Original Article

DOI: 10.4274/haseki.galenos.2022.8449
Med Bull Haseki 2022;60:476-482

Association Between Cerebral Small Vessel Disease and Intracranial Arterial Calcification

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Abstract

Aim: Cerebral small vessel disease (CSVD) is a representative cause of stroke, cognitive impairment, and age-related disability, and it is shown to be associated with some traditional atherosclerotic risk factors. This study investigated relationship between the presence and severity of intracranial arterial calcification (ICAS) and the findings of CSVD.

Methods: Three hundred eighty-nine patients over the age of 40 who underwent non-enhanced cranial computed tomography (CT) and magnetic resonance imaging between January 01 and December 31, 2018, were included in the retrospective study. ICAS was scored on CT. CSVD findings, enlarged perivascular spaces (BGPVS, CSPVS), white matter hyperintensities [white matter hyperintensity was scored at periventricular (PVWMHI), white matter hyperintensity was scored at subcortical (SCWMHI)], cortical atrophy [global atrophy (GA) score, and medial temporal atrophy (MTA), Koedam score] were scored in MR images. The presence of acute, chronic, and lacunar infarcts was recorded. After controlling for age and gender, the correlation between ICAS and CSVD markers was examined.

Results: A positive correlation was found between ICAS score and BGPVS (r: 0.463 p<0.001), PVWMHI (r: 0.235 p<0.001), and GA (r: 0.368 p<0.001). A negative correlation was found between ICAS score and MTA (r: -0.112 p<0.05) and Koedam score (r: -0.196 p<0.001). The ICAS score was significantly high in cases of lacunar and chronic infarcts (p<0.001). No correlation was found between the calcification score and the CSPVS and SCWMHI scores.

Conclusion: The results of this study show that ICAS is correlated with BGPVS, PVWMHI, GA, MTA, Koedam score, and chronic and lacunar infarct.

Keywords: Small vessel disease, intracranial calcification, atrophy, infarct

Introduction

Calcification observed in intracranial arteries (ICAS) is an indicator of atherosclerosis. ICAS is a relatively easy biomarker to detect, which allows the evaluation of the diffuseness of intracranial atherosclerosis (1). There is literature evidence showing that ICAS may be associated with acute ischemic stroke, cerebral small vessel disease (CSVD), and cognitive impairment (1).

Cerebral small-vessel disease is a large group of diseases affecting the small vessels, arterial, venule, and capillary systems of the brain, which includes various pathological processes and etiological factors (2). CSVD is an important cause of stroke, cognitive impairment, and age-related disability (2). There are data showing that vascular brain diseases such as hypertension, aging, and amyloid angiopathy are also effective in CSVD (2). The imaging findings of CSVD include small subcortical infarcts, lacunar infarcts, white matter hyperintensities (WMHI), perivascular spaces, microhemorrhages, and brain atrophy (3). Because of the relationship between traditional atherosclerotic risk factors such as hypertension and CSVD, we hypothesized that ICAS, as an indicator of intracranial atherosclerosis, may also be associated with CSVD. In studies investigating the relationship between CSVD markers and ICAS, findings such as lacunar infarct and WMHI are evaluated separately (4-9). In this study, however, all findings of ICAS and CSVD markers other than microhemorrhage were evaluated together.

This study aimed to investigate the relationship between the presence and severity of ICAS and the findings of CSVD.

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Received: 02.05.2022 **Accepted:** 25.09.2022

Materials and Methods

Compliance with Ethical Standards

This retrospective study was approved by the University of Health Science Turkey, Ankara Kecioren Training and Research Hospital Institutional Review Board (date: 05.10.2018, approval number: 29).

Study Design

Four hundred seventy-five patients over the age of 40 who underwent non-contrast cranial computed tomography (CT) and magnetic resonance imaging (MRI) between January 1 and December 31, 2018, not more than 3 months apart, were screened from PACS. Ninety-six cases were excluded due to poor imaging quality, trauma/operation history, presence of tumor/metastasis, and history of demyelinating disease. The study was completed with 379 cases. Informed consent was not obtained because the study was retrospective.

