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RESEARCH

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Vertebrobasilar dolichoectasia in patients with cerebrovascular ischemic stroke: does it have a role in cerebral microbleeds?

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Abstract

Background: Vertebrobasilar dolichoectasia (VBD) may account for cerebral microbleeds (CMBs) in ischemic cerebrovascular stroke.

Objectives: To examine whether VBD is associated with the involvement of CMBs in any region and, if so, whether it is associated with CMBs among ischemic stroke patients located in posterior circulation territory. For patients with VBD, we also studied ischemic stroke subtypes, and checked whether dolichoectasia was linked to vascular risk factors.

Methods: Two hundred ischemic stroke patients in whom detailed clinical data and brain MRI sequences were obtained, and stroke subtyping with TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment) was performed.

Results: The mean age of patients was (65.22 ± 12.88), male patients were more frequent (67.5%); dyslipidemia was the most frequent risk factor (55%). Cardio-embolic stroke subtype was the most frequent (37%) and (71.5%) of patients had no history of previous use of antithrombotic drugs. Ectasia was found in 28 (14%), dolichosis was found in 50 (25%) and vertebrobasilar dolichoectasia was found in 19 (9.5%) of patients. Cerebral microbleeds were detected in 114 (57%) patients. Mild degree CMBs was the most prevalent among patients 69 (61%) and were located predominantly in both anterior and posterior territories 41 (36%). CMBs were significantly more frequent in hypertensive and older patients.

Conclusions: In patients with VBD, severe degree CMBs were more common and were located as a vascular territory supplied by vessels originating from dolichoectatic parent vessels in the posterior region.

Keywords: Vertebrobasilar dolichoectasia (VBD), Cerebral microbleeds (CMBs)

Introduction

Intracranial arterial dolichoectasia (IADE), or brain vessel dilatative arteriopathy, occurs in approximately 12% of stroke patients and is characterized as an increase in the length and diameter of at least one intracranial artery and subsequent hemodynamic and hemostatic changes [1]. The intracranial arteries that are affected are dilated, elongated and sometimes tortuous. IADE involves the posterior circulation more often than the anterior circulation and affects the basilar artery in 80% of cases [2]. Whereas atherosclerosis involves lipid infiltration and an arterial wall intima inflammatory process, IADE involves rarefaction of the tunica media elastic tissue, and fragmentation of the internal elastic lamina [3].

In the case of arterial rupture, the clinical signs of IADE include brain infarction, cerebral hemorrhage, subarachnoid hemorrhage (SAH), and cranial nerve or

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brainstem compression. IADE may be asymptomatic as well [4]. Cerebral microbleeds (CMBs) are defined as small, homogeneous, round hypo intense foci on gradient echo T2-weighted magnetic resonance imaging (GRE) or susceptibility-weighted image (SWI) with a size of 2 to 10 mm; without corresponding traditional magnetic resonance imaging (MRI) hypo- or hyperintense [5].

Etiologies that underlie CMBs include several arteriopathies, such as hypertensive arteriopathy, cerebral amyloid angiopathy, Moyamoya disorder, and cerebral autosomal dominant arteriopathy and subcortical infarction and leukoencephalopathy (CADASIL) [6]. In addition, the involvement of CMBs is related to an increased risk of intracerebral hemorrhage (ICH) [7, 8]. In research using adaptive MRI techniques, the prevalence of CMBs in community-dwelling elderly people is as high as 11.1–23.5% [9, 10]. The prevalence is higher in ischemic stroke patients (40%) and spontaneous intracerebral hemorrhage (ICH) patients (47–80%). Ethnicity appears to play a role in CMB prevalence, with higher prevalence among participants of Asian origin. CMBs are related to age, hypertension, leukoaraiosis, amyloid angiopathy, atrial fibrillation, and some genes [11].

Our aim in this study is to examine the relationship between the VBD and CMB in ischemic stroke patients and to evaluate the frequency and anatomical distribution of cerebral microbleeds (CMBs) in patients with VBD.

