear how depressive symptoms and dementia are associated with each other. Although there are several common etiological factors, including vascular risk factors and cerebrovascular changes, the underlying mechanisms of this relationship are highly complex and not well understood.[3–5]

In the general population, it has been suggested that changes in frontal-subcortical circuits are involved in the manifestation of neuropsychiatric symptoms, including depressive symptoms.[6] These circuits are networks of frontal and subcortical brain structures (eg, specific frontal areas, the thalamus, and the basal ganglia) that are responsible for the mediation of executive functions, social behavior, and motivational states. As such, interruptions in these circuits may lead to behavioral and mental disturbances. These interruptions may be caused by neurodegenerative processes or vascular burden.[6] For instance, white matter hyperintensities were associated with depression in patients with Alzheimer disease.[7] Basal ganglia calcifications (BGCs) are located in the tunica media of small arterioles and capillaries and may also influence these circuits. Previous studies showed that BGC are common within the aging population. Several studies have found prevalences ranging from 26% to 39% in older adults.[8–10] Although they are common in older age, their clinical impact is still unclear. Observations in patients with primary familial brain calcification (PFBC), who have extended BGC, showed that neuropsychiatric symptoms are common in this population.[11] Mood disorders are the most common behavioral changes in these patients, and roughly up to 50% of PFBC patients develop depression at some point throughout the course of the illness.[11]

As depressive symptoms are also common and burdensome in patients with MCI and dementia[2] and the aetiology is complex and not well understood, it is important to gain more insight in the possible underlying mechanisms. Therefore, in this study, we aimed to explore the association between BGC and depressive symptoms in patients with MCI and dementia.

METHODS

This cross-sectional study used data from an existing cohort of memory clinic patients.[12] All patients referred to the memory clinic of the Tergooi Hospital in Blaricum, the

Netherlands, for cognitive assessment between April 2009 and April 2015 were included in this existing cohort. For the current study, we included patients with MCI and dementia. Patients without Geriatric Depression Scale (GDS) data or a computed tomography scan (CT scan) of the brain were excluded. Each patient received a standard diagnostic protocol, which consisted of a full medical and neurological examination (including the medical history), assessment of vital functions, a cognitive screening, an electrocardiogram, laboratory tests, a CT scan of the brain, and assessment of depressive symptoms using the GDS. All assessments were performed on the same day by a memory clinic team consisting of a geriatrician, a neurologist, a neuropsychologist, and a nurse. After the diagnostic assessment, the results were discussed in a consensus meeting of the memory clinic team. For MCI, the clinical diagnosis was based on the criteria first proposed by Petersen et al.[13] A clinical diagnosis of dementia was based on the criteria described in the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-4*).[14]

Imaging Variables

In our cohort, all patients received a CT scan of the brain. Although it is more common to use magnetic resonance imaging for cognitive evaluation, BGCs are not clearly visible on magnetic resonance imaging. A CT scan is performed as standard imaging for cognitive evaluation in a number of hospital in the Netherlands, including the hospital of the current study, because of the lower costs and wider availability of CT scans. CT imaging of the brain was performed with a 64-detector row CT (Somatom Definition AS; Siemens Healthineers, Erlangen, Germany). Acquisition parameters were 120 kVp, 260 mAs, collimation 64×0.6 mm, pitch 0.55, window center 40 HU, and window width 80 HU. The CARE kV tool, a dose optimization slider for noncontrast examinations, was used as well. Oblique coronal, sagittal, and transversal reconstructions were made with axial slices of 5 mm with soft tissue window and axial slices of 1.5 mm with bone window. CT scans were reviewed by 2 doctors of medicine with a special interest and expertise in neurovascular imaging (either N.M.S.G. or E.J.M.d.B.), who were both blinded for clinical outcomes and all risk factors. The reviewers assessed samples of the scans independently until an adequate interobserver agreement was reached and discussed discrepancies with an experienced radiologist (P.A. d.J.). Subsequently, all scans were divided and assessed independently. Presence and severity of BGC were scored for each patient. Severity was scored as follows: calcifications were considered mild if there was 1 high-attenuation area (a "dot"; Fig. 1A), moderate if there were multiple high-attenuation areas ("multiple dots"; Fig. 1B) and severe if these calcifications were confluent (Fig. 1C). The left and right basal ganglia were scored separately. The highest score (ie, either left or right) was noted.