All MRI examinations were carried out with a 1.5-T Siemens Avanto MR device (Siemens AG, Healthcare Sector, Erlangen, Germany). MRI squences included two-dimensional multislice turbo spin-echo T1-weighted [repetition time (TR)/echo time (TE), 1200/11 ms], fluid-attenuated inversion recovery (FLAIR) (TR/TE, 7000/94 ms; inversion time, 2500 ms), T2-weighted [TR/TE, 4500/84 ms), diffusion-weighted imaging (DWI), TR/TE, 4800/102 Ms, b: 0 and 1000 s/mm^2] in the axial plane, as well as a T1-weighted sequence oriented in the sagittal plane. The slice thickness was 5 mm, with a 1-mm gap between slices.

All CT examinations were carried out with a Siemens 16-slice multislice CT device (Siemens, Sensations, Germany). The slice thickness was 3 mm, with no gap between the slices.

The CT and MR images were independently evaluated by two radiologists at the workstation (Syngo workstation, Earlengen, Germany).

Patient Evaluation

The bone window was used in the detection and grading of ICAS. Foci above 130 HU in the evaluated vessel tracing were accepted as ICAS. The internal carotid artery (ICA) cavernous segment, middle cerebral artery (MCA) M1 segment, anterior cerebral artery A1 segment, vertebral artery V4 segment, and basilar artery were evaluated on the right and left sides. According to the visual 5-point ICAS scoring method defined by Hong et al. (8), grade 0 was scored as no calcification, grade 1 was scored as point calcification, grade 2 was scored as thin continuous or thick non-continuous calcification, grade 3 was scored as thick continuous calcification, and grade 4 was scored as double tract calcification (Figure 1). The total calcification score was determined by summing all scores (min-max: 0-36).

In the evaluation of small vessel disease, areas of cerebral spinal fluid intensity around penetrating vascular structures at the level of basal ganglia (BGPVS) and centrum semiovale (CSPVS) were considered perivascular space (PVS) enlargement on MRI. PVS was evaluated in axial T2A fast spin-echo (FSE) images and scored separately at these levels. Scores were done separately for both hemispheres and the highest score was included in the analyses (0: no PVS; 1: <10 PVS, 2:11- 20 PVS, 3: 21-40 PVS, and 4: >40 PVS) (10) (Figure 2). Scores of 2 and above were considered abnormal (6).

On MRI, WMHI was scored at periventricular (PVWMHI) and subcortical (SCWMHI) levels separately according to Fazekas et al. (11) staging (Figure 3). Scores of 2 and above were considered positive.

Cortical atrophy, global atrophy (GA) score, medial temporal atrophy (MTA) score, and Koedam score were recorded separately on MRI. The scoring methods were

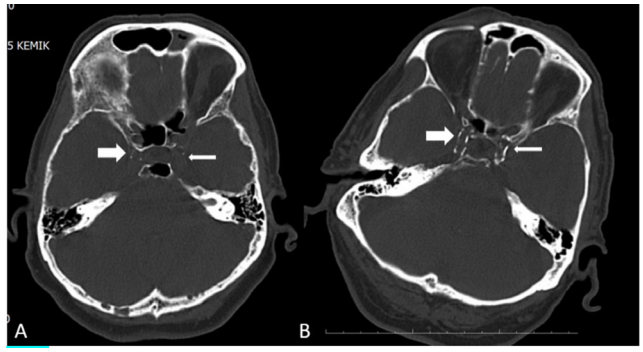

Figure 1. Non-contrast axial CT images with bone window setting showed A); grade 1: point calcification cavernous segment of ICA (thick arrow), cavernous sinus (thin arrow), B); grade 4: double tract calcification cavernous segment of ICA (thick arrow), cavernous sinus (thin arrow)

