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Case study

Chronic kidney disease is independently associated with acute recurrent cerebral infarct in patients with atrial fibrillation

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ABSTRACT

Background and purpose: The present study aimed to determine the frequency and time of recurrent cerebral infarct (RCI) in patients with acute ischemic stroke (AIS) and atrial fibrillation (AF), and to clarify associated factors.

Methods: We retrospectively assessed and compared the clinical features of 79 consecutive patients (male, $n = 56$; median age, 75 y; median baseline NIHSS, 4) who were hospitalized due to AIS accompanied by AF, and who did or did not develop RCI between January 2012 and March 2015.

Results: Direct oral anticoagulants were administered to 59% of the patients after a median of two days from the onset of the index stroke. Stroke recurred in 10 (13%) of the 79 patients about 5 days after admission. The proportion of men was lower (30% vs. 77%, $P = 0.005$) and the patients were older (82 vs. 75 y, $P = 0.049$) in the group with RCI. Chronic kidney disease was significantly more prevalent in the group with RCI (50% vs. 16%, $P = 0.025$) and independently associated with RCI (OR, 6.59; 95%CI, 1.19–36.63; $P = 0.031$).

Conclusions: We found that RCI frequently develops about 5 days after admission in patients with AIS and AF and that chronic kidney disease is independently associated with RCI.

1. Background

The risk of recurrence within the first 2 weeks after an index stroke varies between 0.1% and 1.3% per day among patients with acute ischemic stroke (AIS) accompanied by atrial fibrillation (AF) [1–4]. This is important to understand, but the timing of administering anticoagulation after the index stroke, the type of anticoagulation and factors associated with recurrence remain obscure.

The timing of anticoagulation initiation generally depends on stroke size, etiology and the general health status of the patients (such as blood glucose levels) considering hemorrhagic transformation [5,6]. The American Stroke Association recommends starting oral anticoagulation within 14 days after the onset of neurological symptoms, but how to select the day to start within this period depends on the attending physician [7]. Several randomized controlled trials have shown that administering heparin to patients with AIS within 48 h of an index stroke does not reduce the incidence of recurrence and does not improve outcomes [3,8]. Several types of direct oral anticoagulants (DOACs) have recently been applied, but the effects of these agents on recurrent cerebral infarct (RCI) have not been investigated in detail. There has been reported the close relationship between AF and chronic kidney disease (CKD), and CKD increases thromboembolic risk in patients with AF [9,10]. However, little is known about relationship between RCI and CKD in patients with AF.

Therefore, we retrospectively reviewed the clinical features and types of anticoagulants that were actually administered to patients at our hospital. The goal of this study was to determine the proportion of patients with AIS accompanied by AF who developed RCI and when, and to clarify factors associated with RCI.

2. Methods

2.1. Subjects

Between January 2012 and March 2015, we retrospectively enrolled 79 consecutive patients with AIS and AF who were admitted to Jikei University Hospital, Japan. We assessed the following cardiovascular risk factors from their medical records: hypertension, defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and/or a history of medication with antihypertensive agents; diabetes mellitus (DM), defined as

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medication with oral hypoglycemic agents or insulin, fasting blood glucose ≥69.9 mol/L (126 mg/dL) and/or glycosylated hemoglobin >6.1%, according to the Japan Diabetes Society; hyperlipidemia, defined as medication with anti-hyperlipidemic agents, or serum total cholesterol ≥5.69 mmol/L (220 mg/dL); AF, defined as intermittent episodes that spontaneously terminated or persistent AF determined by electrocardiography, 24 h Holter electrocardiography, or electrocardiographic monitoring; CKD, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and calculated from the plasma creatinine level upon admission ($eGFR = 194 \times (\text{serum creatinine [mg/dL]})^{-1.094} \times age^{-0.287} \times 0.739$ [for women]); a history of ischemic heart disease, a history of stroke and a history of smoking, defined as cigarette use at any time in the life of the patient.

The $CHADS_2$ scores for congestive heart failure, hypertension, age ≥75 years, DM and stroke/transient ischemic attack were obtained from the medical records of each patient. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Hemorrhagic events were defined as intracranial and extracranial bleeding that developed after admission. Good outcomes were defined as scores of 0–1 on the modified Rankin scale (mRS) at 90 days after stroke onset.