Clinical Variables

The following clinical data were retrieved from the patient files: age, sex, cardiovascular risk factors (including hypertension, diabetes mellitus, hypercholesterolemia, and smoking), and cardiovascular comorbidities (including myocardial infarction, stroke, transient ischemic attack, and peripheral arterial disease). Hypertension was defined as hypertension noted in medical history, using antihypertensive drugs, or having a systolic blood pressure $\geq$160 mm Hg or diastolic blood pressure $\geq$90 mm Hg. Diabetes mellitus was defined as diabetes mellitus in medical history or using antidiabetic drugs. Hypercholesterolemia was defined as hypercholesterolemia in medical history or using cholesterol lowering drugs. Smoking was categorized in currently smoking and nonsmoking (including smoking cessation). Stroke was defined as noted in the medical history or cortical infarcts seen on the CT scan. Myocardial infarction, transient ischemic attack, and peripheral arterial disease were defined as noted in medical history.

Depressive Symptoms

Depressive symptoms were measured using the Dutch version of the GDS.[15] The GDS is a self-report questionnaire for depressive symptoms in older adults. Each question needs to be answered with either yes or no. All items are added leading to a total score. In case of an incomplete questionnaire, all completed items were added and this score was noted as the total score. The 30-item version of the GDS (GDS-30) has a score range of 0 to 30 and a cut-off score of 11 or more as an indicator for depressive symptoms (sensitivity: 86%, specificity: 79%).[16] The GDS-30 was used from April 22, 2009 till October 10, 2010, in our cohort. The 15-item version of the GDS (GDS-15) has a score range of 0 to 15 and a cut-off score of 6 or more as an indicator of depressive symptoms (sensitivity: 82%, specificity: 76%).[16] The GDS-15 was used from October 13, 2010, till April 2015. Both variables were combined into 1 dichotomous variable based on the corresponding cut-off score, indicating whether depressive symptoms were present or not.

Statistical Analysis

Baseline characteristics were analysed using descriptive statistics. Cohen k was used to estimate the interobserver agreement of BGC severity in a random sample of 100 CT scans. To test the hypothesis that BGC (explanatory variable) is associated with depressive symptoms (outcome variable), binary logistic regression models were performed including univariate analyses (model 1); age-adjusted and sex-adjusted analyses (model 2); analyses adjusted for age, sex, and cardiovascular risk factors (model 3); and analyses adjusted for age, sex, cardiovascular risk factors, and cardiovascular diseases (model 4). The results were noted as odds ratios (ORs), with a 95% confidence interval (95% CI). A *P*-value below 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software, version 24.0.0.0 (IBM Corp., 2016).

Ethics

Of each patient informed consent was obtained before data were taken into the database. The protocol was approved by the Medical Ethics Committee of Tergooi Hospital.[12]

RESULTS

Cohort Description

A total of 1430 patients with MCI or dementia were included in this cohort. No patients were excluded because of the absence of a CT scan. In total, 376 patients were excluded because of the absence of GDS data. The final study population consisted of 1054 patients (Figure 2).

Of the included patients, 38.0% was male and the median age was 82.0 years (range: 53 to 96 y). Nearly two