CT: Computed tomography, ICA: Internal carotid artery

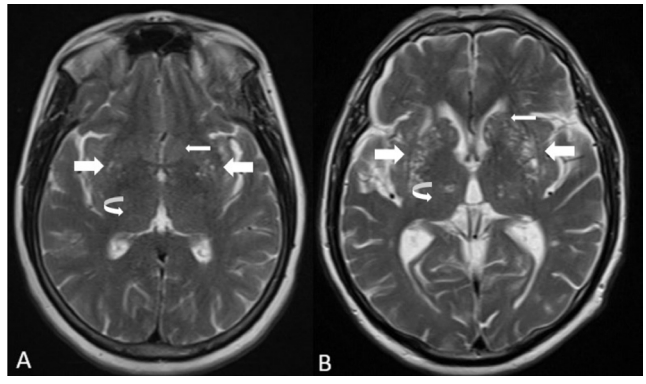

Figure 2. Axial T2W MR images at level of basal ganglia showed A); grade 1 BGPVS (thick arrows), head of caudate nucleus (thin arrow), thalamus (curved arrow). B); grade 4 BGPVS (thick arrows) head of caudate nucleus (thin arrow), thalamus (curved arrow)

MR: Magnetic resonance, BGPVS: Vascular structures at the level of basal ganglia, T2W: T2-weighted

evaluated separately for both hemispheres, and the highest score was recorded.

In GA scoring, the total brain parenchyma was evaluated in axial FLAIR sequences and the scoring method defined by Pasquier et al. (12) was used (0: no cortical atrophy; 1: mild cortical atrophy, slight enlargement of the sulci; 2: moderate atrophy, loss of volume in the gyri; 3: severe atrophy, knife blade-shaped atrophy of the sulci) (Figure 4). Scores of 2 and above were considered positive (13).

MTA scoring was performed on coronal T2-weighted (T2W) FSE images using the scoring method defined by Scheltens et al. (14) (0: no atrophy; 1: only choroidal fissure enlargement; 2: choroidal fissure and lateral ventricular temporal horn enlargement; 3: hippocampus elevation and slight volume loss; 4: severe loss of hippocampus volume). Scores of 3 and above were considered positive (13).

The Koedam scoring was performed on sagittal T1W FSE, coronal T2W FSE, and axial FLAIR FSE images, and the scoring method described by Koedam et al. (15) was used (0: no atrophy; 1: mild sulcal enlargement, without volume loss in the gyri; 2: moderate sulcal enlargement accompanied by volume loss in the gyri; 3: pronounced enlargement of the parietal sulci and knife blade-like appearance). Scores of 2 and above were considered positive (13).

Lacunar infarcts were defined as 3-15 mm in diameter T2W hyperintensities in the subcortical white matter, thalamus, or basal ganglia (16). Perivascular spaces were differentiated from lacunar infarcts by their specific locations and the absence of peripheral gliosis (16). An acute infarct was defined by hyperintensity on DWI and hypointensity on the clear diffusion coefficient map (ADC) (5). Chronic infarct was defined as hyperintensities on T2W, hypointensity on T1W, and no diffusion restriction on DWI and ADC (17). The presence and absence of lacunar, acute, and chronic infarcts were recorded on MRI.

Statistical Analysis

Categorical variables are summarized as frequencies and numbers. Continuous variables were described as medians (interquartile range) or mean ± standard deviation. Normality was assessed using the Kolmogorov-Smirnov test. For the univariate analysis, Pearson's $\chi 2$ test was used for categorical variables, and the Mann-Whitney U test was used for calcification score. Correlations were tested with the Partial correlation analysis after controlling for age and gender. The relationship between acute, chronic, and lacunar infarcts and intracranial calcification was tested using the Mann-Whitney U test. All data was analyzed with IBM SPSS version 20 (Chicago, IL, USA). $P<0.05$ was accepted as statistically significant in all analyses.