Methods

This cross-sectional analytical study was performed in Neurology Department. Two hundred adult patients aged ≥ 18 years of both sexes with acute ischemic stroke who were admitted to Neurology department were included. Patients with transient ischemic attack, hemorrhagic stroke, pacemaker, metal objects, and/or an unstable clinical condition disqualifying the patient to undergo an MRI examination safely, intracerebral lesions related to tumor associated bleeding, arteriovenous malformations, cavernomas or abscesses or pregnant were excluded. The study was approved by the faculty of medicine of Suez Canal Faculty of medicine ethical committee (Committee Number: 2932). Written, informed consent was obtained from all subjects before inclusion in the study.

All patients with an acute ischemic stroke who came to Emergency Department were assigned to complete history taking and laboratory tests: clinical characteristics and risk factors data of patients including: age, gender, smoking habits (current smoker, ex-smoker or non-smoker), hypertension was considered when a patient received anti-hypertensive medication prior to admission or when frequent blood pressure measurement ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic [12] was detected during hospital stay. Diabetes mellitus is considered dependent on history of anti-diabetic drugs or insulin intake or two levels of 126 mg/dL or higher fasting blood glucose [13]; Dyslipidemia was considered when total cholesterol ≥ 200 mg/dL, low density lipoprotein (LDL-C) ≥ 100 mg/dL, high density lipoprotein (HDL-C) ≤ 40 mg/dL in males and ≤ 50 mg/dL in females, or triglycerides ≥ 150 mg/dL or treatment with lipid-lowering drugs [14]. Ischemic heart disease and Prior use of antithrombotic medicines in the last 3 months.

Neurological examination: the purpose of the neurological examination is to confirm the presence of a stroke, to differentiate stroke from stroke mimics (e.g. coma, migraine, encephalitis, tumor, and metabolic encephalopathy) [15]. To determine the severity of the stroke using a standardized neurological examination and score (National Institutes of Health Stroke Scale [NIHSS] [16]. Assessment of consciousness level was done using the GCS (severe: GCS ≤ 8, moderate: GCS 9–12, minor: GCS ≥ 13) [17].

Brain imaging: all ischemic stroke patients underwent CT, MRI, MRA and gradient echo sequence brain scan were done, CT brain scan without contrast was done in ER to exclude hemorrhagic stroke with Machine type: Toshiba Aquilion, Multislice helical, Number of slices: 16, 0.5 mm slice width.

MRI, MRA, gradient echo sequence brain scan: done after admission of patients in Neurology department. Machine type: Philips Achieva 1.5-Tesla superconducting Short bore cylindrical magnet. The 3D time-of-flight MRA was obtained from the genu of the corpus callosum to the lower medulla level through 3D spoiled gradient-echo acquisition. Sequences: T2 coronal, T2 axial, Sagittal T1, MRA. The findings were interpreted by two investigators (senior radiologist and senior neurologist) while unaware of any clinical information.

Ischemic stroke was categorized according to the TOAST classification system [18], based on MRI scan, extracranial carotid doppler and electrocardiography (ECG), Holter monitoring, and transthoracic echocardiography, stroke was classified into the following subtypes: cardio-embolism: evidence of stroke in a vascular territory, Small-artery disease and lacunae: brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated, Large-artery atherosclerosis: cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter are considered to be of potential large-artery atherosclerotic origin, Other determined cause (e.g. extra cranial arterial dissection, primary cerebral vasculitis), Undetermined

causes (e.g. complete workup has been unraveling, two likely causes for a given stroke are identified).