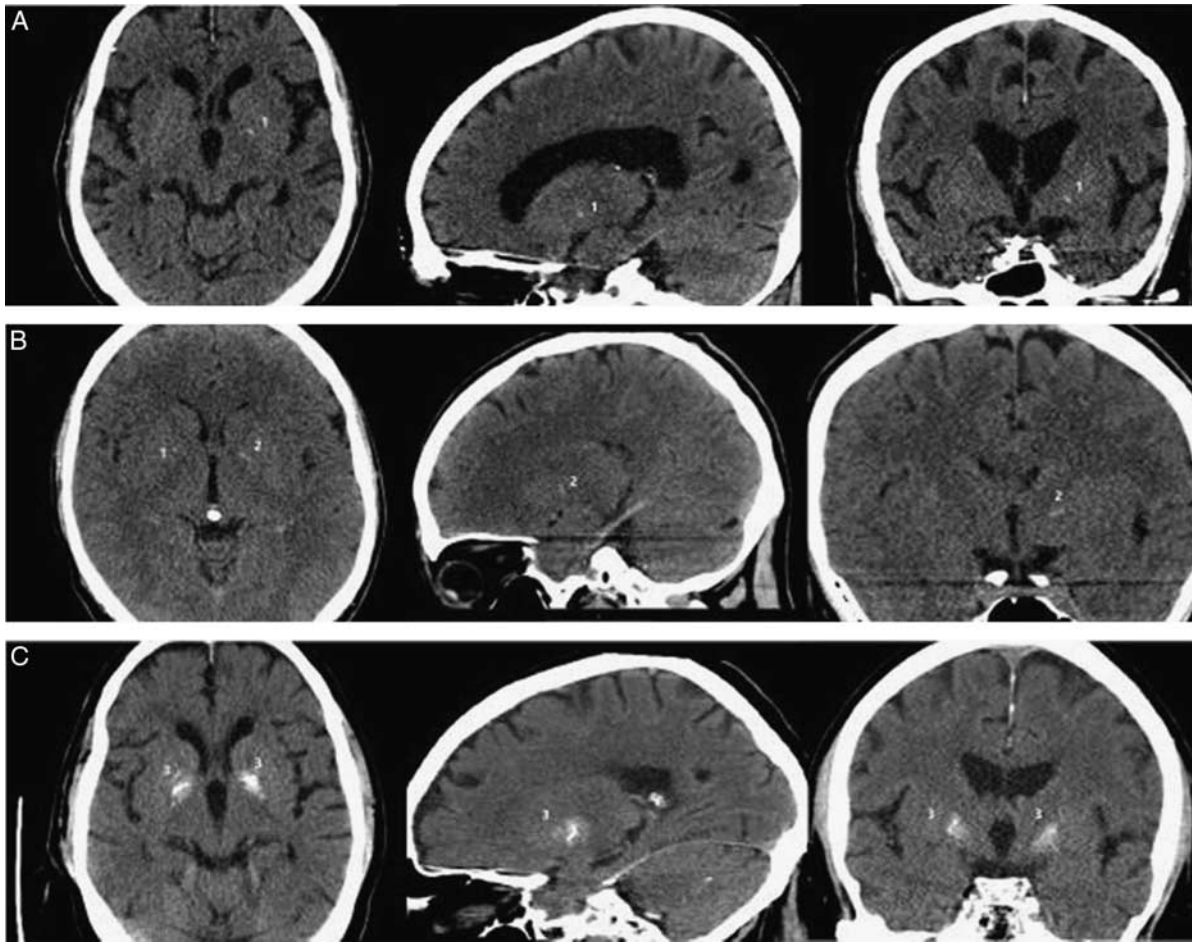

FIGURE 1. The images show mild (A), moderate (B), and severe (C) basal ganglia calcifications. Reprinted from de Brouwer et al.[8] Copyright Elsevier Masson SAS.