Results

Three hundred seventy-nine patients were included in the study. The mean age of the patients was 63.42±13.40 years (range 40-93). 42.2% of the patients were male and 57.8% were female. The MRI findings of the cases are summarized in Table 1. The distribution of MRI findings is shown in Figure 5.

The median total calcification score was 5 (min-max: 0-25). The total calcification scores of female patients were

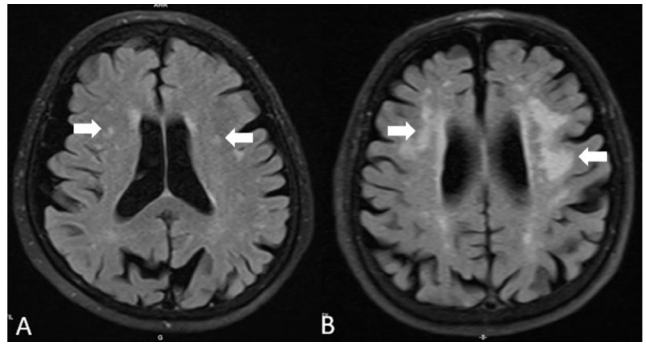

Figure 3. Axial FLAIR MR images showed A); Fazekas grade 1 WMHI (white arrows), grade 3, B) WMHI (white arrows)

MR: Magnetic resonance, WMHI: White matter hyperintensities

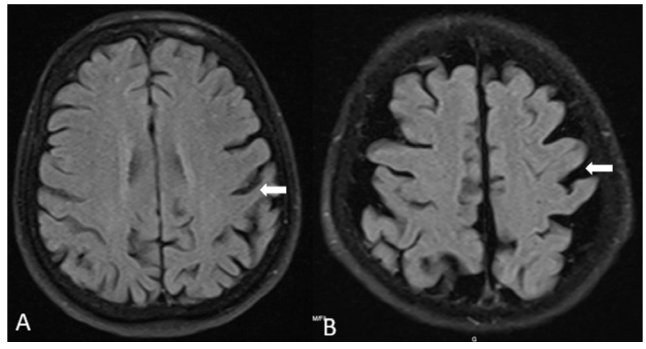

Figure 4. Axial FLAIR MR images at level of supraventricular showed A); global atrophy score grade 1: slight enlargement of the sulci (white arrow), B); global atrophy score grade 3: knife blade-shaped enlargement of the sulci (white arrow)

MR: Magnetic resonance

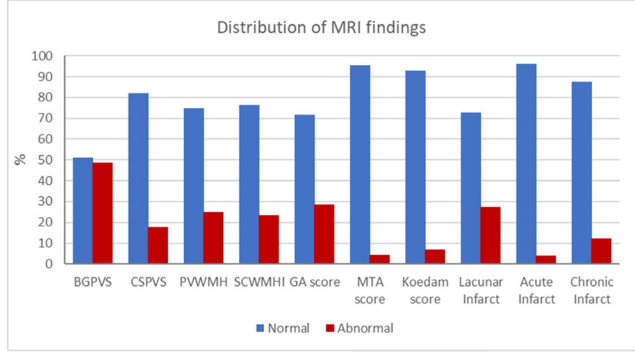

Figure 5. Distrubition of MRI findings

MRI: Magnetic resonance imaging

Table 1. Distribution of MRI findings (abnormal/normal/%)		
	n	%
BGPVS		
Normal (0+1)	194	51.2
Abnormal (≥2)	185	48.8
CSPVS		
Normal (0+1)	311	82.1
Abnormal (≥2)	68	17.9
PVWMHI		
Normal (0+1)	284	74.9
Abnormal (≥2)	95	25.1
SCWMHI		
Normal (0+1)	290	76.5
Abnormal (≥2)	89	23.5
GA score		
Normal (0+1)	271	71.5
Positive (≥2)	108	28.5
MTA score		
Normal (0+1+2)	362	95.5
Positive (≥3)	17	4.5
Koedam score		
Normal (0+1)	352	92.9
Positive (≥2)	27	7.1
Lacunar infarct		
No	275	72.6
Yes	104	27.4
Acute infarct		
No	364	96
Yes	15	4
Chronic infarct		
No	332	87.6
Yes	47	12.4

