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Research article

Intracranial calcifications associated with factors related and unrelated to atherosclerosis in older people: A community dwelling cohort study

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ABSTRACT

The cause of intracranial calcification is not fully understood. The aim of the current study was to identify factors associated with intracranial calcification and to determine whether these factors differ in calcification of different sites. A total of 404 community-dwelling people aged 65 or older were included in the study. All subjects underwent brain computed tomography (CT), blood tests, and a Mini-Mental State Examination (MMSE). Intracranial calcifications were scored using CT. Stepwise regression analysis was performed to examine factors associated with intracranial calcification, with each calcification score used as a dependent variable. Independent variables included age, gender, hemoglobin A1c (HbA1c), dyslipidemia, estimated glomerular filtration rate (eGFR), blood pressure, body mass index (BMI), smoking, serum iron, ferritin, and intact parathyroid hormone (PTH). Stepwise regression analysis detected male gender as a predictor of pineal gland calcification and intact PTH as a predictor of basal ganglia calcification. Age and lifestyle diseases were identified as predictors of calcification of the falx cerebri, internal carotid arteries, and vertebral arteries. These results indicate that the mechanisms of calcifications of the pineal gland and basal ganglia might differ from that of artery calcification, and that causes of intracranial calcification might be classified using factors that are and are not related to atherosclerosis.

1. Introduction

Intracranial calcification on computed topography (CT) is a frequent finding in the elderly population. Common sites include the pineal gland, choroid plexus, habenula, tentorium cerebelli, falx cerebri, basal ganglia, hippocampus, cerebellum dentate nucleus, and

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intracranial arteries [1–10]. The pineal gland and choroid plexus are particularly common, with rates of 70–90 % in elderly people [2–4]. The cause of pineal calcification is unclear, but might involve chronic vascular inflammation, brain tissue hypoxia, high intracranial pressure, and sunlight exposure [2,11,12]. Involvement of butyrate-producing bacteria in this process has also recently been suggested [13]. Moreover, melatonin, which is secreted by the pineal gland, attenuates vascular calcification [14,15], which suggests that pineal gland dysfunction might be involved in calcification. Pineal calcification is also often present in patients with Alzheimer's disease (AD) [16] and might be associated with pineal volume reduction in AD [11,16–22].

Choroid plexus calcification is caused by a decrease of serum fetuin-A, which plays a role in inhibition of the calcification process [23]. Fetuin-A is also related to calcification of the basal ganglia [24] and aortic valve [25]. Hypoparathyroidism is another cause of basal ganglia calcification [26]. A study in mice also suggested involvement of tauopathy in intracranial calcification, although the tau distribution was not completely matched regionally with the calcification [27]. Reported risk factors for hippocampal calcification include age, diabetes mellitus, smoking, hypertension, and hyperlipidemia [8,9]. A histological study showed the presence of calcification at pre-capillaries, capillaries and arteries in the hippocampus in which brain CT showed calcification [28]. Age and lifestyle diseases, including hypertension, diabetes mellitus, dyslipidemia, smoking, peripheral artery disease, and chronic kidney disease, are also involved in calcification of intracranial arteries [29–31].

These findings indicate that there are many conceivable causes of intracranial calcification. We believe that these causes can be roughly divided into two types that are and are not related to atherosclerosis. The aims of the current study are to examine whether intracranial calcifications are associated with each other, to identify factors associated with intracranial calcifications, and to determine whether these factors differ in each calcification. The main objective of the study is to examine and classify the factors that cause intracranial calcifications.

2. Methods

2.1. Subjects

A cohort study of residents in Kyotango city was conducted to examine longevity in subjects aged 65 or older by the Department of Epidemiology for Longevity and Regional Health, Kyoto Prefectural University of Medicine. Kyotango is a rural city located in the northern part of Kyoto Prefecture, and is a longevity area with many centenarians. Subjects in the cohort live in the community and can visit a hospital for various examinations. As a result, the subjects are in relatively good health. In the current study, baseline data of the cohort study were used for 404 subjects. The inclusion criteria were: (i) evaluation using brain CT, blood tests, and a Mini-Mental State Examination (MMSE) [32]; and (ii) no significant history of cerebrovascular disease, arachnoid cyst, or meningioma. The ethics committee of Kyoto Prefectural University of Medicine approved the cohort study. Informed consent for participation was obtained from all subjects.