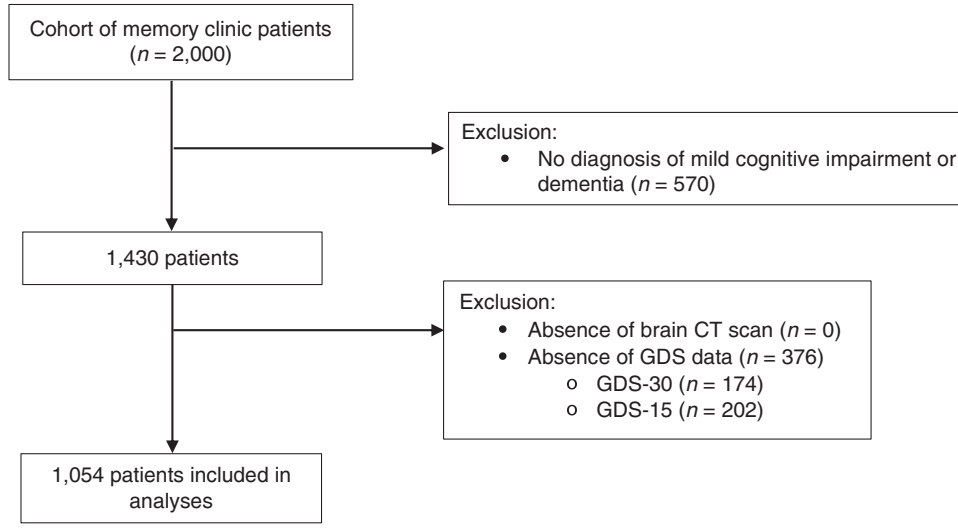

FIGURE 2. Flowchart of the cross-sectional study. CT indicates computed tomography; GDS, Geriatric Depression Scale; *n*, number of patients.

thirds of patients were diagnosed with dementia (66.8%), the rest had a diagnosis of MCI (33.2%). There was <1% missing data in all values except for the GDS. For the GDS-30, 28.1% (n = 32) of questionnaires were incomplete. For the GDS-15, 21.6% (n = 203) of questionnaires were incomplete. In total, there were 223 patients (21.2%) who had a GDS score indicative of depressive symptoms. More baseline characteristics are shown in Table 1.

BGC

After individually assessing 100 CT scans (N.M.S.G., E.J. M.d.B.), the interobserver agreement was calculated and found to be adequate (weighted kappa of 0.74 for the right BGC severity scores and a weighted kappa of 0.79 for the left BGC severity scores). BGC were present in 44.0% of patients, 20.1% was classified as mild, 20.6% as moderate, and 3.3% as severe.

Association of BGC and Depressive Symptoms

There was no association between BGC presence and depressive symptoms [crude OR: 1.07 (95% CI, 0.79 to 1.44)] and no significant association was observed between calcification severity and depressive symptoms [crude OR and 95% CI for mild, moderate, and severe calcifications: 1.00 (0.68 to 1.48), 1.15 (0.79 to 1.67), and 0.96 (0.41 to 2.25), respectively]. Also, after adjustment for several potential confounders, no significant associations were observed between presence or severity of BGC and depressive symptoms. These results are shown in Table 2.

DISCUSSION

This study showed that both depressive symptoms and BGC are common in patients with MCI and dementia. The majority of these BGC were of either mild or moderate severity. There was no significant association between presence of BGC and depressive symptoms nor severity of BGC and depressive symptoms. These results therefore do not support the hypothesised role of (vascular) calcifications in the basal ganglia in the manifestation of depressive symptoms in patients with MCI or dementia.

The prevalence of BGC in our sample (43.9%) is higher than reported in earlier studies (26.1% to 38.7%).[8–10] A possible explanation for this finding is that our sample consists of patients with MCI or dementia, whereas all other studies included patients with all degrees of cognitive functioning. Another factor may be that the median age in our sample (ie, 82.0 y) is relatively high compared with the other studies, which had a median age of 60 to 80 years[9] or a mean age of 67.4 years[8] and 73.4 years.[10] Our results demonstrated a similar prevalence of depressive symptoms in MCI and dementia patients, as mentioned in earlier studies.[1,2] Although observations in PFBC patients, who have extensive BGC, show that depressive symptoms are common,[11] the current study showed no association between BGC and depressive symptoms in patients with MCI or dementia. This suggests that BGC does not play a role in the manifestation of depressive symptoms in this population. It is possible that the impact of the neurodegenerative processes and other vascular damage (such as white matter lesions) outweigh the impact of BGC in these patients.

This study has several strengths. First, this study consists of a large population of patients with cognitive impairment. Second, the findings are generalizable to memory clinic patients with MCI and dementia, as the only exclusion criterium (aside from having objective cognitive impairment) was the absence of a CT scan of the brain and/or a GDS measurement. Third, this is the first study to yield new insights in the association between BGC and depressive

TABLE 1. Baseline Sample Characteristics (n = 1054)

