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The association of vertebrobasilar calcification with etiological subtypes, stroke recurrence and outcome in acute brainstem ischemic stroke

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ABSTRACT

Arterial calcification (AC), a frequent finding on imaging studies, has been reported as a risk factor for ischemic stroke. However few studies have explored the association of AC with etiological subtypes and prognostic implications. The purpose of this study was to investigate the association of AC with demograhics, risk factors and etiological subtypes and to determine whether it predicts stroke recurrence and functional outcome in patients with acute brainstem ischemic stroke. We analyzed our database consisting of patients who were diagnosed as acute brainstem ischemic stroke admitted within 24 hours of onset. Etiological classification of stroke was made based on The Trial of ORG in Acute Stroke Treatment (TOAST) Classification. AC in vertebral and basilar arteries were assessed from baseline brain CT. AC degree was categorized according to calcification along the circumference in the densest calcified segment of each vessel (0 point if no calcification in any of the CT slices, 1 point if calcification <50% of circumference and 2 points if calcification ≥50% of circumference). Three AC categories were defined according to the total AC score as follows: no AC (0 point), mild AC (1–2 points), severe AC (≥3 points). Recurrent stroke within the first 3 months of follow up and modified Rankin Score (mRS) at 3-month were reviewed. 42% of 188 patients had AC in at least of the vertebrobasilar arteries. Severe AC was related to age and the presence of diabetes mellitus and coronary artery disease. The prevalence of AC was significantly higher in large artery atherosclerosis subtype. The presence of AC was marginally associated with recurrent stroke but did not find to be related with functional outcome. Further studies with larger sample size are warranted to explore this topic.

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1. Introduction

Arterial calcifications (AC) are frequently observed on unenhanced brain Computed Tomography (CT) and have been reported to occur in up to 90% of atherosclerotic lesions and considered as an integral part of active process of atherosclerosis [1]. There are studies reporting the presence of AC as a risk factor for ischemic stroke [2–4]. Although most of previous studies looked into carotid artery calcification, it has been suggested that distal internal carotid artery (ICA) calcification was not related with atherosclerotic plaque but with medal wall calcification [4]. The characteristics of vertebrobasilar calcification might be different from those of ICA calcification. Besides, it has been shown that detection of AC on CT may predict major clinical events including recurrent stroke and death in ischemic stroke patients [5,6]. Although vertebral artery (VA) is the second most common artery having AC [2,7], there is no study evaluating the relationship of vertebrobasilar calcification with neurological outcome in acute brainstem ischemic stroke.

In this study, we aimed to investigate the association of AC in VA and basilar artery (BA) with vascular risk factors and etiological subtypes and to determine whether AC predicts stroke recurrence and outcome in patients with acute brainstem ischemic stroke.

2. Methods

2.1. Patients

Between January 2012 and January 2016, we retrospectively identified patients who were admitted to our department with acute brainstem ischemic stroke. Brainstem ischemic stroke was defined as acute neurological deficit with relevant lesions on mecencephalon, pons or medulla oblongata on brain cranial Magnetic Resonance Imaging Diffusion-Weighted Images (MRI-DWI). Inclusion criteria for this study were (1) admittance to our department within 24 hours of symptom onset and (2) having brain CT imaging performed with a same 5-mm slice thickness from the skull base to the vertex.

Demographic characteristics, vascular risk factors, clinical and radiological data were collected from the patients included in the study. The following criteria were considered for vascular risk factors: a history of hypertension (HT) or an observed arterial blood pressure >140/90 mmHg, presence of a history of diabetes mellitus (DM) or a fasting glucose exceeding 126 mg/dl other than that measured during the acute phase, a positive history of hyperlipidemia (HL) or a fasting total cholesterol >200 mg/dl, low density lipoprotein (LDL) >130 mg/dl, and/or a triglyceride (TG) >180 mg/dl. Data for the presence of coronary artery disease (CAD), smoking and previous history of stroke were retrieved from patients' medical records. Patients were excluded if they had significant missing data in clinical charts.

2.2. Diagnosis and etiological classification of ischemic stroke

Diagnostic workup included brain CT, MRI (including DWI), vascular imaging techniques (MR angiography (MRA), Computed Tomography Angiography (CTA), or Doppler Ultrasonography of carotid and vertebral arteries), 12-lead electrocardiography (ECG) and transthoracic echocardiography (TTE). Transesophageal echocardiography (TEE) and 24-hour holter ECG monitoring were performed in patients with no etiological factor and suspected of cardioembolic stroke.

