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Accurate etiology diagnosis in patients with stroke and atrial fibrillation: A role for brain natriuretic peptide

Yuki Sakamoto[a,*], Chikako Nito[a], Yasuhiro Nishiyama[a], Satoshi Suda[a], Noriko Matsumoto[a], Junya Aoki[a], Takashi Shimoyama[a], Takuya Kanamaru[a], Kentaro Suzuki[a], Yuki Go[a], Masahiro Mishina[b], Kazumi Kimura[a]

[a] Department of Neurological Science, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan
[b] Department of Neuro-pathophysiological Imaging, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

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ABSTRACT

Background: Atrial fibrillation (AF) is the leading cause of cardioembolic stroke (CES), and patients with stroke and AF are frequently assumed to have CES. However, strokes presumably due to atherosclerotic pathophysiologies in large or small vessels can also occur in patients with AF. The aims of the present study were to clarify the prevalence of and factors related to a non-cardioembolic etiology in acute stroke patients with AF.

Methods: From March 2011 through May 2017, consecutive acute ischemic stroke patients with AF were retrospectively recruited. The concomitant presence of non-cardioembolic features (small vessel occlusion [SVO] or large artery atherosclerosis [LAA]) on imaging was evaluated. The frequency of and factors associated with co-existing SVO/LAA features were assessed.

Results: A total of 560 consecutive patients with AF and acute stroke (237 women; median age 78 [IQR 71–85] years; NIHSS score 9 [3-20]) were enrolled. Of these, 42 (7.5%) had co-existing SVO/LAA features. Multivariable logistic regression analysis showed that the brain natriuretic peptide level (BNP, OR 0.78, $p = .030$ per 100 pg/mL increase) was independently and negatively associated with co-existing SVO/LAA features and receiver operating characteristic curve analysis revealed the practical cut-off BNP value was 130 pg/mL (sensitivity 54% and specificity 68%).

Conclusion: SVO/LAA features were found in 7.5% of acute stroke patients with AF. A relatively low BNP level on admission was independently associated with co-existing SVO/LAA features. Thorough examination for a more appropriate etiology may be particularly necessary in acute stroke patients with AF and a relatively low BNP level.

1. Introduction

Defining the cause of stroke in the acute setting is critical for patients with acute ischemic stroke in terms of optimal treatment and the strategy for preventing recurrence. Atrial fibrillation (AF) is the leading cause of cardioembolic stroke (CES), [1,2] and patients with acute stroke and AF are frequently assumed to have CES [3]. However, stroke patients often have accompanying risk factors other than AF, such as hypertension, dyslipidemia, diabetes mellitus, and severe arterial stenosis, [4–7] and stroke presumably due to atherosclerotic pathophysiologies in large or small vessels can also occur in patients with AF [8–12]. Indeed, the incidence of stroke in anticoagulated AF patients was almost identical to that in patients without AF in previous reports [13,14]. These reports suggest that non-cardioembolic stroke could appear irrespective of the presence of AF or anticoagulant therapy, and anticoagulant therapy could only reduce the risk of CES and have little effect on non-cardioembolic stroke. Because the recommended treatment strategy differs between patients with cardioembolic and non-cardioembolic etiologies [15,16], non-cardioembolic stroke in AF patients should be managed differently from CES, at least in the acute setting. Nevertheless, the frequency of and predictive factors for non-cardioembolic etiologies in acute stroke patients with AF are not fully known.

Brain natriuretic peptide (BNP) is one of cardiac hormones and it is released in response to end-diastolic pressure overload and ventricular volume expansion [17]. High BNP value was associated with

* Corresponding author at: Department of Neurological Science, Graduate School of Medicine, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
E-mail address: ysakamoto02@gmail.com (Y. Sakamoto).

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cardioembolic etiology in acute stroke patients, and BNP was suggested to be a useful biomarker for cardioembolic stroke diagnosis or ruling out the possibility of underlying cardioembolism among patients with acute stroke [18–20]. However, usefulness of BNP for predicting concomitant stroke etiology in patients with acute stroke and AF has not been elucidated. The aims of the present study were to clarify the prevalence of and factors related to non-cardioembolic etiologies, and assess the utility of BNP levels in discriminating non-cardioembolic etiologies in acute ischemic stroke patients with AF.

