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Impact of Elevated D-Dimer on Diagnosis of Acute Aortic Dissection With Isolated Neurological Symptoms in Ischemic Stroke

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Background: Plasma D-dimer is known to be a useful clinical marker of thrombogenic status, and D-dimer is used as a diagnostic marker for acute aortic dissection (AAD). Little is known, however, regarding the clinical value of D-dimer for diagnosis of asymptomatic AAD in patients with ischemic stroke. We investigated whether D-dimer could be used for early diagnosis of AAD with isolated neurological symptoms in ischemic stroke patients.

Methods and Results: We evaluated a total of 1,236 consecutive patients with symptomatic ischemic stroke without chest or back pain who underwent either head computed tomography or magnetic resonance imaging. D-Dimer was measured within 24 h after onset. There were 9 patients with Stanford type A AAD and they had significantly higher D-dimer than the patients without AAD (mean, 46.47±54.48 μg/ml; range, 6.9–167.1 μg/ml vs. 2.33±3.58 μg/ml, 0.3–57.9 μg/ml, P<0.001). When a cut-off of 6.9 μg/ml was adopted for D-dimer on the basis of receiver operating characteristics analysis, the sensitivity and specificity for AAD were 100% and 94.8%, respectively, while the positive and negative predictive values were 14.7% and 100%, respectively.

Conclusions: D-Dimer might be a useful marker for the early diagnosis of AAD with isolated neurological symptoms in ischemic stroke patients. Whole-body contrast-enhanced computed tomography should be performed in ischemic stroke patients who have high D-dimer. (*Circ J* 2015; **79:** 1841–1845)

Key Words: Acute aortic dissection; D-Dimer; Stroke

Acute aortic dissection (AAD) is a life-threatening condition with a high mortality rate.[1–3] Therefore, rapid and accurate diagnosis of AAD in the emergency room is required. The majority of patients with AAD have typical symptoms such as sudden onset of chest pain or back pain. In addition, neurological symptoms have been reported in AAD patients at an incidence ranging from 6.1 to 42%.[1,4,5] Patients with neurological symptoms have a markedly worse prognosis, perhaps because of missing optimal therapy due to delay in the diagnosis of AAD.[4,6–8]

Editorial p1697

D-Dimer is a degradation product of cross-linked fibrin and is one of the useful clinical biomarkers of thrombogenic status. D-Dimer level is increased in almost all patients with AAD and this marker has been used to rule out AAD in patients presenting with chest pain.[9–11] In addition, D-dimer has been reported to be elevated in patients with acute ischemic stroke compared with healthy volunteers[12] or patients with chronic stroke.[13] Little is known, however, about the usefulness of D-dimer for diagnosing AAD associated with stroke in patients with only neurological symptoms. The purpose of the present study was therefore to investigate whether D-dimer could be a useful marker for early diagnosis of AAD associated with stroke.

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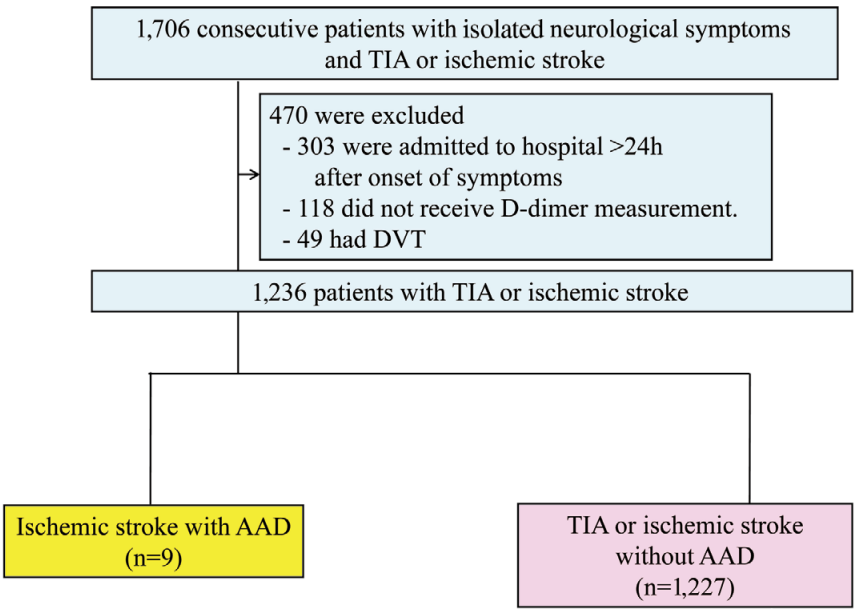

Figure 1. Study enrollment flowchart. AAD, acute aortic dissection; DVT, deep vein thrombosis; TIA, transient ischemic attack.