Considering all variable data, etiological classification of stroke was made based on TOAST criteria [8].

2.3. Evaluation of calcification

A stroke physician who was blinded to clinical findings evaluated the AC on brain CT. Intracranial AC were defined as hyperdense foci with a peak density more than 90 Hounsfield units. AC degree was categorized according to calcification along the circumference in the densest calcified segment of each vessel. AC score was categorized as 0 point (no calcification in any of the CT slices), 1 point (mild calcification, calcification <50% of circumference), and 2 points (severe calcification, ≥50% of circumference).

The total AC score ranged from 0 to 6 (up to 2 points per the most calcified area of both VA, and BA). Three AC categories were defined according to the total AC score as follows: no AC (0 point), mild AC (1–2 points), and severe AC (≥3 points) [9,10].

2.4. Evaluation of recurrent stroke and outcome

The presence of recurrent stroke in 3 month follow-up period and the modified Rankin Score (mRS) at 3-month were reviewed from database. Patients with progressive neurological deficit attributed to the index stroke in the first days of clinical presentation were not recorded as recurrent stroke. In patients with inadequate data retrieval, phone calls were made to gather information on de novo occurrence of recurrent vascular conditions and mRS evaluations.

2.5. Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows Version 23 software was used for statistical analyses. Mean, minimum, maximum, and percentage values were calculated for descriptive data. The Pearson chi-square test or Fischer' exact test were used to compare the differences in categorical variables. Student *t*-test or one-way ANOVA was used for numerical variables. Multivariate analysis were performed with multiple logistic regression to determine the independent factors ($p < 0.1$ in the univariate analysis) associated with recurrent stroke and outcome. Statistical significance was set at a $p < 0.05$.

3. Results

3.1. Baseline demographics and vascular risk factors among patients

Of 255 patients with acute brainstem infarction admitted to our department, 188 (73%) patients fullfilled the inclusion criteria. 12 patients were excluded because of the lack of CT imaging on admission and 35 patients were excluded because

Table 1 – Demographics and vascular risk factors in all patients and in patients without calcification (0 point), with mild (1–2 points) and with severe calcification (≥3 points).

	No calcification n (%)	Mild calcification n (%)	Severe calcification n (%)	All patients n (%)	p
Age, mean ± SD	61.8 ± 12	66.1 ± 12	69.1 ± 8.4	63.9 ± 12	0.009
Sex, female	46 (41.4)	20 (35.7)	6 (28.6)	72 (38.3)	0.48
NIHSS, mean ± SD	4.77 ± 2.54	5.16 ± 3.60	4.33 ± 1.95	4.84 ± 2.84	0.48
Hypertension	70 (71.2)	43 (77.8)	19 (90.5)	141 (75)	0.16
Diabetes mellitus	50 (45)	35 (62.5)	16 (76.2)	101 (53.7)	0.009
Coronary artery disease	22 (19.8)	10 (17.8)	11 (52.4)	43 (22.9)	0.003
Hyperlipidemia	45 (40.5)	29 (51.8)	9 (42.9)	83 (44.1)	0.38
Stroke history	28 (25.2)	16 (28.6)	3 (14.3)	47 (25)	0.43
Smoking	36 (32.4)	15 (26.8)	2 (9.5)	53 (28.2)	0.09

Table 2 – Etiological classifications in patients with calcifications and without calcifications.

Etiological classification	Calcification − n (%)	Calcification + n (%)	Total	p
Large artery atherosclerosis	25 (22.9)	40 (50.6)	65 (34.6)	0.002
Cardioembolic	16 (14.7)	10 (12.7)	26 (13.8)	
Small vessel disease	48 (44)	23 (29.1)	71 (37.8)	
Other causes	8 (7.3)	3 (3.8)	11 (5.9)	
Undetermined causes	12 (11)	3 (3.8)	15 (8)	
Total	109	79	188	

of significant missing data. The mean age of the patients was 63.92 ± 12 years (range: 23–92) and the mean of The National Institutes of Health Stroke Scale (NIHSS) was 4.84 ± 2.84 (range: 16). There were 118 male (67.2%), and 70 female (32.8%). The location of the infarction was in the mesencephalon in 12 (6.3%) patients, in pons in 119 (63.3%) patients and in medulla oblongata in 57 (30.3%) patients. 50.5% of patients exhibited infarction in the left, 48.4% exhibited in right of the brainstem and 1.1% of patients had bilateral infarction. Demographic characteristics and the incidence of risk factors are presented in Table 1.