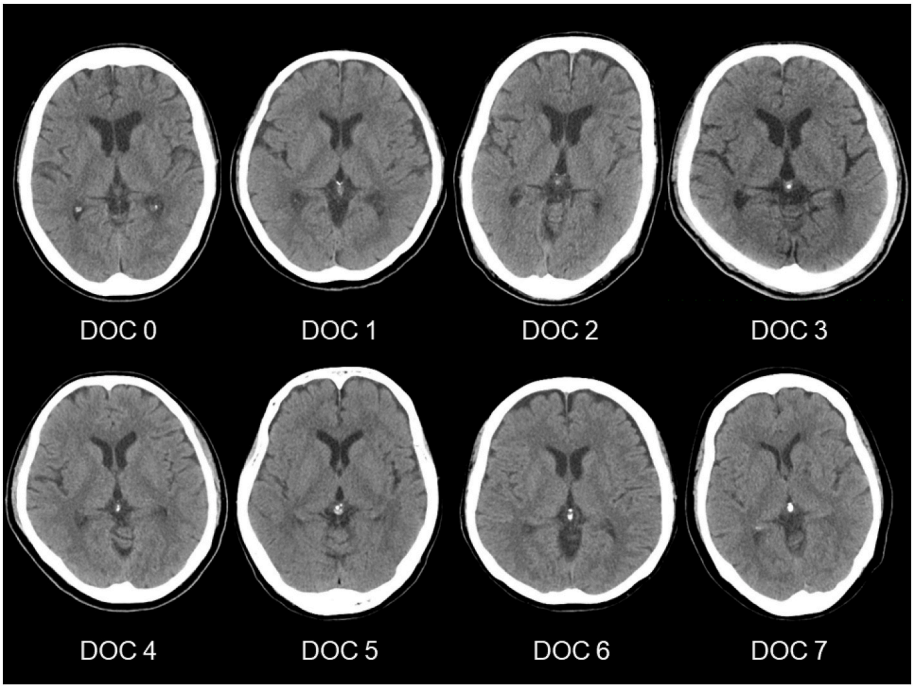

Fig. 1. Examples of degree of calcification (DOC) score of pineal gland.

2.2. Assessment using CT

CT data were acquired using an Aquilion ONE TSX 301C helical CT scanner (Canon Medical Systems). Data were reconstructed with 5-mm slice thickness. Assessment of pineal calcification was performed as described by Kunz et al. [33]. The highest Hounsfield Units (HU) for pineal calcification were scored as 0 (0–50 HU), 1 (51–150 HU), 2 (151–250 HU), 3 (251–350 HU), and 4 (351-1000HU); and the ratio of calcified area to total pineal gland area was scored as 0 (0–24 %), 1 (25–49 %), 2 (50–74 %), and 3 (75–100 %). The highest HU was measured using ShadeQuest/ViewR (FUJIFILM, Tokyo, Japan). The ratio of the calcification area was assessed visually using this viewer. The score for the degree of calcification (DOC) of the pineal gland was calculated as the sum of the HU and calcified area ratio scores (range: 0–7) (Fig. 1). If the pineal gland was present in two slices, the DOC was evaluated for each slice and the DOC score was defined as the mean score of the two slices [16]. Examination of the prevalence of pineal calcification was based on a cut-off value of 90 HU (absent: $\leq$90 HU; present: >90 HU) [31].

Calcification of the choroid plexus, basal ganglia, cerebellum dentate nucleus, hippocampus, and falx cerebri was evaluated using the method of Kockelkoren et al. [34]. Calcification was scored as: 0 = absent, 1 = mild (one dot), 2 = moderate (multiple dots), and 3 = severe (confluent) (Fig. 2). In assessment of calcification of the internal carotid arteries, vertebral arteries, and basilar artery, the scores were: 0 (absent), 1 (calcification <50 % of vessel circumference), and 2 (calcification $\geq$50 % of vessel circumference) (Fig. 3 [D-I]) [31]. The score for aortic arch calcification (also evaluated as representative of extracranial calcification) was categorized as 0 (absent), 1 (single small calcification), 2 (multiple small calcifications), and 3 (one or more large calcifications larger than the radius of the aortic arch) (Fig. 3 [A-C]) [35]. These scores were also visually assessed using ShadeQuest/ViewR (FUJIFILM, Tokyo, Japan) and >90 HU was defined as calcification [31] and the highest score in each region was used as the calcification score for the region.