Table 1. Subject Demographic and Clinical Characteristics

Variables	All patients (n=1,236)	Ischemic stroke		P-value
		With AAD (n=9)	Without AAD (n=1,227)	
Age (years)	73.3±11.5	72.1±13.1	73.3±11.5	0.791
Male	769 (62.2)	3 (33.3)	766 (62.4)	0.073
Hypertension	956 (77.3)	8 (88.8)	948 (77.3)	0.415
Diabetes mellitus	324 (26.2)	2 (22.2)	324 (26.4)	0.775
Hyperlipidemia	570 (46.2)	2 (22.2)	568 (46.3)	0.147
Smoking	615 (49.8)	3 (33.3)	612 (49.9)	0.312
SBP (mmHg)	159.5±27.7	104.6±26.5	159.9±27.3	<0.001
DBP (mmHg)	86.6±17.2	69.5±25.6	86.7±17.1	0.042
Heart rate (beats/min)	78.5±17.1	72.3±20.8	78.5±17.1	0.474
Atrial fibrillation	422 (34.1)	0 (0)	422 (34.4)	NA

Data given as mean±SD or n (%). AAD, acute aortic dissection; DBP, diastolic blood pressure; NA, not available; SBP, systolic blood pressure.

Methods

Patients

Between January 2007 and May 2010, a total of 1,706 consecutive patients presenting with isolated neurological symptoms without chest pain or back pain were admitted to National Cerebral and Cardiovascular Center for the management of ischemic stroke and transient ischemic attacks (TIA).

Definitions of Ischemic Stroke and TIA

All patients underwent computed tomography (CT) or magnetic resonance imaging of the head. Ischemic stroke was diagnosed by cerebrovascular specialists. Stroke was defined as the persistence of neurological symptoms >24 h compatible with neuroimaging findings. The subtypes of stroke were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[14] TIA was defined as transient focal neurological symptoms considered to be of ischemic vascular etiology and with clinical symptoms lasting <24 h.

Definition of AAD

Diagnosis of Stanford type A AAD was confirmed by identifying dissection involving the ascending aorta on whole-body contrast-enhanced CT.[15] Clinical files of patients fulfilling the criteria for Stanford type A dissection were reviewed by a radiologist.

Definitions of Risk Factors

The definition of each risk factor is as follows: hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥9 mmHg; diabetes mellitus, HbA1 ≥6.5% or use of anti-diabetic medication; hyperlipidemia, serum total cholesterol ≥220 mg/dl and/or low-density lipoprotein cholesterol ≥140 mg/dl or use of lipid-lowering therapy; and smoking, smoking for the previous 1 year. The study protocol was approved by the ethics committee of the National Cerebral and Cardiovascular Center.

Measurement of D-Dimer

D-Dimer was measured in the emergency department using latex

Table 2. Clinical Features of AAD Patients

ID no.	Age (years)	Sex	D-Dimer (μg/ml)	Whole-body CT	
				Arch vessel involvement	Extent of dissection
1	51	M	29.7	BCA and R/LCCA	CIA
2	74	M	37.4	BCA, R/LCCA, and LSCA	Distal abdominal Ao
3	67	F	11.8	BCA and R/LCCA	CIA
4	73	F	7.3	BCA	Aortic Arch
5	71	F	167.1	BCA, R/L CCA, and LSCA	CIA
6	53	M	12.9	BCA, R/L CCA, and LSCA	CIA
7	85	F	6.9	BCA, R/LCCA, and LSCA	Distal abdominal Ao
8	93	F	104.5	BCA, R/LCCA, and LSCA	Distal abdominal Ao
9	82	F	40.6	BCA and RCCA	CIA

AAD, acute aortic dissection; Ao, Aorta; BCA, brachiocephalic artery; CIA, common iliac artery; CT, computed tomography; LCCA, left common carotid artery; LSCA, left subclavian artery; RCCA, right common carotid artery.

agglutination immunoturbidimetric assay (Sekisui Medical, Tokyo, Japan), for which the upper limit of normal was 1.0 μg/ml and the detection limit was 0.5 μg/ml. The measurement range of this assay was from 0.5 to 60 μg/ml. Samples with concentration >60 μg/ml were measured after appropriate dilution.

Statistical Analysis

Continuous variables are expressed as mean±SD. Because of the limited sample size, non-parametric Mann-Whitney U-test and chi-squared test were used to identify statistically significant differences of continuous variables. All categorical variables are reported as numbers and percentages. To assess change in D-dimer over time, we used non-parametric Mann-Whitney U-test. To determine the value of D-dimer for predicting AAD in patients with ischemic stroke, receiver operating characteristics (ROC) analysis was performed. All analysis was conducted using PASW Statistics 18 (SPSS Japan, IBM, Japan), and P<0.05 was considered to indicate statistical significance.