Based on MRA scan Vertebrobasilar dolichoectasia was defined as both ectasia and dolichosis which were simultaneously observed in each patient [19]: Ectasia was defined when the diameter of the basilar artery (BA) was > 4.5 mm at any point along its course. Dolichosis of the basilar artery was considered when: it lay lateral to the margin of clivus or dorsum Sella. Or was bifurcated above the plane of the suprasellar cistern. To assess the severity of dolichosis in each patient: the height of BA bifurcation score as [19]: (1) within the supra-sellar cistern, (2) level with the third ventricle floor and (3) indenting and elevating the floor of the third ventricle. The degree of lateral displacement score as [19]: (1) medial-to-lateral margin of the clivus or dorsum sellae, (2) lateral to the lateral margin of the clivus or dorsum sellae and 3 (In) the cerebellopontine cistern. Dolichosis was defined when scores ≥ 2 for the height of BA bifurcation or lateral displacement [19].

Based on gradient echo sequence of MRI Cerebral microbleeds were defined as a homogeneous round signal-intensity-loss lesion 2–5 mm in diameter. The degree of CMBs was classified as [20] Absent, Mild < 5, Moderate 5–10, Sever > 10.

CMB locations was divided into anterior and posterior circulation territories. The anterior circulation of the brain describes the areas of the brain supplied by the right and left internal carotid arteries and their branches. The internal carotid arteries supply the majority of both cerebral hemispheres, except the occipital and medial temporal lobes, which are supplied from the posterior circulation. The Posterior circulation of the brain supply parts of the brainstem, cerebellum, thalamus, subthalamic nucleus, basal nucleus, mesial inferior temporal lobe, and occipital and occipito-parietal cortices [21]. The study sample according to presence or absence of vertebrobasilar dolichoectasia and/or cerebral microbleeds was divided into four groups as following: patients had VBD with CMBs, patients had VBD with no CMBs, Patients had no VBD but had CMBs and Patients had neither VBD nor CMBs.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: Published 2016 by IBM Corp). Qualitative data were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Descriptive data was expressed as median and interquartile range for continuous nonparametric variables, as mean and SD for continuous parametric variables, and count/total and percentages (%) for categorical and dichotomous variables. One-way analysis of variance (ANOVA) was used to analyze the continuous variables between the two studied groups (e.g. age and ectasia diameter) and Chi-test for categorical and dichotomous variables (e.g. smoking and microbleeds location). The level of statistical significance was (P value < 0.05) and high statistical significance is considered when (P value < 0.01) [22].

Table 1 Demographic characteristics among ischemic stroke patients

	Number = 200 (%)
Gender	
Males	135 (67.5%)
Females	65 (32.5%)
Age	Mean (65.22) SD (12.88)

Table 2 Risk factors among ischemic stroke patients

Risk factors	Number (%)
Smoking	95 (47.5%)
Hypertension	91 (45.5%)
Ischemic heart disease	46 (23%)
Diabetes mellitus	92 (46%)
Dyslipidemia	110 (55%)
Previous use of antithrombotic drugs	
No	143 (71.5%)
Antiplatelet	38 (19%)
Anticoagulant	13 (6.5%)
Thrombolytic	6 (3%)

Results

The patients' sample was 200 ischemic stroke patients, the mean age of study sample was (65.22 ± 12.88); males were more predominant 135 (67.5%) patients, while females were 65 (32.5%) patients (Table 1). There was 95 (47.5%) smokers, 92 (46%) diabetics, 91 (45.5%) hypertensive, 110 (55%) had dyslipidemia, and 46 (23%) had ischemic heart disease. Regarding previous use of antithrombotic drugs, 143 (71.5%) were found to have no history of previous use of antithrombotic drugs, 38 (19%) had history of antiplatelet use, 13 (6.5%) had history of anticoagulant use and 6 (3%) had history of thrombolytic drugs use (streptokinase for previous cardiovascular insult) (Table 2). Incidence of stroke subtypes among patients sample was as follow, there was 74 (37%)

Table 3 Stroke subtypes among ischemic stroke patients

Stroke subtypes	Number (%)
Cardio-embolic	74 (37%)
Large artery	32 (16%)
Small artery	48 (24%)
Undetermined causes	40 (20%)
Determined cause	6 (3%)