3.2. *Etiological classification*

The etiological subtypes were classified as follows: 71 patients (37.8%) exhibited Small Vessel Disease (SVD), 65 patients (34.6%) exhibited Large Artery Atherosclerosis (LAA), 26 (13.8%) exhibited Cardioembolic Etiologies (CE) and 11 patients (5.9%) exhibited other causes. 15 patients (8%) exhibited the undetermined etiology. The most common etiological subtypes in patients with AC were LAA and SVD. The incidence of AC was significantly higher in patients with LAA, whereas lower in patients with SVD, other causes and undetermined etiology subgroups (p: 0.002, Table 2).

3.3. *Arterial calcification*

Of all patients, 79 (42%) had AC in at least one of the vertebrobasilar arteries. The degree of AC was mild in 29.8% and severe in 11.2% of the patients. The rate and severity of AC was lowest in the BA. The distribution of AC according to the arteries is represented in Table 3. When patients were grouped as no AC, mild AC and severe AC; the mean of age, the incidence of DM and CAD were significantly highest in patients with severe AC than in patients with mild AC and no AC groups (p: 0.009, p: 0.009, p: 0.003 respectively, Table 1). The incidence of smoking was lowest in patients with severe AC but the difference did not reach statistical significance (p: 0.09, Table 1).

3.4. *Recurrent stroke and outcome at follow-up*

12 of all patients (6.6%) exhibited recurrent stroke in the 3 month follow-up period. 12.7% of patients with AC, whereas 1.9% of patients without AC exhibited recurrent stroke (p: 0.004). The mean of age, NIHSS scores and the presence of HL were higher in patients having recurrent stroke (p: 0.004,

Table 3 – The incidence of arterial calcification in vertebral arteries and basilar artery.

	Patients n (%)
Right vertebral artery	
No calcification	146 (77.7)
Mild calcification	27 (14.4)
Severe calcification	15 (8)
Left vertebral artery	
No calcification	134 (71.3)
Mild calcification	33 (17.6)
Severe calcification	21 (11.2)
Basilary artery	
No calcification	155 (82.4)
Mild calcification	28 (14.9)
Severe calcification	5 (2.7)
All arteries	
No calcification	111 (59)
Mild calcification	56 (29.8)
Severe calcification	21 (11.2)

p: 0.07, p: 0.01 respectively). 10 of these patients had LAA and the remaining 2 patients had SVD etiological subtype.

When 130 patients with LAA and SVD etiological subtypes were analyzed, 16.4% of patients with AC whereas 2.9% of patients without AC exhibited recurrent stroke (p: 0.008). There was no statistical difference with regard to age and sex and NIHSS at onset. Among vascular risk factors, only history of stroke was found significantly higher in patients with recurrent stroke. In logistic regression analysis, the presence of recurrent stroke was found to be associated with stroke history (p: 0.01, Odd's ratio: 0.168, 95% of CI: 0.04–0.64) and it was marginally associated with the presence of AC (p: 0.05, Odd's ratio: 0.193, 95% of CI: 0.03–1.04)

The modified Rankin Scores at 3 month were determined in 182 patients. Of these, 51 (28%) had poor outcome (mRS ≥2). Demographics, risk factors, etiological subtypes and also the presence of AC did not differ according to the functional outcome.

4. Discussion

In this study, we evaluated the association of AC with risk factors, etiological subtypes and investigate the effect of AC in recurrent stroke and outcome at 3-month in acute ischemic brainstem stroke.

We used unenhanced CT scans to evaluate AC because of its accessibility and being a direct method to evaluate AC. In addition, it has been reported that unenhanced CT could more readily demonstrate small amounts of calcifications and it is more sensitive for detection of calcifications when compared to CT angiography [11,12].

In our study, the prevalence of AC was 42%. To the best of our knowledge, there is no study reporting the prevalence of AC in brainstem stroke patients. In the literature evaluating all ischemic stroke patients, the prevalence of intracranial AC varies between 35% and 92% [12–15]. Contrary to our study which we focused on posterior circulation, these reported frequencies in the literature have been found by investigation of overall calcification in cerebral arteries. This wide range of prevalence in studies can be attributed to the different techniques used to detect AC, the differences in demographic characteristics and also ethnic differences in study populations. Indeed, there are racial differences in gene expression profiles contributing to differential risks of arterial calcification [16].