2.2. Thrombolysis

The inclusion and exclusion criteria for the administration of intravenous tissue plasminogen activator (t-PA) and dose (0.6 mg/kg) were in accordance with the findings of the Japan Alteplase Clinical Trial [11]. All patients did not receive antithrombotic agents within 24 h after t-PA infusion. Simultaneously, if a patient had major vessel occlusion and a clinical-diffusion mismatch indicating potentially salvageable ischemic brain tissue, the occluded site and collateral blood flow was immediately assessed by cerebral angiography using standard endovascular procedures. The attending physician selected the thrombolytic agent or procedure (urokinase, angioplasty, Merci®, Penumbra®, Trevo®, or Solitaire®) within insurance constraints.

2.3. Anticoagulation

Patients with transient ischemic attack received oral anticoagulants from the time of admission. Patients with small infarcts were assessed by brain MRI 24 h after admission and then anticoagulation was started when the absence of hemorrhagic transformation was confirmed. The attending physician decided the timing of starting anticoagulation when patients had large infarcts on initial neuro-images or hemorrhagic transformation on follow-up MRI. Attending physicians were also free to decide whether the type of anticoagulation would be heparin, oral anticoagulants or a combination.

2.4. Assessment of recurrence

Patients underwent a second brain MRI 24 h after stroke onset. Patients without neurological deterioration were examined by a third brain MRI about 7 days after onset. Patients with suspected neurological deterioration were immediately assessed by brain MRI. We defined RCI as symptomatic or asymptomatic and with a new ischemic lesion detected by DWI at the second or third brain MRI during hospitalization.

2.5. Statistical analysis

The clinical characteristics and details of treatment, as well as clinical outcomes were compared between patients with and without RCI to identify factors associated with RCI. Continuous and categorical variables were compared using unpaired Student's *t* tests and χ^2 tests, respectively. Variables with $P < 0.20$ in the univariate analysis were entered into a multivariate logistic regression model to identify independent variables that were associated with recurrence. Two-tailed $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA). This study conformed to the ethical principles established in the Declaration of Helsinki, and the Institutional Review Board at Jikei University School of Medicine approved the study protocol.

3. Results

3.1. Back grounds of all patients

Among 79 patients with AIS and AF (56 men; median age 75, interquartile range [IQR] 68–83; median baseline NIHSS 4, IQR 1–16) who were admitted to our hospital during the study period, 20 (25%) were hospitalized with new AF (Table 1). Oral anticoagulants were administered to 28 (35%) patients, and oral anti-platelet agents were administered to 7 (9%) before admission. We administered intravenous t-PA to 17 (22%) patients, and endovascular therapy to 11 (14%). Fig. 1 shows anticoagulation treatment after admission. Anticoagulants were prescribed to all patients who survived and were discharged from the hospital, and 59% of them received DOACs. Anticoagulation was started a median of 2 days after onset of the index stroke. Their length of stay was median 15 days (IQR, 11–30 days).

3.2. Comparison between patients with and without recurrence

Among 10 (13%) of 79 patients who developed RCI, 7 (9%) were symptomatic. Table 1 shows the clinical characteristics of patients with and without RCI. The RCI group contained a smaller proportion of men (30% vs. 77%; $P = 0.005$) and older patients (82 vs. 75 y; $P = 0.049$). CKD was more frequent in patients with RCI (50% vs. 16%; $P = 0.025$). The sensitivity, specificity, positive and negative predictive values of CKD as a surrogate marker of RCI were 50% (95%CI, 0.19–0.81), 84% (95%CI, 0.75–0.93), 31% (95%CI, 0.08–0.54) and 8% (95%CI, 0.01–0.15), respectively. The time from onset to the start of anticoagulation did not significantly differ between the groups as both were 2 days ($P = 0.510$). Asymptomatic hemorrhagic events occurred in two (20%) patients with RCI. The frequency of a good outcome was lower in the group with, than without RCI (10% vs. 51%; $P = 0.015$; Fig. 2).

Table 2 shows details of the group with RCI. Patients with symptomatic recurrence had received a lower dose of warfarin or no anticoagulants before admission. AF was detected in half of the RCI group after admission. Most patients were prescribed with warfarin or DOACs at the time of stroke recurrence. The proportion of patients with RCI that received anticoagulants was similar to that of all patients (Table 1). RCI was detected at a median of 5 days (IQR 2–13 days) after admission.

Table 3 shows that CKD was independently associated with RCI (OR, 6.59; 95%CI, 1.19–36.63; $P = 0.031$) after adjusting for sex, age, alcohol consumption, smoking history and CKD.

4. Discussion

The present study showed that RCI occurred a median of 5 days after admission in 13% of patients with AIS accompanied by AF and that CKD was independently associated with RCI.