Results

Among the 1,706 patients, we excluded 470 patients because they were admitted >24 h after the onset of symptoms (n=303), did not undergo measurement of D-dimer (n=118), or had deep vein thrombosis (n=49). Thus, a total of 1,236 patients (mean age, 73.3±11.5 years; 62.2% men) were enrolled (Figure 1; Table 1).

The classification of stroke in these patients was as follows. A total of 422 patients had cardioembolic stroke, 200 had stroke due to large vessel atherosclerosis, 158 had lacunar infarcts, 221 had stroke of other determined etiology, 68 had stroke of undetermined etiology, and 167 had TIA.

Nine patients had stroke with AAD and 1,227 patients did not have AAD (Figure 1; Table 1). All 9 patients were not suspected to have AAD in the emergency room because they had only neurological symptoms. There were no differences in age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking status, or heart rate between these 2 groups. Systolic and diastolic blood pressure, however, were significantly lower at admission in the patients with AAD than in those without AAD (104.6±26.5 vs. 159.9±27.3 mmHg, P<0.001; 69.5±25.6 vs. 86.7±17.1 mmHg, P=0.042, respectively; Table 1). The clinical features of the AAD patients are summarized in Table 2. On whole-body CT with contrast enhancement, AAD involved arch vessels such as brachiocephalic artery, left carotid artery, or left subclavian artery in all patients, and extended to affect the common iliac artery in patients 1, 3, 5, 6, and 9.

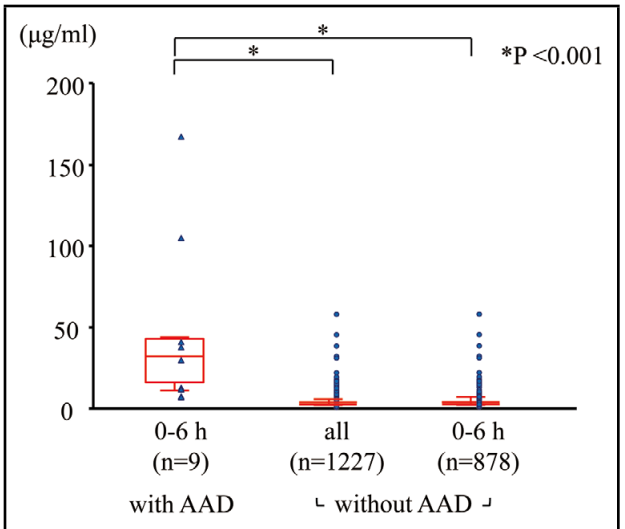

Figure 2. D-Dimer in patients with ischemic stroke with and without acute aortic dissection (AAD). D-Dimer was significantly higher in patients with AAD than in those without AAD. D-Dimer was also significantly higher in patients with AAD than in those without AAD within 6 h after the onset of neurological symptoms.

D-Dimer was significantly higher in patients with AAD than in those without AAD (mean, 46.47±54.48 μg/ml; range, 6.9–167.1 μg/ml vs. 2.33±3.58 μg/ml, 0.3–57.9 μg/ml, P<0.001). In addition, D-dimer within 6 h of admission was significantly higher in the patients with AAD than in those without AAD (mean, 46.47±54.48 μg/ml; range, 6.9–167.1 μg/ml vs. 2.46±3.97 μg/ml, 0.3–57.9 μg/ml, P<0.001; Figure 2). When the cut-off of 6.9 μg/ml was adopted on the basis of ROC analysis, the sensitivity and specificity for AAD were 100%

and 94.8%, respectively, while the positive and negative predictive values (PPV and NPV) were 14.7% and 100%, respectively. In addition, the cut-off was 6.9 μg/ml, even when the 9 patients with AAD were compared with 422 patients with stroke caused by cardioembolism, which is associated with a higher D-dimer level than other stroke types. Under these conditions, the sensitivity and the specificity were 100% and 92.7%, respectively, and PPV and NPV, 22.5% and 100%, respectively.

Discussion

In the present study, patients with ischemic stroke complicated by Stanford type A AAD were found to have significantly higher D-dimer than those without Stanford type A AAD. D-Dimer=6.9 μg/ml was found to be the best cut-off for the diagnosis of AAD in patients with ischemic stroke, having a sensitivity of 100%, specificity of 94.8%, PPV of 14.7%, and NPV of 100%. In the present study, ischemic stroke complicated by Stanford type A AAD was able to be discriminated from acute stroke without AAD by measuring D-dimer level. The present results suggest that elevated D-dimer in patients with neurological symptoms should raise the suspicion of AAD and that contrast-enhanced whole-body CT should be performed.