MRI: Magnetic resonance imaging, BGPVS: Vascular structures at the level of basal ganglia, CSPVS: Vascular structures at the level of centrum semiovale, PVWMHI: White matter hyperintensity was scored at periventricular, SCWMHI: White matter hyperintensity was scored at subcortical, GA: Global atrophy, MTA: Medial temporal atrophy

lower compared of male patients (M/F: 6/4; p<0.05). A positive correlation was found between age and total calcification scores (r=0.659, p<0.001).

After controlling for age and gender, a positive correlation was found between calcification score and BGPVS (r=0.463 p<0.001), PVWMHI (r=0.235 p<0.001), and GA scores (r=0.368 p<0.001). A negative correlation was found between the calcification score and MTA (r=-0.112 p<0.05) and KOEDAM scores (r=-0.196 p<0.001). After controlling for age and gender, no correlation was found between calcification score and CSPVS and SCWMHI scores (p>0.05).

There was no significant relationship between the acute infarct and total calcification score (p>0.05). The total calcification scores of cases with chronic and lacunar infarcts were significantly higher (p<0.001).

Discussion

CSVD is a disease associated with various clinical conditions ranging from acute-chronic ischemia to cognitive impairment. Although the etiology of CSVD includes pathologies such as systemic or vascular inflammation, arteriolosclerosis, cerebral amyloid angiopathy, etc., the exact cause is unclear (3,18). Recent literature showed an association between CSVD and atherosclerotic signs like arterial stiffness (19). In this study, a significant association was found between calcification of major intracranial arteries and enlarged perivascular spaces at the level of basal ganglia, PVWMHI, global, medial temporal, and parietal atrophy, and chronic and lacunar infarcts.

In this study, the relationship between perivascular spaces and ICAS was evaluated separately at the level of BGPVS and CSPVS. A significant relationship was found between BGPVS and the total calcification score. Similarly, a previous study investigating the relationship between increased PVS at the basal ganglia level with carotid siphon calcification reported a significant relationship between BGPVS and calcification grade (6). In another study evaluating the relationship between perivascular spaces and ischemic stroke, a significant relationship was found between BGPVS and lacunar stroke (10). Chen et al. (20) reported no significant correlation between the calcification score and enlarged perivascular spaces. This may be since enlarged perivascular spaces were not separated according to their localization in the study. In this study, there was no significant correlation between CSPVS and calcification score, which may be due to the different PVS etiology at the basal ganglia and CSPVS level (6).

A significant positive correlation was found between ICAS and PVWMHI score, but no correlation was found with SCWMHI. There are studies in the literature showing that WMHI are associated with extracranial carotid artery or intracranial major artery atherosclerosis (4,5,21,22). In a study investigating the relationship between ICAS and WMHI volume, a significant relationship was found between ICAS and enlarged WMHI volume (9). In the study by Babiarz et al. (23), no significant correlation was found between cavernous carotid artery calcification and WMH. Similar to the results of this study, de Leeuw et al. (21) reported a significant association between extracranial carotid artery atherosclerosis and PVWMHI, while there was no significant association with subcortical WMHI. In another study, it was shown that periventricular WMHI and deep WMHI had opposite effects on functional

decline after ischemic SVO, and this was attributed to the difference in the etiological mechanism of the two entities (24). We are also of the opinion that the opposite relationship between periventricular and subcortical WMHI and ICAS in this study is due to the difference in WMHI etiopathogenesis in the two regions.