One rater (T.M., psychiatrist, 17 years of experience in diagnostic imaging for cognitive impairment) blinded to the clinical data evaluated pineal gland, intracranial, and aortic arch calcification. Before the evaluation, T.M. underwent a brief training session conducted by a board-certified radiologist (K.A.). As the sample size for the intraclass correlation coefficient (ICC) was calculated in our previous study [17], 14 randomly selected subjects were reassessed by T.M. The other rater (N.O., psychiatrist, 7 years of experience in diagnostic imaging for cognitive impairment) blinded to the clinical data independently assessed the 14 subjects. Inter- and intra-rater reliability were examined by calculation of the ICC.

2.3. Statistical analysis

Spearman correlation analysis was used to examine relationships among calcification scores. Stepwise regression analysis was performed to examine factors associated with each calcification, with the calcification score used as a dependent variable. Independent

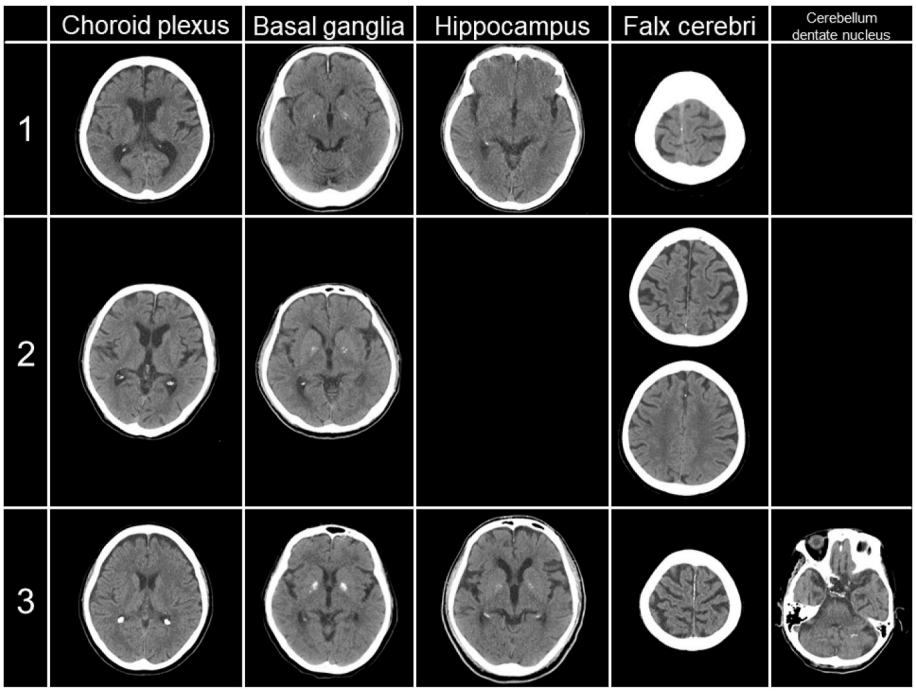

Fig. 2. Examples of scoring of calcification for the choroid plexus, basal ganglia, hippocampus, falx cerebri, and cerebellum dentate nucleus. Images scored as 1 (upper row), 2 (middle row) and 3 (lower row) are shown. When calcification of the falx cerebri was present in two slices in the same case, the calcification was scored as 2. There was no case with a score of 2 in the hippocampus or with a score of 1 or 2 in the cerebellum dentate nucleus.