2. Methods

2.1. Subjects

From March 2011 through May 2017, consecutive acute ischemic stroke patients with AF who were admitted to our stroke unit within 7 days from symptom onset were retrospectively recruited from the prospective registry [21]. Patients without AF were excluded. This study was approved by the institutional ethics committee. Written, informed consent for registering prospective registry was obtained from all patients or their next-of-kin.

3. Clinical characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and past medical histories, were recorded on admission. Cardiovascular risk factors were defined as: 1) hypertension, history of using antihypertensive agents, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg before or ≥ 2 weeks after stroke onset; 2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥ 200 mg/dL, or glycosylated hemoglobin ≥6.5% on admission; 3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level ≥ 220 mg/dL; and 4) current smoker. The prestroke $CHADS_2$ or CHA_2DS_2-VASc score was calculated for each patient based on the published guideline [22]. However, aortic plaque was not assessed as a component of the score. The index stroke was not counted as a "history of ischemic stroke". Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional status was estimated with the modified Rankin scale (mRS). Routine blood biochemistry examinations including BNP were performed on admission. The BNP value was determined using automated chemiluminescence enzyme immunoassay machine (AIA-CL2400, Tosoh Co., Tokyo, Japan). AF was diagnosed with 12-lead electrocardiography, cardiac monitoring during stroke unit stay, or 24-h Holter monitoring during admission. Transthoracic echocardiography was performed by a cardiologist or a well-trained ultrasonographer during hospitalization.

4. Neuroimaging

Magnetic resonance imaging (MRI) studies including diffusion-weighted imaging (DWI) and time-of-flight MR angiography (MRA) were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Echelon Oval, Hitachi Medical Systems, Tokyo, Japan). DWI was obtained using the following parameters: TR/TE, 6000/65 ms; b-values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 128 × 128; and slice thickness, 4.5 mm, with a 2.5-mm intersection gap. The concomitant presence of non-cardioembolic features on admission was defined as: 1) having a sole ischemic lesion in perforating artery territory (basal ganglia, corona radiata, thalamus, and brainstem) and maximum infarct diameter < 15 mm (small vessel occlusion [SVO]) [10]; and/or 2) the DWI lesion was restricted to a single arterial territory with > 50% stenosis of the corresponding artery (large artery atherosclerosis [LAA]). Stenosis of the artery was evaluated with MRA and neck duplex ultrasonography. These non-cardioembolic features on imaging were assessed by consensus reading by 2 experienced vascular neurologist (Y.S. and Y.G.) blinded to other imaging and clinical information. Although almost all (95%) patients were evaluated by MRI on admission, patients having a contraindication to MRI were evaluated with computed tomography (CT), CT angiography, or conventional angiography.

4.1. Statistical analysis

All patients were classified into two groups based on the presence of concomitant SVO and/or LAA features: the ambiguous CES (A-CES) group (AF patients with concomitant SVO and/or LAA features) and the definite CES (D-CES) group (AF patients without concomitant SVO and/or LAA features).

First, the two groups' clinical background characteristics were compared. Univariate analyses were performed using the chi-squared test, Fisher's exact test, and Mann-Whitney *U* test, as appropriate. The data are presented as median values (interquartile range [IQR]) or numbers (%). Second, multivariable logistic regression analysis was performed to identify independent factors associated with co-existing non-cardioembolic features. For relatively small number of outcomes (42 cases), forward stepwise selection of variables (using alpha = 0.05 for the likelihood ratio test for inclusion) was carried out. Variables available on admission in Table 1 (except for the $CHADS_2$ and CHA_2DS_2-VASc scores due to duplication of variables) were included in the models. The relative risks of having non-cardioembolic features are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Third, receiver operating characteristic (ROC) curve analyses were conducted to obtain the practical cut-off values of continuous variables for discriminating the A-CES group from the D-CES group. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC) were evaluated with the identified cut-off values.

All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL). Results were considered significant at $p < .05$.