Basilar artery was the least affected artery and the prevalence of AC in left VA was slightly higher than right VA in our study, as previously reported in one study investigating the distribution of vertebrobasilar calcification in all ischemic stroke patients [17].

As in the literature, the presence and severity of AC was associated with the mean of age, presence of DM and CAD in our patients [2,12,14,18]. In contrary, we did not find any association of AC with HT and HL. Also in our study, the prevalence of smoking was mathematically lower in patients with AC. This should be attributed to that the patients with smoking history were significantly younger than the patients without (p: 0.000). Indeed, in logistic regression analysis, history of smoking did not correlate with the presence of AC.

Similar to the literature, the most common etiological subtype in our study population was SVD followed by LAA subtype [19]. The prevalence of AC was highest in LAA subtype in our patients. Few studies have explored the association of calcifications with specific stroke subtypes. In one study, there was no difference between lacunar and nonlacunar strokes with regard to intracranial AC in anterior circulation whereas aortic AC was more prevalent in nonlacunar strokes than in lacunar strokes in the same study [20]. In another study, intracranial internal carotid artery calcification was found to be associated with stroke of LAA and CE subtypes [12]. The authors tried to explain these findings with the possibility of the presence of internal carotid artery calcification being a reflection of more downstream events in the pathogenesis of atherosclerosis and they suggested that internal carotid artery calcification might be an imaging marker of cardiac and vascular diseases. The prevalence of CE subtype was low and also the percentage of CE etiology did not differ between patients with AC and without AC in our population. Already, most of our patients had infarction in pons and CE is thought to be an unusual mechanism in pontine infarctions [21]. Several studies have reported the association of arterial calcifications with cerebral artery stenosis [14,22,23]. We did not explore the correlations between AC and the severity of vascular stenosis but the prevalence of AC was highest in LAA etiological subtype, which is defined as a stenosis of at least 50% lumen diameter in the relevant artery. Nevertheless, further studies are needed to explore the potential contributions of AC in different stroke subtypes.

Because recurrent stroke was observed mainly in LAA and SVD subtypes and also AC was most prevalent in these subtypes, we executed recurrent stroke analysis only in patients with these etiologies. There are studies reporting that the presence of AC is associated with major clinical events, including ischemic stroke and death in ischemic stroke patients [5,24]. The etiological subtypes were not taken in consideration in one of these aforementioned studies whereas etiological subtypes did not correlate with the presence of AC in the other study. In a recent study, the association of AC with early vascular events, including progression and recurrent stroke, was investigated and the authors reported that the presence of AC might predict early vascular events in noncardioembolic ischemic stroke patients. Contrary to our results, the prevalence of AC was lower in SVD etiological subtype in the present study. However, there was no information about the localizations of ischemic infarctions. In our results, we found a marginal association between AC and the risk of recurrent stroke. However, AC did not affect the 3-month functional outcome. Mechanisms of ischemic stroke differ in anterior and posterior circulation strokes [25].

There are limitations in our study. First, this is a retrospective study with a modest sample size. Also recurrent stroke was present in only 12 patients. This is probably because we could not enroll patients with very severe stroke and referred to Intensive Care Units from emergency department instead of our stroke service unit. Therefore, this study is vulnerable to selection bias and the results should be confirmed with larger studies. Second, we did not analyze the association of AC with vascular stenosis or hypoplasia and

could not explore the association of AC with vascular stenosis in vertebrobasilary arteries. We did not include thalamic, occipital cortex and cerebellar infarctions having blood supply from vertebrobasilar arteries. This is because of rarity of AC in posterior cerebral arteries and other branches of vertebrobasilar system supplying cerebellum. Also brainstem ischemic stroke has a distinctive stroke mechanism with respect to other regions in posterior circulation system.

In conclusion, the degree of vertebrobasilar calcifications was associated with aging and vascular risk factors including DM and CAD and vertebrobasilar calcifications were more prevalent in LAA etiological subtype of brainstem ischemic stroke patients in our study population. We did not find any relationship with vertebrobasilar calcification and recurrent stroke, and functional outcome in brainstem ischemic stroke patients. Further studies with larger sample size are warranted to explore this topic.

Conflict of interest

None declared.

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