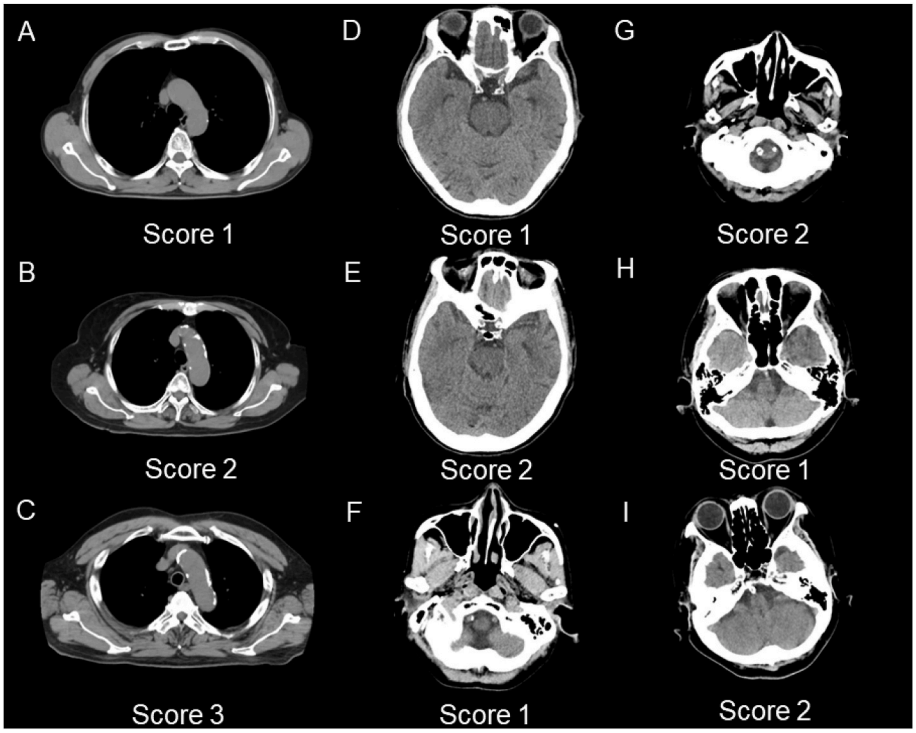

Fig. 3. Examples of scoring of calcification of the aortic arch (A–C), internal carotid arteries (D, E), vertebral arteries (F, G), and basilar artery (H, I).

variables included age, gender, hemoglobin A1c (HbA1c), dyslipidemia, estimated glomerular filtration rate (eGFR), blood pressure, body mass index (BMI), smoking, serum iron, ferritin, and intact parathyroid hormone (PTH). The following factors were converted into dichotomous variables: gender (0: male; 1: female); HbA1c (National Glycohemoglobin Standardization Program) (0: <6.5 %, 1: ≥6.5 %); dyslipidemia (0: low density lipoprotein cholesterol (LDL-C) <140 mg/dl, triglyceride (TG) < 150 mg/dl, high density lipoprotein cholesterol (HDL-C) ≥40 mg/dl; 1: LDL-C ≥140 mg/dl, TG ≥ 150 mg/dl, and/or HDL-C <40 mg/dl); eGFR (0: ≥60 ml/min/1.73 m^2, 1: <60 ml/min/1.73 m^2); blood pressure (0: systolic pressure <140 mmHg, diastolic pressure <90 mmHg; 1: systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg); BMI (0: ≤25 kg/m^2, 1: >25 kg/m^2); smoking (0: absent, 1: present); serum iron (0: <150 μg/dl, 1: ≥150 μg/dl); ferritin (0: ≤200 ng/ml, 1: >200 ng/ml); and intact PTH (0: <30 pg/ml, 1: ≥30 pg/ml). Data were analyzed using SPSS 22 (IBM Corp., Armonk, NY, USA). A p value of 0.05 was considered to be significant. In Spearman correlation analysis, the Bonferroni correction was performed to adjust for multiple comparisons.

3. Results

3.1. Inter- and intra-rater reliability of assessment of calcification

The inter-rater and intra-rater ICCs for each region are shown in Table 1.

Table 1
Inter-rater and intra-rater ICCs for each region.

