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Usefulness of Fibrinogen/Fibrin Degradation Products Value in Differential Diagnosis Between Acute Ischemic Stroke and Acute Aortic Dissection

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Abstract : A post-marketing surveillance study reported fatalities following tissue plasminogen activator administration in acute aortic dissection (AAD) with the symptoms of acute ischemic stroke (AIS) patients. Therefore, it is important to discriminate AAD from AIS. The present study aimed to investigate whether fibrinogen/fibrin degradation products (FDP) value can be useful in differential diagnosis between AAD and AIS. The study group comprised 20 AAD patients (10 men and 10 women; age 63.9 ± 13.6 years) and 159 AIS patients (91 men and 68 women; age 74.2 ± 10.6 years) who were transported to our hospital from 2007 to 2012. The AAD cases were further divided into patent-type AAD and thrombosed-type AAD. FDP values were significantly higher in the AAD group than in the AIS group ($18.15 [5.2-249.9] \mu\text{g/ml}$ vs. $2.3 [1.5-4.45] \mu\text{g/ml}$; $P < 0.001$). In AAD groups, FDP values were significantly higher in the patent-type AAD group ($n = 9$) than in the thrombosed type AAD group ($n = 11$) ($293.2 \mu\text{g/ml} [63.1-419.6 \mu\text{g/ml}]$ vs. $5.6 \mu\text{g/ml} [3.8-7.9 \mu\text{g/ml}]$). FDP values were significantly higher in patients with AAD than in those with AIS, especially those with patent-type AAD compared with AIS patients. High FDP values may be a useful marker for differential diagnosis between patent-type AAD and AIS.

Keywords : acute aortic dissection, acute ischemic stroke, fibrinogen/fibrin degradation products.

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Introduction

Intravenous thrombolysis is the only approved treatment for acute ischemic stroke (AIS) within 4.5 hours from symptom onset. However, because of the narrow time window, the underlying pathogenesis of stroke may not be examined. Therefore, careful selection of appropriate candidates may not be performed. According to the results of a 2007 survey on the use of tissue plasminogen activator (t-PA; a thrombolytic agent) in Japan, 10 patients died after t-PA was used in AIS patients who had acute aortic dissection (AAD) [1]. This

suggests that AAD should be discriminated from AIS.

AAD classically presents as sudden, severe chest, back, or abdominal pain. However, there have been several documented cases presenting with atypical features. Imamura *et al.* showed that painless AAD is not rare, and many patients present with focal neurologic deficits [2]. The diagnosis of AAD has been missed on initial evaluation in up to 38% of patients, and its diagnosis has first been established at postmortem examinations in up to 28% of patients [3–5]. These findings suggest that specific markers are required for suspected AAD.

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D-dimer is known as a marker of AAD [6, 7]. However, a rapid assay to quantify D-dimer is not currently being used in all emergency hospitals. Indeed, we could not also measure D-dimer in the night time in our hospital, so alternative modality is required. On the other hand, fibrinogen/fibrin degradation products (FDP) are used widely for diagnosis of disseminated intravascular coagulation (DIC) [8]. Nagaoka *et al.* reported that measurement of FDP may be useful for initial assessment of patients with suspected AAD [9]. We previously reported four AAD patients with high FDP levels accompanied by symptoms of AIS [10]. Therefore, FDP value may be useful for distinction between AIS and AAD. The present study aimed to investigate whether FDP value is useful for differential diagnosis between AAD and AIS.

Methods

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by our University Ethics committee (No. H26-213). The ethics committee does not require informed consent for retrospective studies, such as this study.

Subjects

This study was a retrospective study. The study group included 20 patients with AAD (AAD group) who were admitted to the University Hospital, University of Occupational and Environmental Health, Japan, between January 2007 and March 2012 (patients with cardiopulmonary arrest on arrival were excluded). A total of 159 patients with AIS (AIS group) served as the control group.

FDP value is routinely measured in our emergency department at the time of admission. Therefore, FDP measurements were available for patients presenting with suspected AAD or AIS.