5. Results

Overall, 561 consecutive patients with AF and acute ischemic stroke were admitted to our stroke center during the study period. After excluding one patient having AF and acute aortic dissection, 560 patients (237 women [42%]; 125 (22%) showed normal sinus rhythm on admission; median age 78 [IQR 71–85] years; NIHSS score 9 [3–20]; onset to arrival 4.5 [2.0–14.0] h) were enrolled into the present study. Of these 560 patients, 18 (3.2%) had concomitant SVO feature, and 25 (4.5%) had LAA feature. In patients having SVO feature, only one showed cortical symptoms. Because both SVO and LAA feature co-existed in one patient, 42 (7.5%, 95% CI 5.3–9.7%) patients belonged to the A-CES group, and the remaining 518 belonged to the D-CES group (92.5%).

Table 1 shows the clinical background characteristics of the included patients. The CHA_2DS_2-VASc score ($p = .024$) was higher, and the NIHSS score ($p = .005$) and levels of D-dimer ($p = .001$) and brain natriuretic peptide (BNP, p = .001, Fig. 1) were lower in the A-CES group than in the D-CES group. Patients in the A-CES group tended to be treated with direct oral anticoagulants at onset ($p = .031$ among anticoagulant status) more than those with D-CES, and paroxysmal AF (pAF) was more common in the A-CES group than in the D-CES group ($p = .007$). Multivariable logistic regression analysis showed that BNP (OR 0.80, 95% CI 0.65–0.98, $p = .029$ for every 100 pg/mL increment) was independently and negatively, and pAF (OR 2.06, 95% CI 1.04–4.06, $p = .037$) was independently and positively associated with co-existing SVO/LAA features (Table 2).

On ROC analysis, the cut-off BNP value for discriminating the A-CES group from the D-CES group was 130 pg/mL (sensitivity 54%, specificity 68%, PPV 12%, NPV 95%, and AUC 0.651). Using this cut-off

Table 1
Clinical background characteristics of all patients and by group.

Variable	Total	A-CES group	D-CES group	p
	n = 560	*n* = 42	*n* = 518	
Female sex, n (%)	237 (42)	20 (48)	217 (42)	0.517
Age, years, median (IQR)	78 (71–85)	80 (72–86)	78 (70–85)	0.312
Risk factor				
Hypertension, n (%)	351 (63)	27 (64)	324 (62)	0.870
Dyslipidemia, n (%)	190 (34)	17 (41)	173 (33)	0.397
Diabetes Mellitus, n (%)	95 (17)	9 (21)	86 (17)	0.397
Current smoker, n (%)	90 (16)	5 (12)	85 (16)	0.661
Congestive heart failure, n (%)	115 (21)	7 (17)	108 (21)	0.691
Prior embolism, n (%)	138 (25)	15 (36)	123 (24)	0.094
History of vascular disease, n (%)	80 (14)	8 (19)	72 (14)	0.359
$CHADS_2$ score, median (IQR)	2 (1–3)	3 (1–4)	2 (1–3)	0.061
CHA_2DS_2-VASc score, median (IQR)	4 (2–5)	5 (2–6)	4 (2–5)	0.024
Anticoagulation at onset, n (%)				0.031
None	395 (70)	25 (60)	370 (71)	
VKA	102 (18)	7 (17)	95 (18)	
DOAC	64 (11)	10 (24)	54 (10)	
Antiplatelet at onset, n (%)	141 (25)	9 (21)	132 (26)	0.712
Preadmission mRS score, median (IQR)	0 (0–1)	0 (0–2)	0 (0–1)	0.888
Onset to arrival, h, median (IQR)	4.5 (2.0–14.0)	8.0 (2.0–30.1)	4.0 (2.0–13.9)	0.067
NIHSS score on admission, median (IQR)	9 (3 − 20)	4 (2 − 13)	10 (3–20)	0.005
Anterior-circulation stroke, n (%)	394 (70)	29 (69)	365 (70)	0.862
Ejection fraction, %, median (IQR)	67 (61–73)	67 (62–74)	67 (61–72)	0.473
Biochemistry on admission, median (IQR)				
aPTT, s	29.6 (26.9–33.7)	29.5 (27.4–32.7)	29.6 (26.8–33.8)	0.810
PT-INR	1.13 (1.03–1.28)	1.14 (1.07–1.30)	1.13 (1.03–1.28)	0.351
Blood glucose, mg/dL	120 (102–145)	121 (99–163)	119 (103–144)	0.783
Creatinine, mg/dL	0.84 (0.67–1.05)	0.83 (0.66–1.22)	0.84 (0.68–1.04)	0.974
eGFR, ml/min	61 (48–76)	60 (44–72)	62 (48–76)	0.336
D-dimer, μg/mL	1.4 (0.9–3.1)	1.0 (0.6–1.7)	1.4 (0.9–3.2)	0.001
Brain natriuretic peptide, pg/mL	194 (105–370)	124 (58–211)	202 (109–376)	0.001
Reperfusion therapy, n (%)	182 (32)	8 (19)	174 (34)	0.060
Paroxysmal atrial fibrillation, n (%)	161 (29)	20 (48)	141 (27)	0.007
mRS score at discharge, n (%)	3 (1–5)	3 (1–4)	3 (1–5)	0.280