Calcification site	Inter-rater ICCs (95 % CI, p value)	Intra-rater ICCs (95 % CI, p value)
Pineal gland	0.970 (0.908–0.991, p < 0.001)	0.970 (0.911–0.990, p < 0.001)
Choroid plexus	0.965 (0.892–0.989, p < 0.001)	1.000
Falx cerebri	0.925 (0.776–0.976, p < 0.001)	0.925 (0.774–0.976, p < 0.001)
Basal ganglia	1.000	1.000
Hippocampus	1.000	1.000
Cerebellum dentate nucleus	1.000	1.000
Aortic arch	1.000	0.895 (0.685–0.966, p < 0.001)
Internal carotid arteries	0.867 (0.585–0.957, p < 0.001)	0.800 (0.398–0.935, p = 0.003)
Vertebral arteries	0.765 (0.267–0.924, p = 0.007)	0.977 (0.931–0.993, p < 0.001)
Basilar artery	1.000	1.000

CI, confidence interval; ICC, intraclass correlation coefficient.

3.2. Prevalence of intracranial and aortic arch calcifications

The characteristics of the subjects are shown in Table 2. The mean MMSE score was 27.0 ± 2.7, indicating that almost all subjects were cognitively normal. The prevalence and scores for calcification in each region are shown in Table 3. The prevalence was highest in the aortic arch, followed by the internal carotid arteries, pineal gland, choroid plexus, and falx cerebri.

3.3. Spearman correlation analysis

The results of Spearman correlation analysis are shown in Fig. 4. There were significant correlations (all p values are Bonferroni corrected) of the calcification score for the basal ganglia with those for the cerebellum dentate nucleus ($\rho = 0.355$, $p < 0.05$) and falx cerebri ($\rho = 0.177$, $p < 0.05$); of the calcification score for the falx cerebri with those for the internal carotid arteries ($\rho = 0.216$, $p < 0.05$) and vertebral arteries ($\rho = 0.199$, $p < 0.05$); and between the calcification scores for the internal carotid arteries and vertebral arteries ($\rho = 0.238$, $p < 0.05$), internal carotid arteries and aortic arch ($\rho = 0.221$, $p < 0.05$), and vertebral arteries and aortic arch ($\rho = 0.272$, $p < 0.05$). The DOC score for the pineal gland was correlated with the calcification score for the choroid plexus before ($\rho = 0.130$, uncorrected $p = 0.009$) but not after Bonferroni correction (corrected $p = 0.405$). There were tendencies for correlations (uncorrected p values) of the calcification scores for the falx cerebri and aortic arch ($\rho = 0.139$, $p = 0.005$), falx cerebri and hippocampus ($\rho = 0.125$, $p = 0.012$), and cerebellum dentate nucleus and vertebral arteries ($\rho = 0.109$, $p = 0.028$).

3.4. Stepwise regression analysis

In stepwise regression analysis (Table 4), gender was detected as a predictor of the DOC score of the pineal gland, and intact PTH was found to be a predictor of the calcification score for the basal ganglia. Age and factors associated with lifestyle disease were identified as predictors of the calcifications scores for the falx cerebri, aortic arch, internal carotid arteries, and vertebral arteries. No factors were identified as predictors of the calcification scores for the choroid plexus, hippocampus, basilar artery, and cerebellum dentate nucleus.

4. Discussion

In this study, the internal carotid arteries, pineal gland, choroid plexus, and falx cerebri were the common regions of intracranial calcification. Calcification of the pineal gland was associated with male gender and that of the basal ganglia was associated with intact PTH. Age and lifestyle disease were related to calcifications of the falx cerebri, internal carotid arteries, and vertebral arteries. These results indicate that the mechanisms of pineal gland and basal ganglia calcification might differ from those of artery calcifications.

The high prevalence and male-dominant findings for pineal gland calcification are consistent with previous findings [2–4,36], although one study found no association between pineal gland calcification and sex [10]. While stepwise regression analysis in the current study did not detect smoking history as a predictor of pineal calcification, a previous study did find that smoking history was more prevalent in elderly subjects with moderate to severe pineal gland calcification, although this result was not adjusted for gender [37]. A recent study also showed a relationship between smoking and pineal gland calcification in people aged 63 and above, even after adjustment of other factors, including gender [36]. Calcification of the pineal gland was not related to those of the vertebral and basilar arteries in the current study, despite the blood supply to the pineal gland from the penetrating branches of the posterior cerebral artery and posterior communicating artery. This and the different factors related to calcification of the pineal gland and vertebral arteries suggests that the mechanism of pineal gland calcification might differ from that of arterial calcification.