Diagnosis of Acute Aortic Dissection or Acute Ischemic Stroke

The diagnosis of AAD was defined by contrast enhanced computed tomography. Standard guidelines [11] were used to diagnose AAD. AAD cases were divided into two categories. One category included those with a patent false lumen (patent-type AAD),

which was defined as the presence of an intimal flap separating the true and false lumen. The false lumen was identified by opacification of contrast media including partial thrombosis [12]. The other category included those with complete thrombosis of a false lumen (thrombosed-type AAD), which was defined as the presence of complete thrombosis of the false lumen [13]. Definitive diagnosis of AIS was performed according to magnetic resonance imaging or computed tomography [14].

Data collection

We investigated blood pressure and past medical history, which were recorded on admission, in each group based on hospital clinical records. We measured the diameter of the superior mediastinum on chest X-ray in each patient. The diameter of the superior mediastinum was assumed to be the total of the diameter from the midline to the superior vena cava line and the diameter from the midline to the aortic arch. We compared laboratory data, including white blood cell (WBC) ($/\mu\text{l}$), platelets ($10^3/\mu\text{l}$), C-reactive protein (CRP) (mg/dl), the international normalized ratio (INR), fibrinogen (mg/dl), activated partial thromboplastin times (APTT), and FDP ($\mu\text{g}/\text{mL}$), between the AAD group and the AIS group.

Statistical analysis

Data are presented as the mean value \pm standard deviation, median, and percentile range. Statistical analysis was performed with statistical software (StatMate IV, ATMS Co., Ltd. Tokyo). The chi-squared test was used for comparison of discrete variables. The Student's *t*-test and Mann-Whitney test were used for comparison between the AAD and AIS groups. The Kruskal-Wallis test was used to compare FDP levels in three groups (patent-type AAD group, thrombosed-type AAD group, and AIS group). $P < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal FDP cutoff value defined as the value with highest sensitivity (1-specificity). We determined FDP cutoff value to differentiate all AAD patients or patent-type AAD patients from those with AIS. The area under the ROC for all AAD patients or patent-type AAD patients versus AIS patients was also calculated at each cutoff value.

Results

Age, gender, and past history

There were 159 patients (91 men and 68 women) in the AIS group. There were 20 patients (10 men, 10 women) in the AAD group. The mean age was significantly higher in the AIS group than in the AAD group (74.2 ± 10.6 vs 63.9 ± 13.6 years, respectively; $P < 0.01$). There were no significant differences in other baseline characteristics between the two groups (Table 1).

Blood pressure and diameter of the superior mediastinum

There was no significant difference in blood pressure between the two groups. The diameter of the su-

perior mediastinum on chest X-ray was significantly enlarged in the AAD group compared with the AIS group (9.66 cm [8.69–10.34 cm] vs 7.91 cm [7.21–8.67 cm], respectively; $P < 0.001$).

Laboratory data

There were no significant differences in CRP levels and platelet count between the two groups. The WBC count was significantly higher in the AAD group than in the AIS group (11,200/ μ l [8,800–124,500/ μ l] vs. 7,100/ μ l [5,900–9,000/ μ l]; respectively; Table 2). There were no significant differences in the INR, fibrinogen, and APTT between the two groups.

Comparison of fibrinogen/fibrin degradation products value

Fibrinogen/fibrin degradation products (FDP) value was significantly higher in the AAD group than in the AIS group (18.15 μ g/ml [5.2–249.9 μ g/ml] vs. 2.3 μ g/ml [1.5–4.45 μ g/ml], $P < 0.001$; Table 2). We classified AAD into patent-type AAD and thrombosed-type AAD groups. FDP value was significantly higher in the patent-type AAD group ($n = 9$) than in the thrombosed type AAD group ($n = 11$) (293.2 μ g/ml [63.1–419.6 μ g/ml] vs. 5.6 μ g/ml [3.8–7.9 μ g/ml], $P < 0.001$). There was no significant difference in FDP value between the thrombosed-type AAD group and the AIS group (Fig. 1).