We could not uncover precise information in the literature about a relationship between CKD and RCI with AF. Recent publications suggest that AF is closely associated with CKD via several

Table 1
Comparison of patients with and without recurrent cerebral infarct. Data are shown as *n* (%), and medians (interquartile range). Abbreviations: BP, blood pressure; DOACs, direct oral anticoagulants; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; t-PA, tissue-type plasminogen activator.

	Total (*n* = 79)	Recurrence (*n* = 10)	Non-recurrence (*n* = 69)	*P*
Male sex	56 (71)	3 (30)	53 (77)	0.005
Age, years	75 (68–83)	82 (74–88)	75 (66–81)	0.049
Backgrounds				
Smoking	42 (53)	2 (20)	40 (58)	0.027
Alcohol	40 (51)	2 (20)	38 (55)	0.040
Risk factors				
Hypertension	53 (67)	8 (80)	45 (65)	0.293
Hypercholesterolemia	36 (46)	6 (60)	30 (43)	0.260
Diabetes mellitus	16 (20)	2 (20)	14 (20)	0.674
Ischemic heart disease	12 (15)	1 (10)	11 (16)	0.528
Chronic kidney injury	16 (20)	5 (50)	11 (16)	0.025
Stroke	22 (28)	2 (20)	20 (29)	0.432
Atrial fibrillation	59 (75)	6 (60)	53 (77)	0.220
Prestroke CHADS2	2 (1–3)	3 (1–3)	2 (1–3)	0.622
Anticoagulants before admission				
Warfarin	23 (29)	4 (40)	19 (28)	0.320
DOACs	5 (6)	0 (0)	5 (7)	0.499
Antiplatelet	7 (9)	0 (0)	7 (10)	0.372
Systolic BP on admission, mmHg	151 (134–177)	165 (144–188)	150 (132–174)	0.159
NIHSS on admission	4 (1–16)	5 (2–13)	4 (1–17)	0.877
NIHSS on discharge	1 (0–3)	3 (2–7)	1 (0–2)	0.505
Intravenous t-PA	17 (22)	2 (20)	15 (22)	0.633
Endovascular therapy	11 (14)	2 (20)	9 (13)	0.422
Initiation of anticoagulation, day	2 (1–4)	2 (1–2)	2 (1–4)	0.510
Hemorrhagic event	7 (9)	2 (20)	5 (7)	0.214
Symptomatic ICH	1 (1)	0 (0)	1 (1)	0.873
Extracranial bleeding	4 (5)	0 (0)	4 (6)	0.575

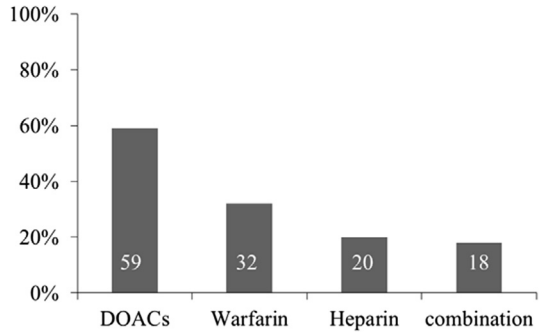

Fig. 1. Proportion of patients treated with various types of anticoagulants after admission. Combination, anticoagulation with heparin plus warfarin or DOACs. Abbreviations: DOACs, direct oral anticoagulants.

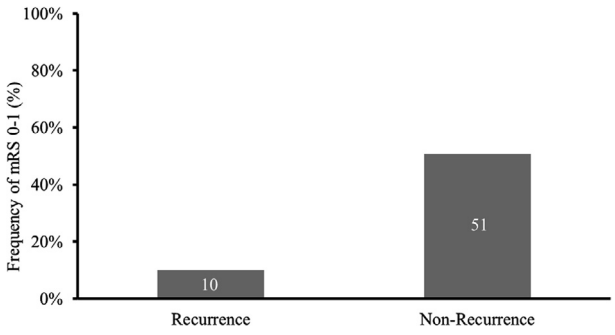

Fig. 2. Association between modified Rankin Scale scores of 0–1 at 3 months after index stroke and recurrent cerebral infarct (RCI). Significantly higher frequency of good outcomes in patients without, than with RIS (51% vs. 10%; $P = 0.015$).

mechanisms. Even moderate kidney dysfunction is associated with persistent inflammation and oxidant stress that play important roles in the initiation and persistence of AF [10,12–15]. CKD invokes activation of the angiotensin system [12,16,17]. Plasma renin activity is inappropriately high in patients with CKD and high levels of angiotensin-converting enzyme might contribute to the development of AF through atrial remodeling [16,17]. AF might lead to a hypercoagulable state via various metabolic pathways [9,10,12]. Subsequent systemic embolism or a decline in cardiac function due to AF would lead to the promotion of CKD [12]. Finally, a relationship between CKD and RCI with AF might arise through AF and CKD independently increasing levels of various coagulation factors and activity that elicits a tendency towards thrombus formation resulting in recurrent stroke [9,10]. Thus, we consider that CKD plays an important role in the development of RCI with AF.