In the current study, calcification of pineal gland was not associated with intracranial vascular or aortic arch calcification. Since

Table 2
Clinical characteristics of subjects (n = 404).

Characteristic	Value
Age, years	73.6 ± 5.9
Gender, male/female	177/227
MMSE score	27.0 ± 2.7
HbA1c (NGSP), 0/1	370/34
Dyslipidemia, 0/1	237/167
eGFR, 0/1	308/96
Blood pressure, 0/1	236/168
Body mass index, 0/1	290/114
Smoking, 0/1	298/106
Serum iron, 0/1	387/17
Ferritin, 0/1	344/60
Intact parathyroid hormone, 0/1	25/379

eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MMSE, Mini-Mental State Examination; NGSP, National Glycohemoglobin Standardization Program.
Age and MMSE score are shown as the mean ± standard deviation.

Table 3
Prevalences and scores of intracranial and aortic arch calcifications in all subjects (n = 404).

Calcification site	Number (male/female)	Prevalence (%)	Score (range)
Aortic arch	340 (155/185)	84	1.7 ± 1.0 (0–3)
Internal carotid arteries	286 (131/155)	71	1.0 ± 0.7 (0–2)
Pineal gland	281 (132/149)	70	3.2 ± 2.1 (0–7)
Choroid plexus	228 (105/123)	56	1.5 ± 1.4 (0–3)
Falx cerebri	173 (102/71)	43	1.2 ± 1.4 (0–3)
Vertebral arteries	83 (47/36)	21	0.3 ± 0.7 (0–2)
Basal ganglia	8 (4/4)	2	0.04 ± 0.29 (0–3)
Hippocampus	7 (3/4)	2	0.04 ± 0.31 (0–3)
Basilar artery	4 (1/3)	1	0.01 ± 0.13 (0–2)
Cerebellum dentate nucleus	1 (0/1)	0.2	0.01 ± 0.15 (0–3)

Scores are shown as the mean ± standard deviation.

melatonin attenuates vascular calcification [14,15], low melatonin secretion might be involved in intracranial calcification, and a smaller uncalcified pineal gland is known to decrease melatonin secretion [38]. A recent retrospective autopsy study indicated involvement of pineal parenchymal calcification in changes of the pineal gland volume [21]. Therefore, pineal calcification might lead to reduced pineal volume, followed by reduced melatonin secretion and a consequent increase in intracranial calcification. However, our results do not seem to support this reasoning, and a further study is needed to examine the relationship of pineal dysfunction with intracranial calcification.

Calcification of the basal ganglia was associated with a low blood level of intact PTH in the current study. This is consistent with previous results showing a relationship of hypoparathyroidism with basal ganglia calcification [26]. However, the prevalence of calcification of the basal ganglia was lower than the range of 22.8 %–38.7 % found in previous studies [5–7]. This might be partly because the current cohort study was conducted in a community-dwelling population, rather than in the clinical setting of patients visiting a hospital. The prevalence of patchy calcification of the basal ganglia in Japanese people aged over 65 years has been found to range from 2.1 % to 3.1 % [6] and the prevalence of basal ganglia calcification in all generations is 1.3 % [4], which are similar to the current results. Our definition of basal ganglia calcification might also have been strict because we used a cut-off of 90 HU, and thus, the prevalence might be underestimated. Moreover, a gender difference was not detected, although previous studies have shown female dominance [5,6]. Thus, a further study is needed to examine the mechanism of basal ganglia calcification.

In the current study, factors related to calcification of the choroid plexus and cerebellum dentate nucleus were not detected. However, calcification of the cerebellum dentate nucleus was correlated with that of the basal ganglia, and calcification of the choroid plexus tended to correlate with that of the pineal gland. A previous study demonstrated a significant correlation between pineal gland calcification and choroid plexus calcification [10], and hydroxyapatite has been identified as the major component of both choroid plexus and pineal gland calcification, although the degree of crystallinity differs [39]. An association of fetuin-A with choroid plexus and basal ganglia calcification has also been shown [23,24]. The fetuin-A level in cerebrospinal fluid is significantly lower in AD cases than in controls [40] and the DOC of the pineal gland in AD is significantly greater than those in other diseases [16]. These results indicate that a reduction of fetuin-A may be associated with calcification of the basal ganglia, choroid plexus, pineal gland, and cerebellum dentate nucleus.