Table 1. Characteristics of the acute aortic dissection and acute ischemic stroke groups

| Baseline characteristics | AAD n=20 | AIS n=159 | <i>P</i> |
|-----------------------------|-------------|--------------|------------|
| Age | 63.9±13.6 | 74.2±10.6 | $P < 0.01$ |
| Male | 10 (50.0) | 91 (57.2) | N.S. |
| Past history | | | |
| Number of hypertension | 11 (55.0) | 82 (51.5) | N.S. |
| Number of diabetes mellitus | 1 (5.0) | 36 (22.6) | N.S. |
| Number of hyperlipidemia | 3 (15.0) | 7 (4.4) | N.S. |
| Number of heart disease | 4 (20.0) | 54 (34.0) | N.S. |
| others | 6 (30.0) | 37 (23.2) | N.S. |

Values are mean \pm standard deviation or the number of patients, N.S.: not significant, AAD: acute aortic dissection, AIS: acute ischemic stroke, (): %

Table 2. Laboratory data on admission in the acute aortic dissection (AAD) and acute ischemic stroke (AIS) groups

| Statistics quartile | AAD n=20 | | | AIS n=159 | | | <i>P</i> |
|---|----------|-------|-------|-----------|-------|-------|-------------|
| | 25% | 50% | 75% | 25% | 50% | 75% | |
| Systolic bloodpressure (mmHg) | 110.3 | 156.5 | 192.5 | 145.0 | 164.0 | 182.0 | N.S. |
| Diastolic blood pressure (mmHg) | 56.0 | 84.5 | 110.3 | 75.0 | 89.0 | 100.0 | N.S. |
| Blood collection data | | | | | | | |
| White blood cell counts ($\times 10^3/\mu$ l) | 8.8 | 11.2 | 12.5 | 5.9 | 7.1 | 9.0 | $P < 0.001$ |
| Platelet ($\times 10^3/\mu$ l) | 16.4 | 18.9 | 22.4 | 16.4 | 16.4 | 22.9 | N.S. |
| C-reactive protein (mg/dl) | 0.1 | 0.2 | 0.5 | 0.1 | 0.1 | 0.3 | N.S. |
| Prothrombin time-international normalized ratio | 1.0 | 1.1 | 1.1 | 1.0 | 1.0 | 1.1 | N.S. |
| Activated partial thromboplastin time (s) | 25.8 | 27.0 | 29.7 | 24.2 | 26.3 | 28.7 | N.S. |
| Fibrinogen (mg/dl) | 198.0 | 258.0 | 359.5 | 244.5 | 291.0 | 333.0 | N.S. |
| Fibrinogen/fibrin degradation products | 5.2 | 18.2 | 249.9 | 1.5 | 2.3 | 4.5 | $P < 0.001$ |
| Chest X-ray | | | | | | | |
| Superior mediastinum diameter (cm) | 8.7 | 9.7 | 10.3 | 7.2 | 7.9 | 8.7 | $P < 0.001$ |

N.S.: not significant

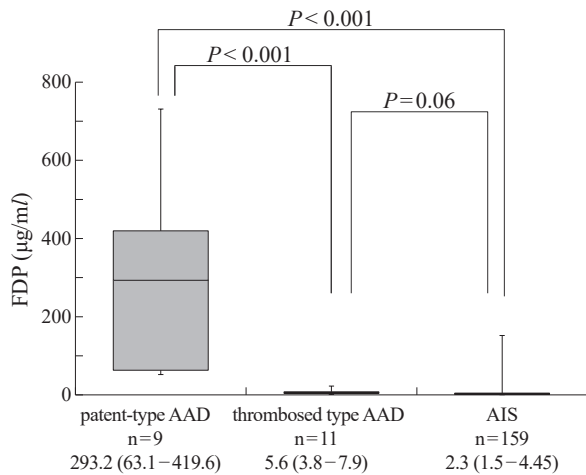


Fig. 1. Comparison of fibrinogen/fibrin degradation products (FDP) value between the acute aortic dissection (AAD) and acute ischemic stroke (AIS) groups.