Table 4 Vertebrobasilar dolichoectasia and cerebral microbleeds incidence

Presence of CMBs	Patients with VBD	Patients without VBD	*P* value
	Number = 19 (%)	Number = 181 (%)	
With CMBs	16 (84%)	96 (53%)	0.009*
Without CMBs	3 (16%)	85 (47%)	

CMBs: cerebral microbleeds; VBD: Vertebrobasilar dolichoectasia

(χ^2) test = Pearson chi-square

* Statistically significant difference between both groups (*P* value < 0.05)

Table 5 Vertebrobasilar dolichoectasia and cerebral microbleeds territorial distribution

CMBs	Patients with VBD	Patients without VBD	*P* value
	Number = 16 (%)	Number = 96 (%)	
Anterior Territory	1 (6%)	35 (36%)	0.129 (NS)
Posterior Territory	12 (75%)	23 (24%)	0.000**
Both Territories	3 (19%)	38 (40%)	0.593 (NS)

CMBs: cerebral microbleeds; VBD: vertebrobasilar dolichoectasia

Both Territories (anterior and posterior territory)

(χ^2) test = Pearson chi-square

NS: no statistically significant difference

** High Statistically significant difference between both groups (*P* value < 0.05)

patients presented with cardio-embolic, 32 (16%) large artery, 48 (24%) small artery, 40 (20%) undetermined causes and 6 (3%) presented with determined cause of ischemic stroke (Table 3).Cerebral microbleeds incidence was significantly more frequent in patients with vertebrobasilar dolichoectasia (84%) than in patients without vertebrobasilar dolichoectasia (53%) (*P* value = 0.009) (Table 4). Cerebral microbleeds were highly significantly more located in posterior territory in patients with vertebrobasilar dolichoectasia (75%) than in patients without vertebrobasilar dolichoectasia (24%) (*P* value = 0.000). No significant difference detected in patients with VBD and patients without VBD regarding anterior and both territories (anterior and posterior) (Table 5). Sever degree

Table 6 Vertebrobasilar dolichoectasia and cerebral microbleeds severity

CMBs Severity	Patients with VBD Number = 16 (%)	Patients without VBD Number = 96 (%)	*P* value
Mild	8 (50%)	59 (61.5%)	0.404 (NS)
Moderate	4 (25%)	28 (29%)	0.528 (NS)
Sever	4 (25%)	9 (9.5%)	0.007*

CMBs: cerebral microbleeds; VBD: vertebrobasilar dolichoectasia

(χ^2) test = Pearson chi-square; NS: no statistically significant difference

* Statistically significant difference between both groups (*P* value < 0.05)

Mild < 5, Moderate 5–10, Sever > 10

cerebral microbleeds (CMBs > 10) was significantly more frequent in patients with VBD than in patients without VBD (*P* value = 0.007). No significant difference detected in patients with VBD and patients without VBD regarding moderate and sever degree CMBs (Table 6).

Discussion

Regarding the demographic characteristics and the risk factors associated with CMBs. This study found that the mean age of patients was (65.22 ± 12.88 years), (67.5%) male, whereas (32.5%) female, (47.5%) smoker, (46%) diabetic, (45.5%) hypertensive, (55%) dyslipidemia, and (23%) ischemic cardiac disease. Such findings were approximately in line with Jung et al. study [23]. Which was done in (167) patients with an acute ischemic stroke in which male patients constituted (53.9%) and female patients (46.1%); this is also consistent with the O'Donnell et al. [24]. Male patients (57.6%) and female patients (42.4%) and Altafi et al. [25] (54.54%) were male patients and (46%) were female patients [25] in Marinigh et al. [26].

Cerebral infarction increased with advancing age, where (85.6%) of patients were between (46 and 90 years of age) and (14.4%) were patients (about 45 years of age) who agree with our study showing that the mean age of our patients was (65.22 ± 12.88 years of age).