Cerebral atrophy, one of the MRI findings of CSVD, was evaluated with a GA score, MTA score, and Koedam score. A significant positive correlation was found between the ICAS score and the GA score, while a significant negative correlation was found between ICAS and MTA and parietal atrophy (Koedam score) scores. Similarly, in a study conducted on the Japanese population (25), a significant correlation was found between the brain atrophy index and carotid plaque score. In another study, it was reported that carotid intima-media thickness was associated with sulcal enlargement in the brain (26). In a study investigating the relationship between ICAS and brain volume, a significant relationship was found between ICAS and total brain volume (27). In contrast, Erbay et al. (28) found no correlation between ICAS and cortical-volume loss. In contrast with the results of this study, Kang et al. (29) found a significant relationship between intracranial and carotid artery stenosis and hippocampal volume in patients with mild cognitive impairment. Vinke et al. (30) compared ICAS and CSVD findings and found no significant association with cerebral atrophy. There are differences between the three above-mentioned studies and this study. Visual scoring methods without software assistance were used in this study, which may have led to a difference in results. A result of this study was the negative correlation between ICAS and MTA and Koedam scores. Data on the relationship between ICAS and MTA or Koedam score are limited in the literature. Kang et al. (29), a positive correlation was shown between intracranial or carotid artery stenosis and hippocampal atrophy. However, MTA and parietal atrophy (Koedam score) are more likely to be associated with Alzheimer's disease (AD) than with vascular dementia (31,32). Studies showing that there is no relationship between AD and intracranial or carotid artery atherosclerosis (33,34) may indirectly explain the negative correlation found between ICAS and these atrophy patterns.

No significant relationship was found between acute infarct and ICAS. We believe this is due to the small number of cases with acute infarct in the study population (n=27). A significant relationship was found between lacunar infarct, chronic infarct, and ICAS. In a previous study investigating the relationship between cavernous carotid artery calcification and MCA infarct, no significant relationship was reported (35). Yilmaz et al. (36) found a significant relationship between ICAS and large vessel or cardioembolic cerebral infarct. In the study by Vinke et al. (30), a significant relationship was found between ICAS and lacunae. In these studies, the differences in both the ICAS grading systems and types of ischemic stroke (acute, chronic, TIA, etc.) included in the analyses explain the differences in the results. Additionally, a recently published study showed that intima-media localization of arterial calcification has different clinical consequences related to conditions such as collateralization and luminal stenosis (37).

Study Limitations

There are certain limitations to the present study. First, measuring calcification manually can affect the objectivity of calcification grading. However, it was defined that there are some disadvantages to both manual and automatic measurement methods in the literature (38). Moreover, a study in the literature comparing semiautomatic and manual measurements reported a good level of concordance between the two methods (39).

Due to the retrospective design of the study, other atherosclerotic risk factors such as hypertension, diabetes, and smoking could not be included in the analyses. These risk factors may be associated with CSVD or ICAS, but the focus of our study was to demonstrate the relationship between ICAS and cerebral small vessel disease.

Conclusions

The results of this study showed that ICAS is correlated with BGPVS, PVWMHI, GA, Koedam score, and chronic and lacunar infarcts. It was concluded that the relationship between ICAS and increased PVS at the basal ganglia and CSPVS levels was different. Similarly, the relationship between ICAS and PVWMHI was different from that of SCWMH. ICAS is a frequently encountered condition in daily practice, and the results of this study suggest that it may be associated with CSVD. Therefore, including ICAS severity in patient reports can guide CSVD risk management and treatment planning.

Ethics

Ethics Committee Approval: This retrospective study was approved by the University of Health Science Turkey Ankara Kecioren Training and Research Hospital Institutional Review Board (date: 05.10.2018, approval number: 29).

Informed Consent: Informed consent was not obtained because the study was retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.O., O.G., Design: C.O., Data Collection or Processing: C.O., O.G., Analysis or Interpretation: C.O., O.G., Literature Search: C.O., Writing: C.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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