Receiver operating characteristic curve analysis

Receiver operating characteristic (ROC) curve analysis showed that FDP was predictive of diagnosis of AAD (area under the ROC curve: 0.87 ± 0.03 , $P < 0.05$). The sensitivity and specificity were 75% and 81%, respectively, at a cutoff value of 5.6 µg/ml. The area under the curve for patent-type AAD was 0.95 ± 0.04 . The sensitivity and specificity were 100% and 97.4%, respectively, at a cutoff value of 52.4 µg/ml (Fig. 2).

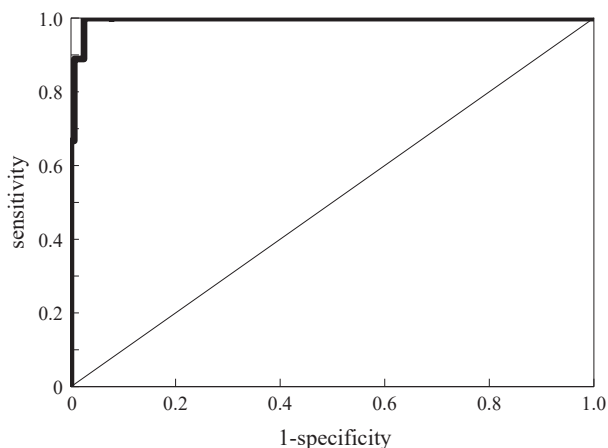


Fig. 2. Comparison of fibrinogen/fibrin degradation products value between the thrombosed-type acute aortic dissection, patent-type acute aortic dissection, and acute ischemic stroke groups.

Discussion

AIS treatment was dramatically changed by approval of tissue plasminogen activator treatment. Intravenous thrombolysis is the only approved treatment for AIS within 4.5 h from symptom onset. However, approximately 30% of patients with Stanford type A dissection show initial neurologic symptoms [15]. For AIS patients who are eligible for thrombolysis, AAD is particularly challenging because of the difficulty of diagnosis within a narrow time window and the high risk of life-threatening complications for thrombolysis. Therefore, markers are required for suspected AAD. The incidence of decreased blood pressure is unclear, but caution is needed in patients who do not have especially high blood pressure in the acute stage, despite a history of hypertension [16]. In our study, there was no significant difference in blood pressure between the AAD and AIS groups. Therefore, blood pressure may not be discriminate between AAD and AIS. The diameter of the superior mediastinum was significantly enlarged in the AAD group compared with the AIS group. Thus, the superior mediastinum diameter on chest X-ray maybe a useful measure. However, previous studies have reported that the rate of enlargement of the diameter of the superior mediastinum on chest X-ray in AAD is 10%–29% [17, 18]. Therefore, chest X-ray alone cannot be used for discrimination. Carotid ultrasonography may also be useful for discrimination, as it can be used to visualize AAD [19]. However, this is difficult to implement in actual clinical practice.

In this study, the WBC count was significantly higher in the AAD group than in the AIS group. The systemic inflammatory reaction in AAD is provoked by acute aortic injury and is reflected in WBC count [20]. WBC count may be useful for different diagnosis between AAD and AIS. However, because we cannot classify infection disease by WBC count independently, we may not be able to use WBC count as a marker of AAD independently.

D-dimer is known marker of AAD [6, 7]. However, a rapid assay to quantify D-dimer is not currently being used in all emergency hospitals. Therefore, an alternative modality is required to determine AAD. In the present study, FDP value was significantly higher in the