Age and factors associated with lifestyle disease were associated with calcification of the falx cerebri, as well as the aortic arch and internal carotid and vertebral arteries. Calcification of the falx cerebri was also correlated with that of the internal carotid and vertebral arteries. Factors related to hippocampal calcification were not detected, but previous studies have found relationships with age and lifestyle diseases [8,9]. Thus, age and lifestyle disease might be associated with calcification of the falx cerebri and hippocampus, as well as arterial calcification. Fetuin-A has been suggested not to be involved in vascular calcification in hemodialysis patients [41], but has been linked with calcification of the aortic valve [25]. Therefore, the relationship between fetuin-A and vascular calcification is unclear.

Collectively, the current results and those in previous studies [2,8,9,11,12,23,24,26,29–31,37] suggest that the factors associated with calcifications in the pineal gland, basal ganglia, choroid plexus, and cerebellum dentate nucleus are not related to atherosclerosis, whereas those associated with calcifications in the falx cerebri, hippocampus, and the internal carotid and vertebral arteries are atherosclerosis-related factors.

There are some limitations in the study. First, the assessments of calcifications may be limited because the CT slice thickness was 5 mm and a partial volume effect might have affected the results. Second, the coefficients in the Spearman analysis and stepwise regression analyses were low, which may be because many of the cohort of residents in Kyotango city were healthy. Third, we did not examine factors associated with calcification such as fetuin-A. Within these limitations, we conclude that different factors are associated with calcification in the pineal gland, basal ganglia, and other regions; and that the cause of intracranial calcification might be classified using factors that are and are not related to atherosclerosis. A further study is needed to evaluate the mechanisms of intracranial calcification.

5. Conclusion

In the current study, calcifications of the falx cerebri, internal carotid arteries, and vertebral arteries were linked to atherosclerosis-