Another research by Marwat et al. [27] identified that the incidence of cerebral infarction increased with increasing age as (2.3%) in the age group (40–50 yeas), (27.2%) in the age group (51–60 years), and (47.7%) in the age group (60 years or older).

Hypertension is considered an important risk factor for the occurrence of ischemic strokes and was found in (62.3%) in study by Lip et al. [28] and (67.3%) in another report by O'Donnell et al. [24] which is higher than our research as it was detected in (45.5%) patients.

Banerjee et al. [29] reported diabetes mellitus in (66.8%) of patients in his study which is higher than our

study result recorded in (46%) patients. Dyslipidemia has been reported by Djelilovic-Vranic et al. [30] in (35.3%) of patients in his study which is lower than our study found in (55%) of patients.

Smoking cigarettes is a well-known risk factor for strokes and has a strong association with the thrombotic cycle. In the Framingham study [31] it was found that after correction for age and hypertension, the relative risk of ischemic stroke in smokers was found (2.3 in men and 3.1 in women) and a strong dose–response relationship. The risk of ischemic stroke was increased in heavy smokers relative to the medium smokers. After 5 years of cessation of smoking, the risk of stroke returned to non-smoker levels [31]. In our study, smoking was reported in (47.5%) which is less than the findings of an older study conducted by Labresh and Reeves [32] which found that smoking was associated with (55%) ischemic stroke patients [32].

In a retrograde study conducted by Vernooij et al. [33] on (245) ischemic stroke patients, (23.1%) used platelet aggregation inhibitors primarily, 61 (5.9%) used anticoagulant drugs exclusively, and 10 (4.1%) used thrombolytic drugs. This study is approximate to our study results, which showed that (19%) had used antiplatelet drugs, (6.5%) had used anticoagulant drugs and (3%) had used thrombolytic drugs. Regarding ischemic heart disease, we found that (23%) of patients were recorded to have ischemic heart disease, which is approximate to study by Park et al. [19] who found that (17%) of ischemic stroke patients had ischemic heart disease [19].

In study by Thijs et al. [34], stroke subtypes using TOAST classification were determined in (3748) patients with ischemic stroke The cause of the index stroke was large artery disease in 605 (16.1%), cardio-embolism in 583 (15.6%), SVD in 492 (13.1%), other determined causes in 623 (16.6%), and undetermined cause in 1445 (38.6%) patients. While in our study, we found that (37%) had cardio-embolic, (24%) had small artery, (16%) had large artery, (20%) had undetermined cause, (3%) had determined cause of stroke. Detection of CMBs and their territorial distribution depends on MRI gradient echo time (TE) sequence and according to their count the degree of severity was detected [5, 35]. Dilatation and elongation of basilar artery was detected in brain MRA image [19, 36].

Ectasia of basilar artery study by Ichikawa et al. [37] showed that strong association was found between CMBs and basilar artery dilation [37]. This agrees to our findings that CMBs were significantly more frequent in patients with ectasia (82%) than in patients without ectasia (52%) (P value < 0.05). Study by Zhai et al. [38] investigated cerebral microbleeds territorial distribution, found that basilar artery ectasia was significantly associated with lobar anterior territory CMBs and infratentorial posterior territory CMBs evenly, which is in contrast to our study as we found that CMBs were more frequently found in posterior territory of patients with ectasia (70%) and more frequent in anterior territory in patients without ectasia (39%). In our study we found that sever degree CMBs were more frequently detected in patients with ectasia of basilar artery (22%) than those without ectasia of basilar artery (9%), this is in agreement with study by Nakajima et al. [39] who found strong association between ectasia of basilar artery and sever degree CMBs.