AAD group compared with AIS group. Nagaoka *et al.* reported that FDP may be useful for distinguishing acute myocardial infarction with AAD [9]. Moreover, we classified the AAD group into a patent-type AAD group and a thrombosed-type AAD group, and compared FDP value between the three groups. FDP value in the patent-type AAD group was significantly higher than those in the AIS group and thrombosed-type AAD group. However, there was no difference in FDP value between the thrombosed-type AAD group and the AIS group. The difference in FDP between patent-type AAD and thrombosed-type AAD relates to the absence of continuous flow communication through an intimal tear in thrombosed-type AAD. A false lumen that becomes enlarged rarely crushes the true lumen in thrombosed-type AAD. This enlargement does not usually lead to branch obstruction in thrombosed-type AAD. Thus, the incidence of AIS may be low in thrombosed-type AAD compared with patent-type AAD. Indeed, Kaji *et al.* reported that the incidence of AIS was significantly higher in patent-type AAD [21]. These findings suggested that FDP value may be useful for initially assessing patients for discrimination between AAD, especially patent-type AAD, and AIS. About extension of aortic dissection in this study, Stanford A type cases were 12 examples and Stanford B type cases were 8 examples in AAD group. It is not clear that FDP value is different by difference of aortic dissection type. We could not also examine change of FDP value by the time course due to retrospective study. There is a need for further study.

Study limitations

This was a retrospective analysis of a single center, which may have introduced some bias in the patients. A larger number of cases is required in a future study. The mechanism underlying the increased FDP value in patent-type AAD compared with thrombosed-type AAD is also unclear. Further studies are required to clarify this mechanism and assess strategies for differential diagnosis between AAD and AIS.

Painless AAD patients often present with a disturbance of consciousness or a neurologic deficit, so it is preferable to incorporate the description about lack of symptomatic information. However, it is impracticable to evaluate symptoms due to retrospective study.

Conclusion

We found that FDP value was significantly higher in patients with AAD, especially those with patent-type AAD compared with AIS patients. High FDP value may be a useful marker for differential diagnosis between patent-type AAD and AIS.

Conflict of Interest

The authors declare no conflicts of interest.

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急性虚血性脳卒中と急性大動脈解離の鑑別診断におけるフィブリノゲン/フィブリン分解産物の有用性

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要 旨：急性虚血性脳卒中の症状を有する急性大動脈解離症例に組織プラスミノゲンアクチベータ (tissue plasminogen activator) を使用し, 死亡に至った事例が報告されている。それゆえ急性大動脈解離と急性虚血性脳卒中の鑑別が重要である。本研究ではフィブリノゲン/フィブリン分解産物 (FDP) 値が急性大動脈解離と急性虚血性脳卒中の鑑別に有用であるかを調査した。研究対象者は, 2007年から2012年に当院へ搬送された, 20名の急性大動脈解離症例 (男性10名, 女性10名, 平均年齢 63.9 ± 13.6 歳) および159名の急性虚血性脳卒中症例 (男性91名, 女性68名, 平均年齢 74.2 ± 10.6 歳) であった。さらに大動脈解離症例を偽腔開存型急性大動脈解離群と血栓閉塞型大動脈解離群に分類した。FDP値は急性虚血性脳卒中群と比較し急性大動脈解離群で有意に高くなっていた ($18.15 [5.2-249.9] \mu\text{g}/\text{mL}$ vs. $2.3 [1.5-4.45] \mu\text{g}/\text{mL}$, $P < 0.001$)。急性大動脈解離症例において, 血栓閉塞型大動脈解離群 ($n=11$) と比較して, 偽腔開存型大動脈解離群 ($n=9$) で有意にFDP値が高くなっていた ($293.2 \mu\text{g}/\text{mL} [63.1-419.6 \mu\text{g}/\text{mL}]$ vs. $5.6 \mu\text{g}/\text{mL} [3.8-7.9 \mu\text{g}/\text{mL}]$)。結論として, 急性虚血性脳卒中群と比較し急性大動脈解離群, 特に急性虚血性脳卒中と比較し, 偽腔開存型大動脈解離群でFDP値が有意に高くなっている。FDP値の上昇は急性虚血性脳卒中と偽腔開存型急性大動脈解離の鑑別に有用なマーカーとなる可能性がある。

キーワード：急性大動脈解離, 急性虚血性脳卒中, フィブリノゲン/フィブリン分解産物。