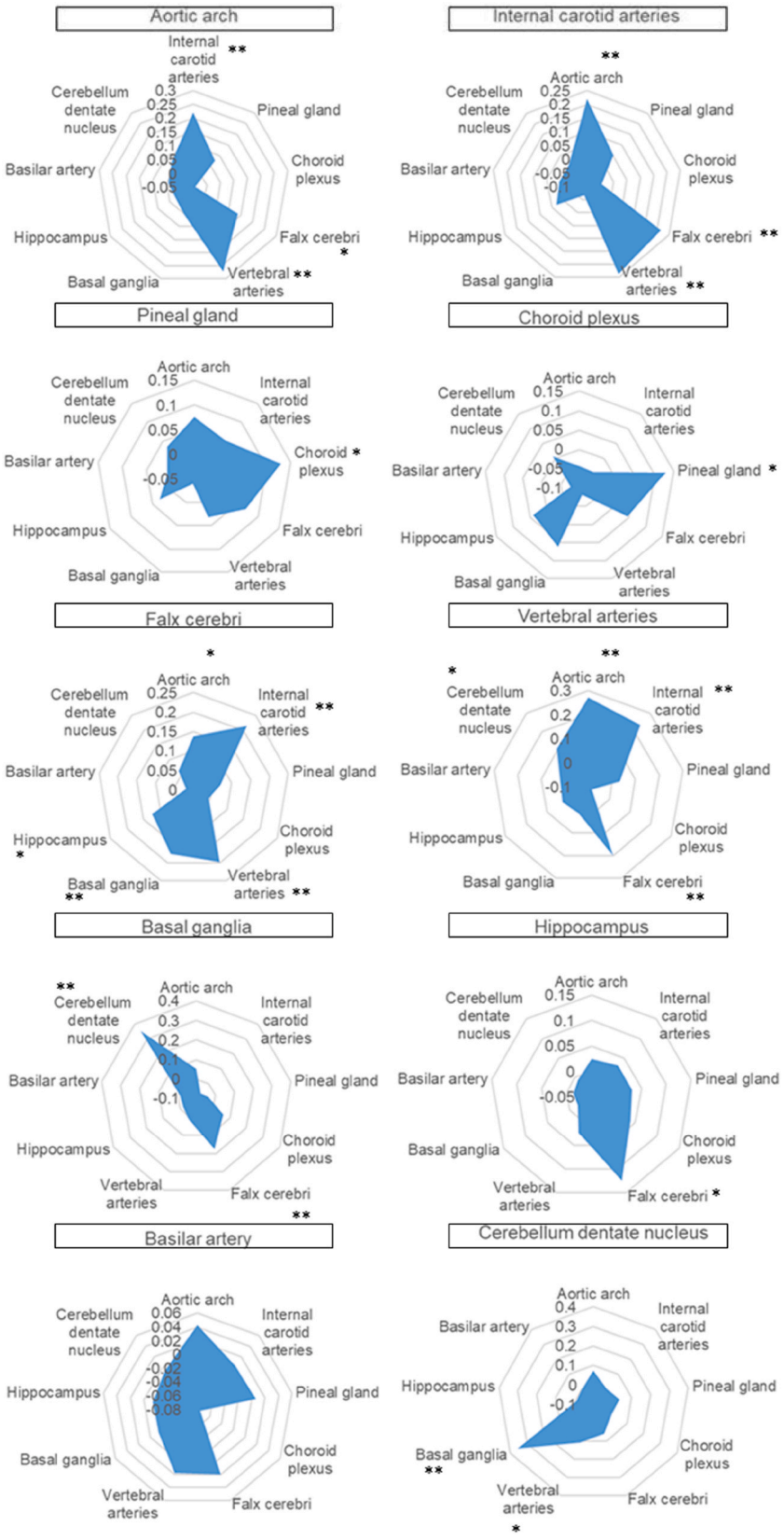

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Fig. 4. Results of Spearman correlation analysis. Radar charts shows the correlation coefficients for each calcification site.
** Bonferroni corrected $p < 0.05$
* uncorrected $p < 0.05$..

Table 4
Results of stepwise multiple regression analysis.

Variable	Adjusted R^2	β	95 % CI	P value
DOC score of pineal gland	0.020			0.002
Female		−0.637	−1.045–−0.229	0.002
Calcification score of basal ganglia	0.009			0.030
Parathyroid hormone-intact		−0.131	−0.249–−0.013	0.030
Calcification score of falx cerebri	0.122			0.001
Female		−0.597	−0.865–−0.329	<0.001
Age		0.051	0.029–0.073	<0.001
Hemoglobin A1c		0.779	0.302–1.256	0.001
Calcification score of aortic arch	0.153			0.027
Age		0.049	0.035–0.064	<0.001
Hemoglobin A1c		0.533	0.219–0.847	0.001
Smoking		0.304	0.105–0.503	0.003
Body mass index		0.218	0.025–0.412	0.027
Calcification score of internal carotid arteries	0.064			0.010
Age		0.023	0.011–0.035	<0.001
Body mass index		0.248	0.093–0.403	0.002
Serum iron		0.458	0.110–0.805	0.010
Calcification score of vertebral arteries	0.094			0.024
Age		0.032	0.021–0.042	<0.001
Smoking		0.180	0.041–0.318	0.011
Dyslipidemia		0.145	0.019–0.270	0.024

CI, confidence interval; DOC, degree of calcification.

related factors, while calcifications of the pineal gland and basal ganglia were associated with factors unrelated to atherosclerosis. The results of this study and previous studies suggest that the causes of intracranial calcification can be roughly divided into two types that are and are not related to atherosclerosis.

Ethics statement

The study was approved by the ethics committee of Kyoto Prefectural University of Medicine (ERB-C-885).

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Data availability statement

The authors do not have permission to share data.

CRediT authorship contribution statement

Teruyuki Matsuoka: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nozomu Oya:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Ayu Imai:** Writing – review & editing, Conceptualization. **Weiyi Sun:** Writing – review & editing, Conceptualization. **Yurinosuke Kitabayashi:** Writing – review & editing, Methodology, Conceptualization. **Kentaro Akazawa:** Writing – review & editing, Methodology. **Kei Yamada:** Writing – review & editing, Supervision. **Koji Ikeda:** Writing – review & editing, Supervision, Conceptualization. **Satoaki Matoba:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Jin Narumoto:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Satoaki Matoba reports financial support was provided by JST COI. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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