A-CES group: AF patients with concomitant small vessel occlusion and/or large artery atherosclerosis.
D-CES group: AF patients without concomitant small vessel occlusion and/or large artery atherosclerosis
AF, atrial fibrillation; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; aPTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio; eGFR, estimated glomerular filtration rate.
*including ischemic stroke and systemic embolism
** including ischemic heart disease and peripheral artery disease

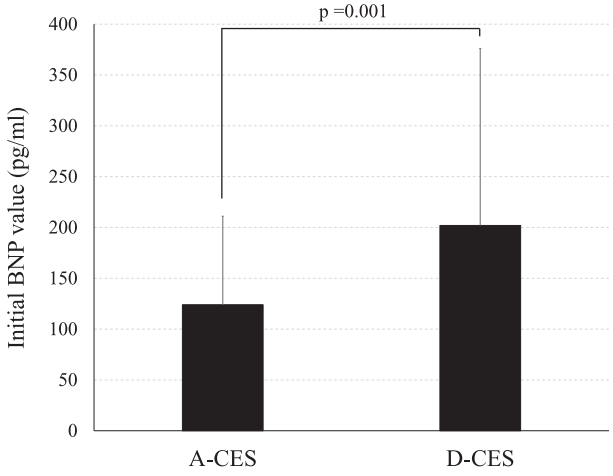

Fig. 1. Initial brain natriuretic peptide levels in the A-CES and D-CES groups. The initial brain natriuretic peptide level is lower in the A-CES group than in the D-CES group (p = .001). Data are shown as medians (boxes) and interquartile range (bars).

value, patients with BNP < 130 pg/mL had a 2.7-fold higher risk of having concomitant SVO/LAA features (OR 2.66, 95% CI 1.33–5.30, p = .006, Table 3).

Table 2
Multivariate logistic regression model for having concomitant SVO/LAA etiology.

Variables	OR	95% CI	p
Anticoagulation at onset, n (%)			
None	1.00	Ref.	
VKA	0.46	0.13–1.63	0.228
DOAC	2.27	0.99–5.17	0.051
PT-INR (per 1.0)	2.25	0.91–5.54	0.078
BNP (per 100 pg/mL)	0.80	0.65–0.98	0.029
Paroxysmal AF (vs. chronic AF)	2.06	1.04–4.06	0.037

The variables identified by the forward selection procedure are listed. SVO, small vessel occlusion; LAA, large artery atherosclerosis; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; PT-INR, prothrombin time-international normalized ratio; BNP, brain natriuretic peptide; AF, atrial fibrillation.

6. Discussion

The present study showed that 7.5% of patients with acute stroke and AF had concomitant SVO/LAA features. A relatively low BNP level (cut-off value < 130 pg/mL) on admission was independently associated with co-existing SVO/LAA features.

The frequency of patients having concomitant SVO/LAA features was 7.5% (95% CI 5.3–9.7%) in the present study. This percentage seems to be relatively low compared to past reports, which showed that

Table 3
Multivariate logistic regression model for having concomitant etiology using practical BNP cut-off.