We identified recurrence in nine (11%) of 79 patients during the first 14 days after the index stroke. These findings contradict the notion that the risk of early recurrence varies between 3% and 5% within the same period [3,4]. This could be explained by the timing of anticoagulation at our institution. A recent study has associated anticoagulation with a lower risk of recurrence or hemorrhagic events when started on days 4 and day 14 after AIS compared with any other period [18]. The guidelines of the American Stroke Association recommend starting anticoagulation within and after 14 days for patients with low and high risk of hemorrhage, respectively [7]. Therefore, we might have started anticoagulation too early. DOACs with a potentially low risk of hemorrhagic events were developed to prevent stroke due to AF [19]. However, recommendations regarding the timing of starting anticoagulation for Asian patients with acute stroke have not been established, and thus a prospective randomized control trial is needed, especially for DOACs.

Acute recurrence started from day 5 after the index stroke, and subacute recurrence developed in one patient on day 38 in the present study. Our findings partially agree with previous reports showing that acute RCI developed within 10 days after the index stroke in an American cohort, and that subacute RCI developed 34 days thereafter in European and Asian cohorts [1,18]. RCI might tend to be bimodal; that is, developing around one week and 1 month after an index stroke. Therefore, patients with AIS accompanied by AF should be carefully monitored during these periods.

Table 2
Details of patients with recurrent cerebral infarct. Abbreviations: AC, anticoagulation therapy; AF, atrial fibrillation; PT-INR, international normalized ratio of prothrombin time; Wf, warfarin.

Sex	Age	Prestroke CHADS2	Prestroke AC (control)	NIHSS on admission	Af point out	Recurrence (day)	AC after admission
M	74	3	Wf (PT-INR 1.0)	38	Before admission	Symptomatic (9)	Wf
F	95	2	Wf (PT-INR 1.4)	1	Before admission	Symptomatic (2)	Wf
M	67	1	None	26	Day 1	Symptomatic (2)	None
F	83	3	None	1	Day 1	Symptomatic (4)	Dabigatran
F	83	4	None	1	Before admission	Symptomatic (7)	Dabigatran
F	80	2	None	5	Before admission	Symptomatic (38)	Dabigatran
F	90	3	None	14	Day 7	Symptomatic (12)	None
F	74	0	None	9	Before admission	Asymptomatic (7)	Wf/heparin
F	89	3	Wf (PT-INR 1.6)	4	Before admission	Asymptomatic (7)	Apixaban
M	72	1	None	3	Day 3	Asymptomatic (10)	Apixaban

Table 3
Multivariate logistic regression analysis of good outcomes. Good outcomes are defined as modified Rankin Scale scores of 0–1. Abbreviations: BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

	Univariate		Multivariate	
	OR	95%CI	OR	95%CI
Female sex	1.79	1.79–33.40	3.10	0.37–26.07
Age	1.08	1.00–1.16	1.02	0.92–1.12
Alcohol	0.20	0.04–1.03	0.36	0.03–4.31
Smoking	0.18	0.04–0.92	0.48	0.05–5.15
Systolic BP on admission	1.01	0.99–1.04	1.02	1.00–1.05
CKD	5.27	1.30–21.32	8.20	1.30–51.56

Univariate analysis selected female sex as a risk factor for recurrence. Whether or not sex is a risk factor in patients with AF remains controversial. Female sex has been considered as a risk factor for stroke in patients with AF and it is one element of CHA_2DS_2-VASc, but several recent studies have contradicted this notion [20–23]. The formula for calculating eGFR includes sex as a coefficient. Thus, female sex, which is a confounding factor for CKD, weakly influenced recurrence in the multivariate analysis.

The present study has several limitations. The relatively small cohort was from a single center and the severity of stroke was mostly mild or moderate. In addition, attending physicians selected the type of anticoagulation that was administered to their patients.

5. Conclusions

CKD is an important factor for stroke recurrence in patients with AF. Ischemic stroke can recur in patients with AIS accompanied by AF during the early phase after admission and thus such patients require careful monitoring during this period.

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