Dolichosis of basilar artery in our study was found to be strongly associated with cerebral microbleeds incidence (82%) than those without dolichosis (47%) (P value < 0.01), this is in agreement to study by Zhang et al. [40] who found strong association between dolichosis and cerebral microbleeds. Anterior and posterior territories cerebral microbleeds were more frequently found in patients with dolichosis in study by Sandhu et al. [41], in contrary to our study that showed frequent CMBs in posterior territory of patients with dolichosis (63%) and frequent CMBs in anterior territory of patients without dolichosis (45%). Our study results agreed with Sandhu et al. [41] in the strong association between dolichosis and severity of CMBs. Pooling ectasia and dolichosis of basilar artery together, vertebrobasilar dolichoectasia in our study was found to be strongly associated with cerebral microbleeds incidence, CMBs were more frequently found in patients with VBD (84%). This is higher than study by Park et al. [19] which showed that (33.3%) of patients with VBD had CMBs [19]. In other study by Thijs et al. [34] found a strong association between intracranial arterial dolichoectasia and the presence of cerebral microbleeds. Of the patients with IADE, (16.3%) [33/202] had microbleeds at any location compared with (4.7%) [65/1372] of the patients without IADE, which is also lower than our study results. Regarding cerebral microbleeds territorial distribution and vertebrobasilar dolichoectasia, our study showed posterior territory predilection (75%) vs (6% and 19%) in anterior and mixed territories, respectively, while in patients without VBD, CMBs were more frequent in mixed territories (40%) than anterior and posterior territory (36% and 24%), respectively. In other study by Park et al. [19] cerebral microbleeds were observed posteriorly in (66.7%) and anteriorly in (45.8%) patients with VBD, but posteriorly in (16.5%) and anteriorly in (15.2%) patients without VBD which is in agreement to our study.

Thijs et al. [34] investigated the territorial distribution of cerebral microbleeds in accordance with intracranial arterial dolichoectasia and demonstrated that microbleeds were more frequent in brain stems, deep regions, and cortico-subcortical areas in patients with intracranial

arterial dolichoectasia compared to those without intracranial arterial dolichoectasia [34].

By distinguishing between posterior and anterior circulation, Thijs et al. [34] demonstrated that in patients with vertebrobasilar dolichoectasia, CMBs were found more frequently and significantly in the posterior territory [34].

Del brutto et al. [42] found that there was strong association between vertebrobasilar dolichoectasia and moderate to severe degree cerebral microbleeds [42] this is in approximate to our study which showed that sever degree CMBs were more frequent in patients with VBD (25%) than in patients without VBD (9.5%) (P value < 0.05).

Conclusions

In our research, dolichoectasia of the basilar artery is found in a significant proportion of ischemic–stroke patients. The existence of basilar dolichoectasia appears to increase the risk of cerebral microbleeds that indicate a specific etiopathogenesis of pathological degeneration in the arterial media that can be shared in vertebrobasilar dolichoectasias dilative arteriopathy.

Abbreviations

CMBs: Cerebral microbleeds; GCS: Glasgow coma scale; IADE: Intracranial arterial dolichoectasia; ICH: Intracerebral hemorrhage; NIHSS: National Institutes of Health Stroke Scale; SAH: Subarachnoid hemorrhage; TOAST: Trial of ORG 10172 in acute stroke treatment; VBD: Vertebrobasilar Dolichoectasia.

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Author contributions

OA carried out the Study conception and design, participated in its design and coordination and drafted the manuscript. NM carried out the design of the study, the Analysis and interpretation of data and helped to draft the manuscript. MW carried out the Study conception and design, participated in its design. HM participated by acquisition of data and performed the statistical analysis. ES participated in the sequence alignment, interpretation of data and Drafting of manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data can be publicly available at the Faculty of Medicine, Suez Canal University.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics committee of Suez Canal Faculty of medicine on October 19, 2016. Committee Number: 2932. An informed written consent was taken from all the participants in the study.

Consent for publication

Participants signed an informed consent for publication.

Competing interests

The authors declare that they have no competing interests (financial or non-financial).

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