		Severity of BGC			
Characteristic	**n (%) (Unless Otherwise Mentioned)**	**None (n = 590)**	**Mild (n = 212)**	**Moderate (n = 217)**	**Severe (n = 35)**
Male	401 (38.0)	242 (41.0)	83 (39.2)	62 (28.6)	14 (40.0)
Age in years (median, range)	82.0 (53-96)	—	—	—	—
Cardiovascular risk factors					
Hypertension	759 (72.0)	437 (74.1)	147 (69.3)	154 (71.0)	21 (60.0)
Diabetes mellitus	191 (18.1)	107 (18.1)	39 (18.4)	37 (17.1)	8 (22.9)
Hypercholesterolemia	131 (12.4)	82 (13.9)	19 (9.0)	28 (12.9)	2 (5.7)
Smoking	105 (10.0)	54 (9.2)	25 (11.8)	19 (8.8)	7 (20.0)
Cardiovascular comorbidities					
Myocardial infarction	118 (11.2)	74 (12.5)	15 (7.1)	24 (11.1)	5 (14.3)
Stroke	109 (10.3)	59 (10.0)	31 (14.6)	15 (6.9)	4 (11.4)
TIA	61 (5.8)	44 (7.5)	10 (4.7)	6 (2.8)	1 (2.9)
Peripheral arterial disease	100 (9.5)	53 (9.0)	23 (10.8)	21 (9.7)	3 (8.6)
Type of cognitive disorder					
Mild cognitive impairment	350 (33.2)	199 (33.7)	75 (35.4)	62 (28.6)	14 (40.0)
Dementia	704 (66.8)	391 (66.3)	137 (64.6)	155 (71.4)	21 (60.0)
BGC presence	464 (44.0)	—	—	—	—
BGC severity					
Mild	212 (20.1)	—	—	—	—
Moderate	217 (20.6)	—	—	—	—
Severe	35 (3.3)	—	—	—	—
Geriatric Depression Scale					
GDS score above cut-off*	223 (21.2)	122 (20.7)	44 (20.8)	50 (23.0)	7 (20.0)

*For the GDS-15, a score of 6 is an indication of depressive symptoms. For the GDS-30, a score 11 is an indication of depressive symptoms.
BGC indicates basal ganglia calcifications; GDS, geriatric depression scale; n, number of patients; TIA, transient ischemic attack.

TABLE 2. Associations Between Basal Ganglia Calcification and Depressive Symptoms

	OR (95% CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
BGC presence	1.07 (0.79-1.44)	1.07 (0.79-1.44)	1.06 (0.78-1.43)	1.08 (0.79-1.46)
BGC severity				
None	Ref.	Ref.	Ref.	Ref.
Mild	1.00 (0.68-1.48)	1.03 (0.70-1.51)	1.02 (0.69-1.50)	0.99 (0.66-1.47)
Moderate	1.15 (0.79-1.67)	1.13 (0.78-1.65)	1.13 (0.77-1.64)	1.20 (0.82-1.76)
Severe	0.96 (0.41-2.25)	0.94 (0.40-2.22)	0.90 (0.38-2.13)	0.93 (0.39-2.21)

Model 1 = crude model.
Model 2 = model 1 + adjusted for age and sex.
Model 3 = model 2 + adjusted for cardiovascular risk factors.
Model 4 = model 3 + adjusted for cardiovascular diseases.
BGC indicates basal ganglia calcifications; CI, confidence interval; OR, odds ratio; Ref., reference.

symptoms in patients with MCI or dementia. Lastly, the analyses in this study were corrected for a broad range of potential confounders, including cardiovascular risk factors and cardiovascular diseases.

A limitation of this study is that there were missing values in the GDS data. Imputation of missing values of the GDS was not possible, as this is the outcome measure. It is possible that the patients who were excluded because of this missing value were either at lower risk or at higher risk of having depressive symptoms. This selection bias might have influenced the association between BGC and depressive symptoms shown in this study. Post hoc sensitivity analyses showed that the distribution of presence and severity of BGC and of risk factors for depression (eg, age and cardiovascular risk factors) was comparable between the included and excluded patients. This implies that the effect of potential selection bias in this study is limited.

This study demonstrated that both BGC and depressive symptoms are common in patients with MCI or dementia. No associations were demonstrated between the presence or severity of BGC and depressive symptoms. Thus, BGC does not seem to play a role in the manifestation of depressive symptoms in older adults with MCI or dementia.

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