Variables	OR	95% CI	p
Age (per 10 years)	1.49	1.02–2.19	0.038
Anticoagulation at onset, n (%)			
None	1.00	Ref.	
VKA	0.46	0.14–1.58	0.218
DOAC	2.21	0.97–5.04	0.060
Initial NIHSS (per 1.0)	0.95	0.92–0.99	0.021
PT-INR (per 1.0)	1.98	0.91–4.32	0.088
BNP < 130 pg/mL	2.66	1.33–5.30	0.006

The variables identified by the forward selection procedure are listed. BNP, brain natriuretic peptide; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health stroke scale; PT-INR, prothrombin time-international normalized ratio; BNP, brain natriuretic peptide; AF, atrial fibrillation.

9.8% of AF and stroke patients had etiologies of classical TOAST criteria other than CES [12], 8.7% had SVO [11], 11% had ipsilateral carotid artery stenosis or occlusion [4], and 16.9% had LAA [9]. Differences in the definition of SVO (< 15 mm was used in the present study and < 20 mm in another [11]) or modality of artery imaging for LAA (predominantly MRA in the current study and angiography or contrast-enhanced MRA or CTA in another [9]) may explain the relatively low rate of concomitant SVO/LAA features in the present study. One previous study included only anterior-circulation stroke [4]. Co-existing SVO/LAA features in acute stroke patients having AF is uncommon, but at least nearly 10% of AF and acute stroke patients have non-cardioembolic features. Thorough examination for detecting the true or "more appropriate" cause of stroke is essential even for acute stroke patients with AF seemingly having CES, because treatment approaches other than anticoagulation may be effective for patients with strokes due to SVO or LAA.

Univariate analysis showed that the rate of patients treated with anticoagulants (especially DOACs) and pAF was more common in the A-CES group than the D-CES group, and this result seems to be plausible; patients with pAF or anticoagulant therapy may have a lower risk of CES than those with chronic AF or not under anticoagulation, but stroke from non-cardioembolic cause may not differ significantly. Indeed, multivariable analysis also revealed that pAF was the independent predictor for having SVO/LAA etiology. BNP on admission was independently and negatively associated with A-CES in the present study. A high BNP level in the acute phase suggested CES in stroke patients [18–20], largely due to the association between the presence of AF and a relatively high BNP level [23,24]. In addition, in patients with AF and acute stroke, a high BNP level was reported to be associated with atrial dilatation, low flow velocity, spontaneous echo contrast, and intracardiac thrombus [25,26]. Moreover, a high BNP level was shown to be related to structural heart disease [27]. A high BNP level in acute stroke and AF patients raises the possibility of definite CES, probably because a high BNP level in such patients was associated with factors that facilitate intracardiac thrombus formation. Considering a high NPV and availability as one of the routine blood biochemistry examinations on admission, the initial BNP level seems to be a useful screening biomarker for discriminating ambiguous from definite CES.

The present study had some limitations to be addressed. First, the definition of A-CES in the present study was somewhat arbitrary; A-CES could include embolic stenosis of the artery or embolic small infarct on basal ganglia. Because there are no gold standard definitions of non-cardioembolic etiologies in acute stroke patients with AF, whether the true etiology of the A-CES was non-cardioembolic could not be assessed. Moreover, due to the retrospective design, other possible co-existing causes were not systematically explored with pre-defined protocol. Second, the number of the included patients were small, especially patients with concomitant SVO and/or LAA features. Low prior probability (7.5%) of co-existing SVO/LAA features affected PPV and NPV, so interpretation of these figures needs caution. Furthermore, the sensitivity and specificity of the BNP value for discriminating non-cardioembolic etiology were relatively low, partly due to small sample size. Third, the BNP level in acute stroke is known to be associated with infarct size or the initial NIHSS score [25,28,29], and CES patients showed a large infarct volume and a high NIHSS score [30]. Therefore, although BNP was an independent predictor for concomitant SVO/LAA features on multivariable regression analysis, whether a high BNP level is a primary determinant or a secondary consequence of definite CES remains to be determined. The present findings should be confirmed in a prospective cohort with a pre-defined examination protocol.

In conclusion, imaging-defined SVO and/or LAA was found in 7.5% of patients with AF and acute ischemic stroke. A relatively low BNP level on admission was independently associated with co-existing SVO/LAA features. Thorough examination for more appropriate etiologies may be particularly necessary in acute stroke patients with AF and a relatively low BNP level.

Conflict of interest

None.

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