When thrombolytic therapy is being considered for acute ischemic stroke, making an exact diagnosis is essential. The National Institute of Neurological Disorders and Stroke rt-PA stroke study group showed that initiating thrombolytic therapy with i.v. recombinant tissue plasminogen activator (rt-PA) within 3 h of onset of ischemic stroke improved clinical outcome.[16] Recently, initiation of i.v. rt-PA within 6 h after the onset of ischemic stroke has also been reported to improve outcome.[17] In contrast, when patients who have ischemic stroke complicated with AAD are given rt-PA, most reports suggest that the outcome will be poor.[18,19] In the present study, we found that D-dimer was significantly higher in patients with AAD than in patients without AAD. Importantly, D-dimer in patients with AAD was also higher than in patients without AAD within 6 h after the onset of symptoms. This suggests that we can rapidly identify patients with ischemic stroke complicated by AAD using the D-dimer assay, and that thrombolytic therapy with rt-PA can be administered safely after performing this test.

Eggebrecht et al reported on the usefulness of D-dimer for differential diagnosis of chest pain in patients with AAD, pulmonary embolism, and acute myocardial infarction,[9] but there has been little information regarding the use of D-dimer to discriminate ischemic stroke complicated by Stanford type A AAD from stroke without AAD. Some observational studies have shown that D-dimer is significantly increased in stroke patients compared with healthy controls.[20,21] In the present study, D-dimer in patients without AAD (2.33±3.58 μg/ml) was higher than in previous studies (0.1–1.74 μg/ml).[20–22] In stroke patients, D-dimer has been reported to increase along with age, progression of stroke, and acute ischemic stroke subtype.[23,24] In the present study, there were 422 patients with cardioembolic stroke. The high D-dimer level in the present patients without AAD could be explained by the greater number of patients with cardioembolic stroke than in the previous studies.[20–22]

We also found that D-dimer was higher in patients with stroke plus AAD than in patients with AAD alone, as reported in previous studies.[9,11] Weber et al found that D-dimer level depends on the severity of AAD.[10] Therefore, the difference in D-dimer level between the present and previous studies could have arisen because 8 out of 9 patients had dissection extending to the distal abdominal aorta or iliac artery (Table 2).

Clinical Implications and Limitations

The present findings provide an insight into the usefulness of D-dimer for the differential diagnosis of ischemic stroke combined with Stanford type A AAD and that without AAD. Importantly, routine measurement of D-dimer could lead to accurate diagnosis in patients who present to the emergency department with neurological symptoms suggestive of ischemic stroke. Although we enrolled only patients admitted to National Cerebral and Cardiovascular Center, a specialized institute, we included 167 patients with TIA, which is commonly seen in community hospitals. Therefore, the D-dimer results could be applied in these hospitals. In addition, it is possible that the severity of AAD could affect D-dimer level, but the severity of AAD is equivalent to that in patients admitted to departments of cardiology, cardiovascular surgery and cerebrovascular medicine in terms of Stanford type A AAD.

There are several limitations of the present study. First, it was a retrospective non-randomized, and single-center study, and therefore it could have been affected by selection bias. The risk of bias, however, was kept to a minimum by relying on strict exclusion criteria and by enrolling consecutive patients with ischemic stroke.

Second, the study had a small AAD group due to the low incidence of symptomatic ischemic stroke without chest or back pain complicated by Stanford type A AAD. Therefore, PPV was relatively low. D-Dimer, however, was found to be elevated in AAD despite these limitations. Under these conditions, prior use of ultrasound could avoid unnecessary CT. If a larger number of patients can be enrolled in the future, PPV would increase. Importantly, prospective multicenter studies on a large scale are needed to confirm the present results.

Third, an increase in D-dimer indicates activation of coagulation and subsequent fibrinolysis. Elevation of D-dimer is known to occur in various diseases,[25–33] but we found no evidence that the present patients had other diseases affecting D-dimer level. Therefore, elevation of D-dimer in patients with ischemic stroke reflects the presence of AAD.

Finally, some patients without AAD did not undergo whole-body contrast-enhanced CT,[34] but we confirmed the absence of AAD in the ascending or descending aorta on transesophageal and transthoracic echocardiography.[35,36]

Conclusions

In patients presenting with neurological symptoms, D-dimer might be a useful marker to discriminate ischemic stroke complicated by Stanford type A AAD from stroke without AAD in the emergency setting. Whole-body CT should be performed in stroke patients with high D-dimer, although further large-scale studies are necessary to confirm the present results.

Disclosures

The authors declare no conflicts of interest.

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